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Models of Physical Activity:

Active Lifestyle Promotion for adults and elderly people affected by Chronic Obstructive Pulmonary Disease

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Title

Models of Physical Activity:
Active Lifestyle Promotion
for adults and elderly people affected by Chronic Obstruction Pulmonary Disease

.... you need a great physical
to chase dreams.

S.Benni



MODELS OF PHYSICAL ACTIVITY: ACTIVE LIFESTYLE PROMOTION FOR ADULTS AND ELDERLY PEOPLE AFFECTED BY CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background

Chronic Obstructive Pulmonary Disease, i.e. COPD, is characterized by a progressive airflow limitation, not fully reversible, due to an abnormal inflammatory response of the lungs (B.R. Celli, MacNee, et al. 2004; GOLD 2013). Exercise intolerance, symptoms such as dyspnea and several extra-pulmonary effects, for example skeletal muscle wasting, may contribute to increase patients disabilities, affecting their quality of life and reducing the maintenance of an active lifestyle (Kim et al. 2008; Caress et al. 2010; Glaab et al. 2010; Huertas & Palange 2011; Vorrink et al. 2011). Despite lung function parameters don't improve after pulmonary rehabilitation, exercise training is considered the most effective non-pharmacological intervention to improve COPD patients health and exercise capacity (B.R. Celli, MacNee, et al. 2004; Nici et al. 2006; D. E. O'Donnell et al. 2008; Fromer & C. B. Cooper 2008; GOLD 2013). Unfortunately, there are few available health-care structured programs of physical activity (Valero et al. 2009; Dourado et al. 2009) and a considerable proportion of eligible patients decline participation or drop out (Faulkner et al. 2010). Reasons for decline and drop-out from pulmonary rehabilitation and exercise training programs have seldom been investigated systematically (Fischer et al. 2007).

Moreover, a considerable debate continues with regards to what kind of model of physical activity and exercise training intervention is more effective to improve COPD patients health related parameters (W.D-C Man et al. 2009a), to increase their quality of life (Monninkhof et al. 2003), their share of physical activity (Hirvensalo et al. 2003; Sørensen et al. 2008) and to maintain an active lifestyle over the time (Leidy 2008; Leinonen et al. 2007).

Finally, evidences support notions that daily physical activity, health related quality of life, muscle strength and performance are likely intimately interlinked. Although, muscle wasting is common in COPD patients across all disease stages (Seymour et al. 2010), leading to a low skeletal muscle strength of lower limb (Kim et al. 2008; Donaldson et al. 2012), surprisingly it has been observed that eccentric contraction results greater compared to healthy control subjects (Mathur et al. 2007). The majority of research about COPD leg muscle function has used isometric or concentric quadriceps torque (Butcher et al. 2012), but there is lack of knowledge about the association between eccentric muscle strength and fast-velocity muscle contractions in COPD patients (Mathur et al. 2007; Butcher et al. 2012).

Purpose

The aims of this research are to:

- outline motivation and barriers which reduced COPD patients recruitment in a exercise training program and hindered an active lifestyle acquisition, in order to determine the recruitment feasibility;
- over the time access modifications in several COPD health related parameters provided by two different and easily applied-field models of adapted fitness activity for COPD patients in order to evaluate their effects in the long-term maintenance of an active lifestyle;
- investigate COPD patients strength performances as a function of contraction modalities and velocities to access lower limb muscle functionality comparing with healthy control group.

Design

The first study is a qualitative research, designed as a single-centre, multi-practice, randomized, parallel-group clinical trial, in which recruitment steps were recorded in order to assess patients' motivation of decline or drop out.

The second study is a descriptive research, designed as a longitudinal randomized controlled trial, in which baseline (T1), 3 months (T2), 6 months (T3) and follow up (T4) evaluations were performed to verify changes in anthropometry, functional health-related, lifestyle and quality of life parameters.

The third study is a case/control research, designed as a cross over and observational trial, in which architectural muscle measurements, concentric and eccentric quadriceps contractions at two different velocities, lifestyle and health-related parameters of both COPD patients and healthy control subjects were recorded to highlight differences of muscle functionality.

Ethical approval by Department of Neurological, Neuropsychological, Morphological and Movement Sciences, University of Verona, Medical Hospital Management approval of ULSS20, and informed consent by patients and subjects evaluated were obtained.

Subjects

The first study concerned the several steps of recruitment patients, starting by an initial number of 269 COPD males, established from the Respiratory Division of ULSS 20. Subsequently, it was recorded the motivations leading to participate at an exercise and physical activity program by 132 eligible patients and, finally, it were analyzed magnitude and characteristics of intrinsic motivation to practice physical activity of 38 recruited COPD patients.

The second study involved 38 COPD males patients for 6-months of exercise training and 3-months of follow up. Patients were aged 65 ± 5 years, affected by mild to severe COPD and didn't show any evidences of clinical instability, instable cardiac diseases, malignances and bone fractures. Participants were randomized for both disease stage, intrinsic motivations and share of practiced physical activity, and assigned to one of the three evaluation groups: Fitness Center based group (FC=13), Educational PA group (EDU=12) and Control group (CG=13).

The third study analyzed 60 males subjects, 35 COPD patients with mild to severe disease and 25 Healthy Control. COPD patients were aged 67.21 ± 4.7 years, affected by mild to severe COPD ($FEV_1 = 64.76 \pm 20.08\%$ of predicted; $FEV_1/FVC = 57.35 \pm 13.56\%$ of predicted) and didn't show any evidences of clinical instability, instable cardiac diseases, malignances and bone fractures. Healthy control subject were aged 65.15 ± 5.69 years and did not show pulmonary limitations ($FEV_1 = 115.06 \pm 17.43\%$ of predicted; $FEV_1/FVC = 101.87 \pm 6.62\%$ of predicted) and evidences of clinical instability, cardiovascular and metabolic diseases, malignances and bone fractures.

Measures

The first qualitative study was based on administration of a semi-structured interview and the EMI-2 structured questionnaire (Markland & Hardy, 1997).

Over the time, in the second descriptive research, several evaluations were performed. Body mass and bone density compositions were assessed by DXA scan. Functional health-related parameters, such as 6 minutes walking test, one-repetition maximum of leg press, leg extension, bicep curl and chest press, back scratch test, sit & reach test and one leg stance test, were recorded. Lifestyle was investigated with International Physical Activity questionnaire, i.e. IPAQ-short form, and SenseWear PRO-2 acquisitions. Finally, quality of life was collected using Maugeri Respiratory Failure questionnaire, i.e. MRF-26.

The third study was focused on assessing muscle architectural measurements, i.e. fascicle length, thickness and pennation angle of vastus lateralis (Acuson P50, Siemens, Germany), and both concentric and eccentric quadriceps performances at 30deg/s and 210deg/s at isokinetic dynamometry (Cybex Norm, USA). Also measurements of functional health-related parameters and lifestyle were recorded.

Results

The major cause of not-participation was related to mismatched inclusion criteria (65.53%). No-interest in exercise training (8.94%), lack of available time (6.81%) and inability to access at the physical activity structures (1.7%) were the most commonly cited reasons to decline participation. Recruitment of this study showed higher adherence (25.7%), confirmed by the lower number of drop out after 6 months of program (10.52%). Low total scores of intrinsic motivation to practice physical activity were recorded in COPD patients (mean 81.69pt \pm 48.08; 44.27% of maximum total score) although they seems to be motivated by quality of life-related items (mean improving health = 39.69pt \pm 12.73, 59.09% of maximum item score; mean management of body weight = 13.49pt \pm 6.65, 58% of maximum item score; mean decreasing stress = 17.06pt \pm 7.24, 58.52% of maximum item score). Significant improvements in total score motivation were observed after 3 months (+43.99%, $p < 0.05$) and after 6 months of exercise training (+47.42%, $p < 0.05$) by the FC group. After three months, FC subjects showed significant increases in both Socio/Emotional aspects ($p < 0.01$), Weight management ($p < 0.05$) and Enjoyment items ($p < 0.01$). At the end of the 6 months, significant improvement in FC groups were observed in Socio/Emotional aspects ($p < 0.01$) and in Enjoyment items ($p < 0.05$).

In the second study, 4 patients dropped out during the 6 months trial and 3 in the follow up period. No accident occurred. Between T1-T2, FC group shows significant improvement in %BMC (0.112 \pm 0.029, $p < 0.01$), Biceps curl 1RM (1.9kg \pm 0.6, $p < 0.05$), Chest press 1RM (8.1kg \pm 1.7, $p < 0.001$) and Balance test (48.5sec \pm 14.2, $p < 0.05$). EDU group shows significant modification in FAT (-736.4g \pm 240.0, $p < 0.05$), BMI (-0.332 \pm 0.106, $p < 0.05$), Leg Extension 1RM (7.2kg \pm 2.4, $p < 0.05$), Chest Press 1RM (6.1kg \pm 1.7, $p < 0.05$) and Back Scratch (2.7cm \pm 0.7, $p < 0.01$). The CG group shows significant differences in BMI (-0.588 \pm 0.157, $p < 0.01$), FAT (-1086.4g \pm 365, $p < 0.05$), and TBM (-1849.8g \pm 494.1 $p < 0.01$). Between T1-T3, the FC shows significant improvement in %BMC (0.071 \pm 0.024 $p < 0.05$), Chest Press 1RM (9.8kg \pm 2.4, $p < 0.01$), Balance (57.0sec \pm 13.3, $p < 0.01$), IPAQ moderate activity (1024 \pm 272, $p < 0.01$), IPAQ sedentary hours (-3.3 \pm 0.7, $p < 0.01$) and MRF-26 (-2.3 \pm 0.7, $p < 0.05$). EDU group shows significant modification in 6MWT Borg score (-1.37 \pm 0.41 $p < 0.05$), IPAQ walking activity (618 \pm 208, $p < 0.05$), IPAQ sedentary hours (-3.6 \pm 0.7, $p = 0.000$) and MRF-26 (-2.1 \pm 0.7, $p < 0.05$). CG group did not shows significant differences. At follow up, FC shows significant changes in %BMC (-0.069 \pm 0.020 $p < 0.05$), 6MWD (-48.2 \pm 14.8, $p < 0.05$), Leg Extension 1RM (-9.3 \pm 2.8, $p < 0.05$), Chest Press 1RM (-11.6 \pm 2.1, $p = 0.000$), Sit & Reach (-3.8 \pm 0.9, $p < 0.01$), Balance (-21.0 \pm 7 $p < 0.05$).

EDU group shows significant modification in 6MWT Borg score (-1.36 ± 0.41 $p < 0.05$), Leg Press 1RM (-32.6 ± 9.1 , $p < 0.05$), Leg Extension 1RM (-10.5 ± 1.9 , $p < 0.001$), Chest Press 1RM (-14.3 ± 1.3 , $p = 0.000$), Back Scratch (-4.3 ± 1.3 , $p < 0.05$), IPAQ sedentary hours (-3.5 ± 0.9 , $p < 0.01$) and MRF-26 (-2.9 ± 0.8 , $p < 0.05$). CG group shows significant difference in Chest Press 1RM (-10.9 ± 2.6 , $p < 0.01$). No significant modification were observed in SenseWear PRO-2 administration.

In the third study, healthy control subjects were significantly different in lung function parameters, i.e. FEV₁ ($p < 0.001$) and FEV₁/FVC ($p < 0.001$), and in exercise capacity, such as 6MWT performances ($p < 0.001$) and 1RM Leg Press ($p < 0.05$) than COPD patients. Of all contractions performed, only concentric 30deg/s peak torque was significantly higher in healthy control subjects compared to COPD patients ($p < 0.05$). No differences in muscle architecture, fast concentric and/or eccentric peak torque were observed between groups. However, significant differences were found between groups in eccentric/concentric peak torque ratio (30 deg/sec $p < 0.001$; 210 deg/sec $p < 0.01$). Finally, significant correlations were found between FEV₁ and 6MWT (0.719 $p < 0.001$), 1RM Leg Press (0.449 $p < 0.001$), peak torque contraction at 30 deg/sec (0.427 $p < 0.01$; 0.280 $p < 0.05$), at 210 deg/sec (0.285 $p < 0.05$; 0.276 $p < 0.05$) and eccentric/concentric peak torque ratio at both velocities (-0.562 $p < 0.001$; -0.292 $p < 0.05$). Same results were observed between FEV₁/FVC and parameters assessed.

Conclusion

Recruitment of COPD patients becomes very challenging especially if exercise training and physical activity programs are complex or have restrictive entry criteria (Bell-Syer, 2000). Indeed, cause of not-participation into our program was related to mismatched inclusion criteria. Considered the impossibility to modify inclusion/exclusion criteria, the higher adherence (25.7%) and the lower number of drop out recorded by our study (10.52%) compared to literature (recruitment 25.7% vs. 6.5% Faulkner's study,; drop out 10.52% vs. 29.26% Pitta's study, 2008; 27.92% Steel's study, 2008; 25% Woo's study, 2009; 46.87% Ringbaek's study, 2010) suggest that our great effort practice of recruitment, managed by only one person and characterized by persistence and flexibility strategies towards patients, seems to be more effective to establish a relationship of confidence between patients and the exercise specialist. Although patients provided low total scores of intrinsic motivation to practice physical activity, significant improvements in health-related and pleasure motivation items were observed after participation into an exercise training. These findings suggest that an high, structured and constantly supervision of an exercise specialist could be useful to increase participation at exercise training, improve motivation to practice physical activity and decrease risk of poor exercise adherence, which is the most important reason for declining effect of pulmonary rehabilitation (Ringbaek et al. 2010). Moreover, considered that it's well-known the low ratio of COPD patients with a true knowledge about characteristics of physical activity for pulmonary rehabilitation (Karapolat et al. 2012) and that a lack of perceived benefits, a low influence of specialist, a program timing and a disruption to usual routine may reduce COPD patients interest and motivation to take part in a pulmonary rehabilitation program (Keating et al. 2011; Fischer et al. 2007), it should be improve the level of liaison between specialist physicians and other healthcare professionals engaged in pulmonary management, in order to increase COPD patients perceptions of illness, to enhance the chances of treatment disease modalities and to provide more realistic information about benefits on health related quality of life available by practice of physical activity and maintenance of an active lifestyle.

According to expert panel position stand (Glaab et al. 2010), the second study confirms the need of a multifaceted approach in PR programs. Our study demonstrates that also an easily applied-field models of COPD specific APA training could be efficient in order to improve some of these HRQL. The improvements in bone mass content, strength of trunk muscles and patients' self-perceived disability seem to be better provide by the "well rounded" APA program. Moreover, our study shows that APA exercise specialist support is necessary to provide and maintain long-term significant health's gains. Finally, our trial highlights that improvement in functional exercise capacity does not automatically turn into a more active lifestyle. According to Conn (2008), furthers studies are aimed to identify feasible, acceptable and effective APA intervention, which transfer achievements provide reachable changes in lifestyle, both at short- and long-term.

The third study, i.e. the case/control research about differences of lower muscle functionality, highlighted that COPD patients are characterized by lower health related parameters and performed lower concentric contraction compared to healthy controls subjects. Interestingly, COPD preserved eccentric contractions and fast concentric torque. Considered that eccentric contraction seems to involve fast twitch motor units (Duchateau & Enoka 2008) and COPD hypoxia leads fiber shift towards IIX fibers (H.R. Gosker, Van Mameren, et al. 2002), COPD males seem to develop a favorable profile to minimize the strength loss likely due to neural-muscular modification. Moreover, as observed in our study, the favorable profile of COPD patients in preservation of eccentric contraction seems to confirm the notion about the great contribution of eccentric strength in functional performance of patients with COPD (Butcher et al. 2012). Finally, considered the effectiveness of eccentric training to produce muscle hypertrophy, strength gains and neural adaptation without stressing cardiopulmonary system (Roig et al. 2008) further investigations seem to be necessary in order to verify the usefulness of eccentric training as a modalities to provide greater strength improvements, to reduce muscle wasting and to enhance quality of life of COPD patients.

Key words: COPD; adults and elderly people; exercise training; physical activity; active lifestyle, recruitment; adherence; motivation; type of modalities training; functional health related parameters; quality of life; behavior change; muscle wasting; eccentric contraction; low and fast contractions; isokinetic device

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Models of physical activity: active lifestyle promotion for adults and elderly people affected by Chronic Obstructive Pulmonary Disease



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LIST OF ABBREVIATIONS

ADL	Activity of daily living
AAT	Alpha-1 antitrypsina
APA	Adapted physical activity
ATP	Adenosine Triphosphate
ATS	American Thoracic Society
BMC	Bone mass content
BMI	Body mass index
CG	Control group
COPD	Chronic Obstructive Pulmonary Disease
DPA	Daily Physical Activity
DXA	Dual Energy
EDU	Educational group
EGFR	Epidermal growth factor receptor
ERS	European Respiratory Society
ExT	Exercise Training
FC	Fitness Center group
FFM	Fat free mass
FEV ₁	Forced Expiratory Volumes at 1 second
FVC	Forced Vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HC	Healthy control
HRQL	Health related quality of life
IL-1 β	interleukin-1 beta
IL4	Interleukin-4
IL6	interleukin-6
IL8	Interleukin-8
IPAQ	International Physical Activity Questionnaire
LTB4	Leukotriene B4
MRF-26	Maugeri Respiratory Failure questionnaire-26
PA	Physical Activity
PaCO ₂	Arterial partial pressure of CO ₂
PaO ₂	Arterial partial pressure of O ₂
QoL	Quality of Life
TBM	Total Body Mass
TNF- α ,	Tumour necrosis factor-alpha
VEGF	Vascular Endothelial Growth Factors
VO ₂ / VO _{2max}	Oxygen consumption/ Maximal oxygen uptake
1RM	One repetition maximum
6MWT/ 6MWD	Six minute walking test / Six minute walking distance

THE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Definition of COPD

COPD is a slowly progressive lung disease characterized by airflow obstruction with breathing-related symptoms resulting in a gradual loss of function (Mannino 2001; Qaseem et al. 2007; B.R. Celli, MacNee, et al. 2004; GOLD 2013). The symptoms of COPD range from chronic cough, sputum production, and wheezing to more severe symptoms, such as dyspnea, poor exercise tolerance, and, at the end stage, signs or symptoms of right-sided heart failure (Qaseem et al. 2007). In literature there are two different definitions of COPD provided by the ATS/ERS (1995; 2004) and GOLD (2001; 2006; 2010; 2013) (Viegi et al. 2007) (Table 1.1).

Table 1.1 – COPD definition

ATS/ERS definition	GOLD definition
Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease state characterized by airflow limitation that is not fully reversibly. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systematic consequences (B.R. Celli, MacNee, et al. 2004).	Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients (GOLD 2013).

ATS/ERS position stand (2004) updates the position papers on COPD published by the two Society in 1995 (N. M. Siafakas et al. 1995). Both societies felt the need to update the previous documents due to the increasing in prevalence and overall importance of COPD as an health problem, the need to highlight advances in the research field ad to support the dissemination of the GOLD to the battle against COPD (B.R. Celli, MacNee, et al. 2004). The GOLD program was initiated in 1998 and its aim was to produce recommendations to manage the COPD, based on the best scientific information available. Its committee was established in 2002 and reviewed the published research on COPD management and prevention to establish the impact on recommendations. GOLD strategies aim to manage short-term impact of COPD, relieving and reducing impact of symptoms on patients, and long-term impact to reduce the risk of adverse health events that may affect the patients (GOLD 2010b; GOLD 2010a; GOLD 2013).

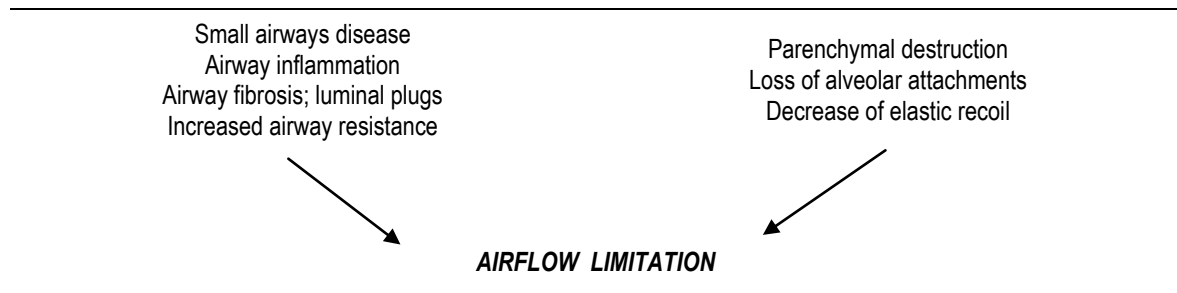
Pathology, Pathogenesis and Patophysiology of COPD

Despite different definitions provided, COPD is a respiratory disorder largely caused by smoking, characterized by progressive airway obstruction, no-reversibility, lung hyperinflation, systemic manifestations and high frequency of exacerbations (D. E. O'Donnell et al. 2008). Several risk factors, such as smoking and others noxious particles inhaled, cause an inflammatory response of the lungs, which lead into a pulmonary and systemic chronic inflammation (B.R. Celli, MacNee, et al. 2004; van der Vlist & Janssen 2010; GOLD 2013).

Pathology

The chronic airflow limitation in COPD is caused by a persistent inflammation of proximal and peripheral airways, lung parenchyma and pulmonary vasculature. The chronic inflammation leads to an increased number of specific inflammatory cell types in different parts of the lung and structural changes results from repeated injury and repair. In fact, when injured, normal lungs undergo tissue-repair processes that return the tissue to normal or near normal functioning. However, in the presence of the tissue destruction associated with emphysema, these repair processes are altered, and the balance between destruction and repair is affected. Therefore, this imbalance between the lung's repair and defense mechanisms results in a small airway fibrosis (B.R. Celli, MacNee, et al. 2004; Nici et al. 2006; D. E. O'Donnell et al. 2008; GOLD 2010b; GOLD 2013). Remodeling of the small airways is a key factor in development of the COPD irreversible airflow limitation and describes persistent changes that occur within the structural components of the airways in response to inflammation (B.R. Celli, MacNee, et al. 2004; D. E. O'Donnell et al. 2008; GOLD 2013). Caused by these structural changes in the airway walls, the resistance in the peripheral airways increases, resulting in the major sites of obstruction (D. E. O'Donnell et al. 2008; Fromer & C. B. Cooper 2008; GOLD 2013; Rabe et al. 2007). Moreover, the relative contributions of which components, i.e. more injury processes or less repair mechanisms, vary from to person. The destruction of the parenchymal tissue in the lungs could result into emphysema disease, which is characterized by enlarged alveolar sacs and structural damage to the expiratory bronchioles (Nici et al. 2006; D. E. O'Donnell et al. 2008; GOLD 2013). In general, inflammatory and structural changes (Table 1.2) in airways increase with disease severity and persist on smoking cessation (GOLD 2013; Rabe et al. 2007).

Table 1.2 - Mechanisms Underlying Airflow Limitation in COPD



(from GOLD 2013)

Pathogenesis

COPD is an insidious and progressive disease: there are no characteristic symptoms in the early stages of the disease, and, in later stages, the symptoms are partially, but not fully, reversible. COPD usually occurs in mid-life following long-term exposure to noxious particles or gases when the normal protective and repair functions in the lungs are overwhelmed or functioning sub-optimally (Fromer & C. B. Cooper 2008). This exposure of chronic irritants causes an inflammation in the respiratory tract of COPD patients, which is an exaggeration of inflammatory responses normally seen in the respiratory tracts of individuals who smoke, but do not have COPD (Fromer & C. B. Cooper 2008; Rabe et al. 2007; GOLD 2013). The mechanisms for this amplified inflammation are not yet understood, but, probably, genetically determined. Indeed, it has been reported that some patients could develop COPD without any history of cigarette smoking (Figure 1.a) (GOLD 2010b; GOLD 2013; Rabe et al. 2007; Nici et al. 2006). However, chronic inflammation is usually characterized by presence of chronic or recurrent increase in bronchial secretion sufficient to cause expectoration, i.e. most days of a minimum of 3 months per year for the least two successive years and cannot be attributed to other pulmonary or cardiac causes (B.R. Celli, MacNee, et al. 2004; Rabe et al. 2007; Fromer & C. B. Cooper 2008; GOLD 2010b; GOLD 2013).

Inflammatory cells and mediators

COPD is characterized by a specific pattern of inflammation involving neutrophils, macrophages and lymphocytes, and high levels of inflammatory markers, such as i C-reactive protein, TNF- α , interleukin IL-8, IL-6 and monocyte chemo-attractant protein-1, were observed in the lungs and serum circulation. These cells release inflammatory mediators and interact with structural cells in the airways and lung parenchyma. The wide variety of inflammatory mediators attract inflammatory process, i.e. pro-inflammatory cytokines, and induce structural changes, i.e. growth

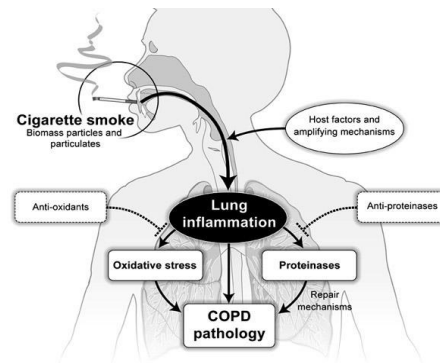


Figure 1.a: Pathogenesis of the COPD

(from GOLD 2010b)

factors, and correlate with measurements of COPD including FEV₁, dyspnea levels and exacerbation rates. (Table 1.3) (GOLD 2010b) Fromer & C. B. Cooper 2008).

Oxidative stress and Protease-Antiprotease Imbalance

Moreover, lung inflammation is further amplified by oxidative stress and by an imbalance of proteinases, such as elastase which degrades connective tissue in the lungs, and antiproteinases, such as AAT, in the lungs (B.R. Celli, MacNee, et al. 2004; GOLD 2013). The oxidant/antioxidant balance is generated by cigarette smoke, inflammation, respiratory infections, genetic factors and dietary factors, and released from activated inflammatory cells, such as macrophages and neutrophils. However, the several adverse consequences of oxidative stress can occur in the lungs, including an increased inflammation, an activation of inflammatory genes, an inactivation of protective antiproteases, a stimulation of mucus secretion and a stimulation of increase plasma exudation (Van der Vlist & Janssen 2010; GOLD 2013). The protease-antiprotease imbalance is thought to contribute to the irreversible lung damage seen in COPD, particularly in patients with emphysema and it may be caused by worsening lung inflammation or by environmental or genetic factors (B.R. Celli, MacNee, et al. 2004; GOLD 2010b; GOLD 2013). Indeed, AAT deficiency is an important genetic factor for the development of COPD: AAT is an antiprotease which exerts a protective effect on lung tissue by inhibiting the elastase that breaks down lung connective tissue. Approximately 3% of COPD patients have this deficiency (B.R. Celli, MacNee, et al. 2004; Rabe et al. 2007; Fromer & C. B. Cooper 2008; GOLD 2010b; GOLD 2013)

Table 1.3 – Inflammatory cells and mediator in COPD

Inflammatory cells	Neutrophils	Increase in sputum of normal smokers
		Further increase in COPD and related to disease severity
		Few neutrophils are seen in tissue and they may be important in mucus hypersecretion and release of proteases
	Machrophages	Greatly increase in airway lumen, lung parenchyma and bronchoalveolar lavage fluid
		Produce increased inflammatory mediators and proteases in COPD patients in response to cigarette smoke
		They may show defective phagocytosis
	T Lymphocytes	Increase CD4+ and CD8+ in airway wall and lung parenchyma
		Increase CD8+/CD4+ ratio
		Increase CD8+ Tcells (Tc1) and Th1 cells
		CD8+ cells may be cytotoxic to alveolar cells, contributing to their destruction
	B Lymphocytes	Increase in peripheral airways and within lymphoid follicles
		May be a response to chronic colonization and infection of the airways
	Eosinophils	Increase proteins in sputum during exacerbations
		Increase eosinophils in airway during exacerbation
	Epithelial cells	May be activated by cigarette smoke to produce inflammatory mediators
Inflammatory mediators	Chemotactic factors	Lipid mediators, i.e. s LTB ₄ ; attracts neutrophils and T lymphocytes
		Chemokines, i.e. IL8; attracts neutrophils and monocytes
	Proinflammatory cytokines	TNF- α , IL-1 β and IL6; amplify the inflammatory process and may contribute to some of the systemic effects of COPD
	Growth factors	Transforming TGF- β ; may induce fibrosis in small airways

(from GOLD 2010b)

Pathophysiology

The physiologic changes that occur as COPD worsens include mucus hyper-secretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, abnormal gas exchange, pulmonary hypertension and cor pulmonale (Figure 1.b) (Fromer & C. B. Cooper 2008).

Mucus hyper-secretion

Mucus hyper-secretions, resulting in a chronic productive cough, is a feature of Chronic Bronchitis and is not necessarily associated to airflow limitation. Conversely, not all patients with

COPD have mucus hyper-secretion. When present, it is due to an increased number of goblet cells and enlarged mucosal glands in response to chronic airway irritation. Several mediators and proteases stimulate mucus hyper-secretion, activating the EGFR (GOLD 2010b; GOLD 2013).

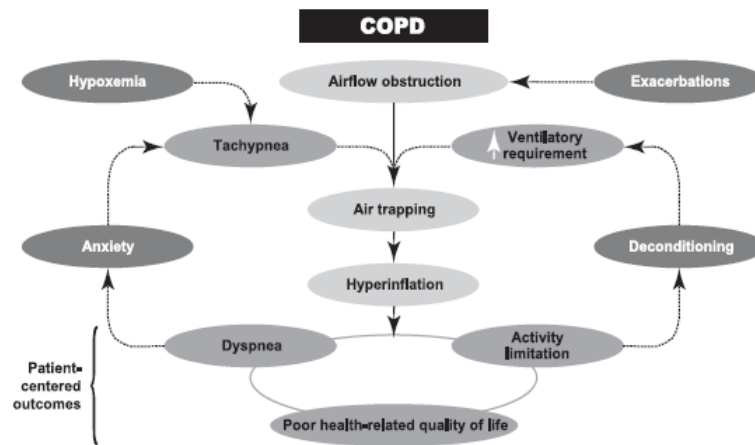


Figure 1.b – Influence of pathophysiologic characteristics of COPD on patient outcomes

(from Fromer & Cooper 2008)

Airflow limitation and Pulmonary Hyperinflation

The extent of inflammation, fibrosis and luminal exudates in small airways is correlated with the reduction in lung function parameters and probably with the accelerated decline in FEV₁ characteristic of COPD patients (GOLD 2013). In fact, expiratory flow limitation is the pathophysiological hallmark of COPD (D. E. O'Donnell et al. 2008). Therefore, chronic inflammation causes an expiratory flow limitation (Fromer & C. B. Cooper 2008). Proximal and peripheral airways disease, coupling with destruction of the lung parenchyma and vasculature, lead to the loss of alveolar attachment. This loss of alveolar attachment compromises the ability of patients to expel air during expiration, which is due to a diminished lung recoil. Air trapping and lung hyperinflation result from this wasting air expiration. Indeed it's well known that hyperinflation occurs when air is trapped within the lungs after each breath and it's caused by an imbalance between volumes of inhaled and exhaled air. Evidences suggest that, in patients with COPD, the time to exhale is more prolonged, inspiratory capacity is reduced and functional residual capacity is increased than healthy people, particularly during exercise, i.e. dynamic hyperinflation. As COPD progresses, the insidious physiologic changes, especially hyperinflation, cause progressively worsening dyspnea, first as patients exercise, and over time, even at rest. Acute-on-chronic hyperinflation has been shown to contribute to shortness of breath during exercise,

acute exacerbation in COPD and reduced QoL in patients (D. E. O'Donnell et al. 2008; GOLD 2013; Viegi et al. 2007; Fromer & C. B. Cooper 2008; GOLD 2010b; Rabe et al. 2007).

Gas Exchange Abnormalities

Gas exchange abnormalities result especially in hypoxemia, i.e. decreased level of O₂ in arterial blood, and hyper-capnia, i.e. increased CO₂ concentration in arterial blood. In general, gas transfer for oxygen and carbon dioxide worsen as the disease progress. Reduced ventilation may also be due to reduced ventilator drive. This may lead to carbon dioxide retention when it is combined with reduced ventilation due to a high work of breathing because of severe obstruction and hyperinflation coupled with ventilator muscle impairment. The abnormalities in alveolar ventilation and a reduced pulmonary vascular bed further worsen the V_A/Q abnormalities (GOLD 2010b; GOLD 2013).

Pulmonary hypertension

Pulmonary hypertension may develop late in the course of COPD and is due mainly to hypoxic vasoconstriction of small pulmonary arteries, eventually resulting in structural changes that include intimal hyperplasia and later smooth muscle hypertrophy/hyperplasia. There is an inflammatory response in vessels similar to that seen in the airways and evidence of endothelial cells dysfunction. The loss of pulmonary capillarity bed in emphysema may also contribute to increase pressure in the pulmonary circulation. Progressive pulmonary hypertension may lead on to right ventricular hypertrophy and, eventually, to right-side cardiac failure, i.e. cor pulmonale (GOLD 2010b; GOLD 2013).

Diagnosis of COPD

COPD runs an insidious course, measured over years, with an often undiagnosed initial phase (B.R. Celli, MacNee, et al. 2004). Most individual with COPD are not diagnosed until the disease is well advanced (D. E. O'Donnell et al. 2008). Usually, patients tend to underreport their symptoms because they may be minimal or perceived to be a normal part of ageing or clinically insignificant (Viegi et al. 2007; Fromer & C. B. Cooper 2008). So, to accurately diagnosis COPD, patient histories, physical examinations and lung function testing need to be provided (Fromer & C. B. Cooper 2008). A mass screening of asymptomatic individuals for COPD is not supported and recommended by the current evidence (D. E. O'Donnell et al. 2008). In presence of some indicators (Table 1.4) in an individual over age 40, a diagnosis of COPD need to be confirmed

physiologically through assessment of lung function with simple spirometry (B.R. Celli, MacNee, et al. 2004; Fromer & C. B. Cooper 2008; GOLD 2010b; GOLD 2013). Moreover, AAT deficiency testing should be considered if symptoms of COPD occur in patients younger than 45 years of age where a link with obvious risk factors cannot be made, in patients with lower-lobe predominant emphysema, or in patients within a family cluster of COPD cases where there has been no remarkable exposure to primary or secondary tobacco smoke (Fromer & C. B. Cooper 2008).

Table 1.4 – Key indicator for considering a diagnosis of COPD

Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probabilities of a diagnosis of COPD. Spirometry is needed to establish a diagnosis of COPD	
Dyspnea	<p>Progressive (worsens over time)</p> <p>Usually worse with exercise</p> <p>Persistent (present every day)</p> <p>Described by the patients as an “increased effort to breathe”, “heaviness”, “air hunger” or “gasping”</p>
Chronic Cough	May be intermittent and may be unproductive
Chronic sputum production	Any pattern of chronic sputum production may indicate COPD
History of expose to risk factors	<p>Tobacco smoke</p> <p>Occupational dusts and chemicals</p> <p>Smoke from home cooking and heating fuels</p>

(from GOLD 2010b)

Medical history

COPD is a generally a progressive disease but it has a variable natural history and not all individuals follow the same clinical course over time. Chronic cough and phlegm may predominate in some patients, whereas others may report only effort dyspnea. Some individuals show a rapidly accelerated lung function decline, while others a slowly progressive, roughly “stable” decline is observed (Viegi et al. 2007). Therefore, healthcare providers should provide a detailed medical history to consider a diagnosis of COPD for any patient, especially those over 40 years of age, which present some indicator risk, such as dyspnea, chronic cough, chronic sputum production and history of expose to risk factors (GOLD 2010b; GOLD 2010a; GOLD 2010c;

GOLD 2013). The medical assessment should to consider topics about patients' exposure to risk factors, past medical history, family history of COPD or other respiratory diseases, pattern of symptoms development, history of exacerbation or previous hospitalizations for respiratory disease, presence of co-morbidities, impact of disease in on patient's life, social and family support and possibilities for reducing risk factors (B.R. Celli, MacNee, et al. 2004; Fromer & C. B. Cooper 2008; GOLD 2010a; GOLD 2010b; GOLD 2013).

Physical examination

Although it is an important part of patients care, the physical examination is rarely diagnostic in COPD. Indeed, physical signs of airflow limitation are usually not present in the early stage of COPD and they could be observed until significant impairment of lung function has occurred. Moreover their detection has a relatively low sensitivity and specificity. The aim of the physical examination should be to elicit the presence of respiratory and systemic effects of COPD through inspection of central cyanosis, chest wall abnormalities, resting respiratory, pursed-lip breathing, resting muscle activation, ankle ore leg edema, palpation and percussion to assess the presence of hyperinflation and auscultation (B.R. Celli, MacNee, et al. 2004; GOLD 2010b; GOLD 2013).

Measurement of airflow limitation

Considered that patients may not have significant symptoms at the time of initial diagnosis, lung function measurements are an essential and objective tools to check the presence of a pulmonary disease, to provide the right diagnosis and evaluate the stage of airflow obstruction (Gooneratne et al. 2010; M.R. Miller, Hankinson, et al. 2005). To assess COPD, the most important spirometric parameters are the FVC, which is the volume delivered during an expiration made as forcefully and completely as possible starting from full inspiration, and the FEV₁, i.e. the volume delivered in the first second of an FVC maneuver. Also the FEV₁/FVC ratio expressed as a percentage should be calculated (M.R. Miller, Hankinson, et al. 2005; GOLD 2010c). When compared with predicted normal values determined on the basis of age, height, sex, and ethnicity, a measure of the severity of airway obstruction can be determined. Spirometry is however only one way of interpreting COPD disease severity. Other measures, such as the MRC dyspnea scale for measuring breathlessness, exacerbation frequency, BODE-index, QoL assessment, and exercise capacity, may help to build a more complete picture. Finally, spirometry is a reliable method of differentiating between obstructive airways disorders, i.e.

COPD, asthma, and restrictive diseases, where the size of the lungs is reduced, i.e. fibrotic lung disease (B.R. Celli, MacNee, et al. 2004; Rabe et al. 2007; GOLD 2010b; GOLD 2013; GOLD 2010c; M.R. Miller, Hankinson, et al. 2005).

Interpreting measurement

Spirometric classification has proved useful in predicting health status and is applicable to populations and not to substitute clinical judgment in the evaluation of the severity of disease in individual patients (Gooneratne et al. 2010). Assessment of airflow abnormalities is provided by observation of pulmonary function values, i.e. FEV_1 and FV_1/FVC in volume-time curve, and also by the analysis of expiratory flow rate seen in through the flow-volume curve morphology (Figure 1.c, Figure 1.d) (GOLD 2010c). Assessing bronchodilator reversibility is important to determine whether fixed airway narrowing is present. In patients with COPD, post-bronchodilator FEV_1/FVC remains < 0.7 , whereas FEV_1 may improve significantly, i.e. change of $> 12\%$ and > 200 mL in FEV_1 can occur in COPD. In addition, degree of bronchodilator reversibility can vary from day to day. Larger changes in FEV_1 do not negate a diagnosis of COPD, although the greater these changes are the greater the likelihood that the patient has asthma, either instead of or in addition to COPD (GOLD 2010b; GOLD 2010a; GOLD 2010c; GOLD 2013).

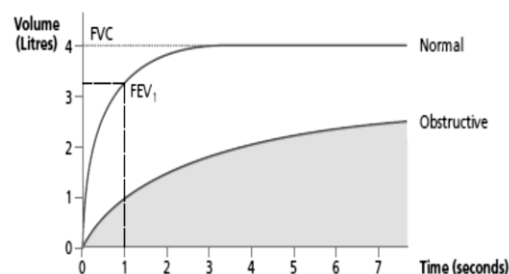


Figure 1.c – FEV_1 and FVC in volume-time curve;
 $FEV_1 < 80\%$ predicted normal; FVC usually reduced but to a lesser extent than FEV_1 ; FEV_1/FVC ratio < 0.7

(from Bellamy et al. 2005)

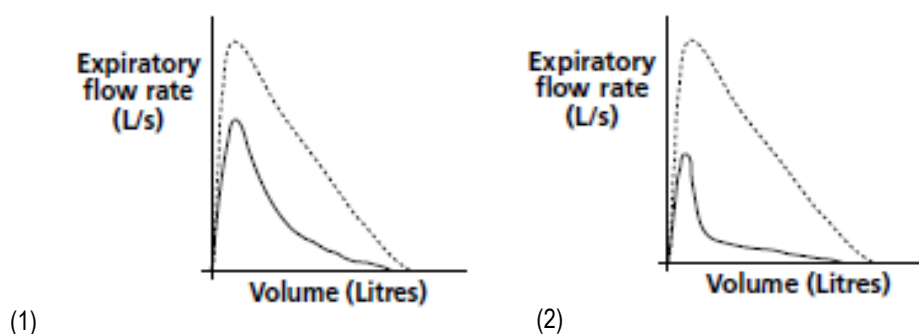


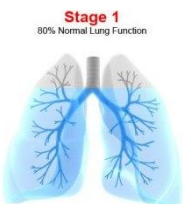



Figure 1.d – Morphology of flow-volume curves in obstructive (1) and severe obstructive disorder (2);
 (1) PEF is reduced and the decline in airflow to complete exhalation follows a dipping curve;
 (2) particularly with emphysema, the characteristic “steep pattern” is seen in the expiratory flow trace.

(Bellamy et al. 2005)

COPD classification

The updated GOLD guidelines disregarded the stage 0 “at risk” provided previously by ATS/ERS statement, and are based only to the grading of FEV₁% predicted level (Viegi et al. 2007; GOLD 2010b; GOLD 2013). Stage 0 has been removed because there is incomplete evidence that patients with this stage 0, i.e. post-bronchodilator FEV₁/FVC >0.7; FEV₁% pred. ≥80, necessarily progress to stage I COPD (Fromer & C. B. Cooper 2008). Therefore the severity of COPD is classified according to the degree of abnormality in spirometric readings, the level of symptoms and the presence of comorbid conditions that can lead to complications (B.R. Celli, MacNee, et al. 2004; Fromer & C. B. Cooper 2008; GOLD 2010b; GOLD 2013) (Table 1.5).

Table 1.5 – GOLD spirometric criteria for COPD severity

The spirometric criterion required for a diagnosis of COPD is a FEV ₁ /FVC ratio below 0.7 after bronchodilator			
	classification	lung parameters	symptoms
 <p>Stage 1 80% Normal Lung Function</p>	Stage I MILD COPD	FEV ₁ /FVC <0.7 FEV ₁ ≥ 80% pred.	symptoms of chronic cough and sputum production may be present, but not always;
 <p>Stage 2 50% - 80% Normal Lung Function</p>	Stage II MODERATE COPD	FEV ₁ /FVC <0.7 50% ≤ FEV ₁ < 80% pred.	shortness of breath on exertion; cough and sputum production;
 <p>Stage 3 30% - 50% Normal Lung Function</p>	Stage III SEVERE COPD	FEV ₁ /FVC <0.7 30% ≤ FEV ₁ < 50% pred.	greater shortness of breath; reduced exercise capacity and presence of fatigue; repeated exacerbations;
 <p>Stage 4 Less Than 30% Normal Lung Function</p>	Stage IV VERY SEVERE COPD	FEV ₁ /FVC <0.7 FEV ₁ < 30% pred. or FEV ₁ <50% pred. plus chronic respiratory failure	impaired quality of life;

(adapted from GOLD 2010c; GOLD 2010b; GOLD 2013)

Respiratory failure is defined as a Pa,O₂, less than 8.0 kPa or 60 mmHg, with or without a PaCO₂ greater than 6.7 kPa or 50 mmHg, while breathing air at sea level, and it may lead to effects on the heart such as cor pulmonale, i.e. right heart failure. At this stage, QoL is very impaired and exacerbations may be life threatening (B.R. Celli, MacNee, et al. 2004; Rabe et al. 2007).

Differential diagnosis

Chest radiography helps in differential diagnosis and other tests be useful to better determine the phenotype and physiological characteristics of individual patients (Table 1.6) (Celli et al. 2007; GOLD 2013). In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiologic testing techniques, and it is assumed that asthma and COPD coexist in these patients. In these cases, current management is similar to that of asthma. Other potential diagnoses are usually easier to distinguish from COPD (Rabe et al. 2007; GOLD 2013).

Table 1.6 – Differential diagnosis of COPD	
Diagnosis	Suggestive features
COPD	Mid-life onset Slowly progressing symptoms Long history of smoking
Asthma	Early onset Varying symptoms Symptoms during the night/early morning Presence of allergy, rhinitis and/or eczema A family history
Congestive heart failure	Airflow limitation that is largely reversible Fine basilar crackles on auscultation Dilated heart on chest radiography Pulmonary edema
Bronchiectasis	Volume restriction not airflow limitation on pulmonary function test Large volume of purulent sputum Commonly associated with bacterial infection Coarse crackles/clubbing on auscultation
Tuberculosis	Bronchial dilation and bronchial wall thickening on chest radiography/CT Onset at all ages Lung infiltrate on chest radiography Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Younger onset and in nonsmokers History of rheumatoid arthritis/fume exposure Hypodense areas on expiration on Computed Tomography suggestive of bronchiolitis
Diffuse panbronchiolitis	Effects mostly male nonsmokers Almost all have chronic sinusitis Diffuse small centrilobular nodular opacities and hyperinflation on chest radiography and High Resolution Computed Tomography

(from Celli et al. 2004)

Risk factor of COPD

Conventionally, risk factors are subdivided into endogenous or host risk factors and exogenous or environmental risk factors (N. M. Siafakas et al. 1995; Viegi et al. 2007). Identification of cigarette smoking as the most commonly encountered risk factor has led to incorporate smoking cessation programs into all of prevention and management COPD interventions. However, although smoking is the best-studied COPD risk factor, consistent evidences from epidemiologic studies about COPD nonsmokers patients (Figure 1.e) (Salvi & Barnes 2009) had well established that cigarette smoke is not the only one cause to develop chronic airflow obstruction (Rabe et al. 2007). The well-recognized host risk factors are genetics, age, gender and asthma, instead the environmental risk are smoking, socio-economic status, occupation, environmental pollution, perinatal events, childhood illness, recurrent bronchopulmonary infections and diet (Figure 1.f) (Viegi et al. 2007).

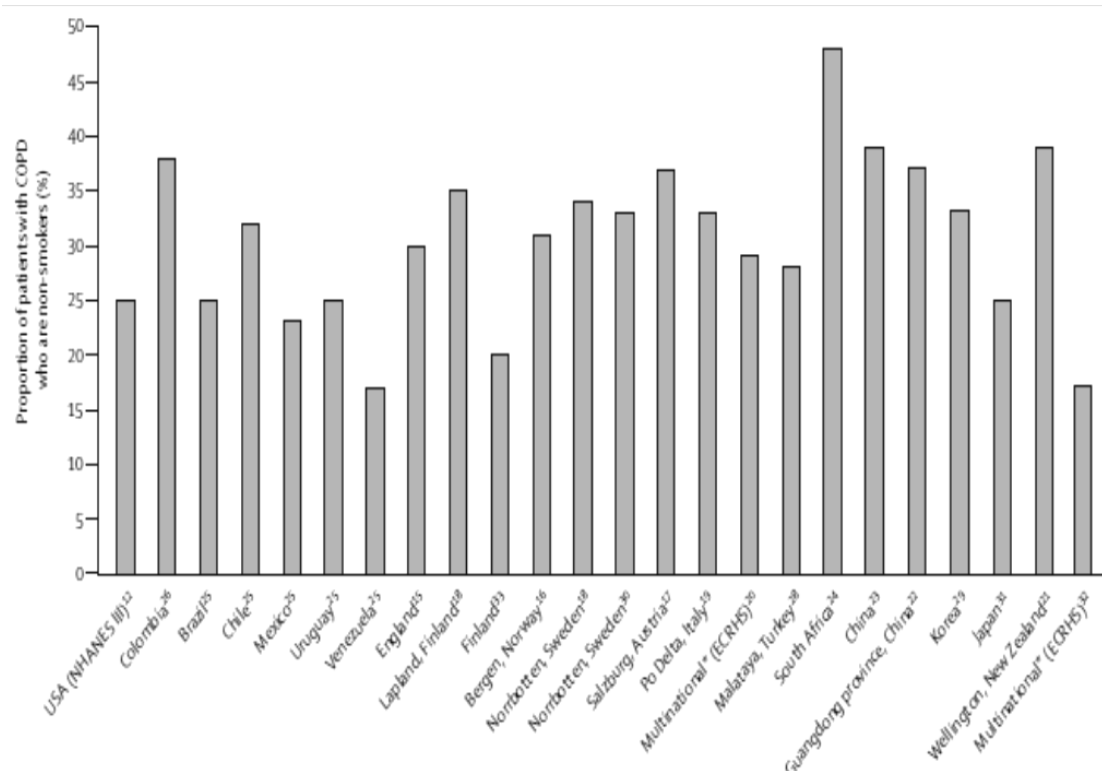


Figure 1.e – Proportion of patients with COPD who are non-smokers worldwide;

* Australia, Belgium, Denmark, France, Germany, Iceland, Ireland, Italy, Netherlands, New Zealand, Spain, Sweden, Switzerland, UK, and USA

(from Salvi & Barnes 2009)

Variables	ERS %		Clinical %		ATS %	
	Males	Females	Males	Females	Males	Female
Age [†]	NS	NS	71***	85***	63***	89***
Height [‡]	NS	NS	34*	46*	49***	28§
Pack-yrs [†]	22***	36*	30***	45**	32***	34*
Familial history for COPD	NS	NA*	90**	NS	53*	NS
Childhood respiratory infections	63*	81**	39§	71*	55*	NS
Work exposure to dusts/chemicals	NS	NS	NS	NA§	53**	NS
Low socioeconomic condition	NS	NS	NS	NS	41§	NS

Figure 1.f – Increased risk of COPD by sex associated with risk factors;

NS: no-significant; NA: not applicable; # derived by multiple regression models; [†] expressed in decades; [‡] expressed in dm; § borderline significance (0.1>p>0.05); * p<0.05; ** p<0.01; ***p>0.001;

(from Viegi et al. 2007)

Genetic factors

Results from studies assessing genetic components of COPD are not always consistent, probably reflecting differences in disease diagnosis criteria (Viegi et al. 2007). COPD was recognized as a polygenic disease and a classic example of gene-environment interaction (Rabe et al. 2007; Viegi et al. 2007; GOLD 2013; GOLD 2010b). In fact, in the Kurzius-Spencer study (2001) it was reported a significant correlation between FEV₁ slopes among all sibling pairs, suggesting a strong genetic component relating susceptibility to smoking and rate of decline in FEV₁. Moreover, several studies involving families with members with symptomatic disease reported evidence of genetic influence on FEV₁ (Viegi et al. 2007). Although genetic association needs to be further investigated, the best documented genetic risk factor is the severe hereditary deficiency of AAT, i.e. major circulating inhibitor of serine proteases and a rare recessive trait most commonly seen in Northern European origins' individuals (Rabe et al. 2007; GOLD 2010b; GOLD 2013). Premature and accelerated development of panlobular emphysema and decline in lung functioning were observed in both smokers and nonsmokers with the severe deficiency (Viegi et al. 2007; GOLD 2010b).

Age, lung growth and gender

Age is often listed as a risk factor for COPD, but it is yet unclear if healthy aging as such leads to COPD or if age reflect the sum of cumulative exposure through life (Figure 1.g) (GOLD 2013). Aging process itself results in a decline of pulmonary function, i.e. average annual decline of FEV₁ about 26/29 ml/year for men and 22/25 ml/year for women (Burrows et al. 1983; Cheng et al. 2003; Pelkonen et al. 2003). Moreover, lung growth is related to process occurring during gestation, birth and exposures during childhood and adolescence. Therefore, any factors that affects lung growth has the potential for increasing an individual's risk of developing COPD. Indeed, several studies confirmed a positive association between birth weight and FEV₁ in adulthood (Lawlor et al. 2005; GOLD 2010b; GOLD 2013). The role of gender in determining COPD risk remains unclear (GOLD 2010b). In the past, most studies showed a COPD greater prevalence and mortality in males than females, but recent data show that the prevalence of the disease is now almost equal between genders, probably reflecting the changing patterns of tobacco smoking (Rabe et al. 2007; GOLD 2013).

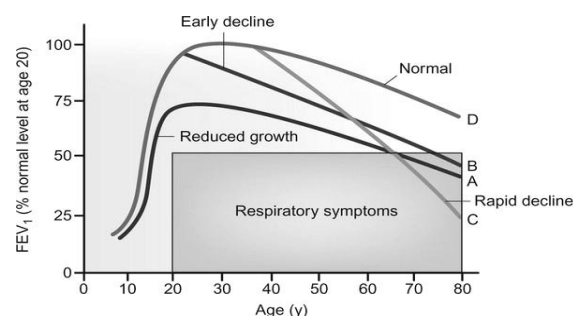


Figure 1.g – Different type of decline in FEV₁

(adapted from GOLD 2013)

Asthma and Bronchial Hyper-reactivity

Asthma seems to be a risk factor for the development of COPD although the evidence is not conclusive. The Tucson Epidemiological Study of Airway Obstructive Diseases highlighted that adults with asthma show a twelve-fold higher risk to develop COPD over time than those without asthma, after adjusting for smoking (Silva et al. 2004). Moreover, Vonk et colleagues (2003) observed that the 20% of patients with asthma develop functional sign of COPD, irreversible airflow limitation and reduced transfer coefficient (Vonk et al. 2003; GOLD 2010b; GOLD 2013). In the European Respiratory Community Health Survey, bronchial hyper-responsiveness was second only to cigarette smoking as the leading risk factor for COPD, responsible for 15% of the

population attributable risk. The pathology of chronic airflow limitation in asthmatic non-smokers and non-asthmatic smokers is markedly different, suggesting that the two disease entities remain different even with similar reduction in lung function (Tashkin et al. 1996).

Exposure to particles

Because individuals may be exposed to a variety of different types of inhaled particles over their lifetime, it is helpful to think in terms of the total burden of inhaled particles (Figure 1.h) (Rabe et al. 2007; GOLD 2010b).

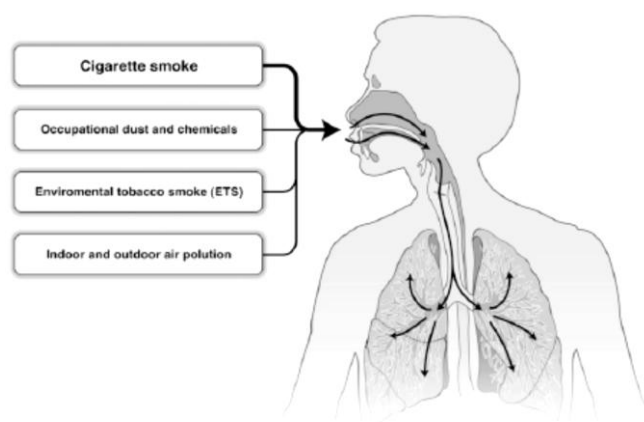


Figure 1.h – COPD risk related to the total burden of inhaled particles

(from Rabe et al. 2007)

Cigarette smoking is the most commonly encountered risk factor for COPD (GOLD 2013), showing higher prevalence of respiratory symptoms and lung function abnormalities, greater annual decline in FEV₁ and COPD mortality rate than nonsmokers (Rabe et al. 2007; GOLD 2013). The occurrence of respiratory symptoms increases with number of cigarettes smoked and decreases with smoking cessation. Moreover, age of starting smoking, total pack-yr smoked and current smoking status are all predictive of COPD mortality (Figure 1.i) (Viegi et al. 2007). Other type of tobacco, i.e. pipe, cigar, water pipe and marijuana, are also risk factors for COPD, and this smokers have greater COPD morbidity and mortality rates than nonsmokers, although their rates are lower than those for cigarette smokers (Rabe et al. 2007; GOLD 2013). Smoking during pregnancy may also pose a risk for the fetus, by affecting lung growth and development in utero and possibly the priming of the immune system (Rabe et al. 2007). Finally, passive exposure to cigarette smoke may also contribute to respiratory symptoms and COPD by increasing the lungs' total burden of inhaled particles and gases (Rabe et al. 2007; GOLD 2013).

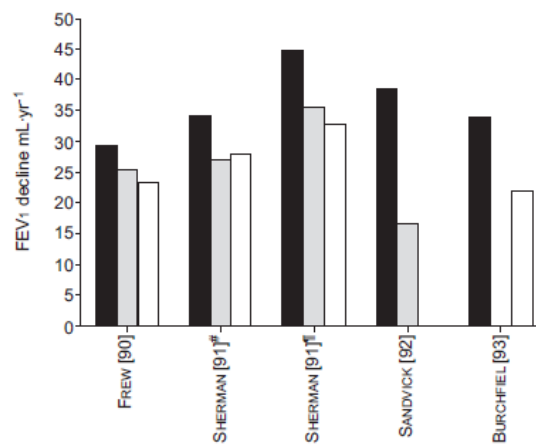


Figure 1.i – FEV₁ decline associated with tobacco smoke in longitudinal studies;
 (■) current smokers; (▒) former smokers; (□) never smokers;
 (#) males; (f) females;

(from Viegi et al 2007)

Occupational exposures, including organic and inorganic dusts and chemical agents and fumes, are an underappreciated risk factor for COPD. In USA, it was observed that of almost 10.000 adults aged 30-75 years, the fraction of COPD attributable to work was 19.2% overall, and 31% among never-smokers (GOLD 2010b; GOLD 2013). Moreover, an ATS statement establish occupational exposures as a cause for 10 to 20% of either symptoms or functional impairment consistent with COPD and risks are higher in females (ATS 2003; Rabe et al. 2007; GOLD 2010b; GOLD 2013). Furthermore, a large cohort study observed increased rates of lung cancer in COPD male Swedish construction workers (Viegi et al. 2007). Evidence about indoor pollution from biomass cooking and heating in poorly ventilated dwellings as risk factor for COPD (Rabe et al. 2007). Indoor air pollution may increase risk of irritation phenomena, allergic sensitization, acute and chronic respiratory disorders and lung function impairment. Finally, several studies reported increased rates' prevalence of COPD diagnosis or symptoms in urban and more polluted areas and elevated risk due to pollutants for COPD or respiratory hospitalization and for disease parameters in advanced COPD panels (Viegi et al. 2007).

Infections

Viral and bacterial infections may contribute to the pathogenesis and progression of COPD, and bacterial colonization is associated with airway inflammation and exacerbations (GOLD 2010b; GOLD 2013). History of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood (Rabe et al. 2007; GOLD 2010b;

GOLD 2013). History of tuberculosis is associated with airflow obstruction in adults older than 40 years (GOLD 2010b; GOLD 2013). In addition, tuberculosis is both a differential diagnosis to COPD and a potential comorbidity (GOLD 2013).

Socio-economic status

Poverty is clearly a risk factor for developing COPD, but the its components effect are unclear. Several studies observed an inversely risk of COPD development related to socioeconomic status. It is not clear, however, whether this pattern reflects exposures to cigarette smoke, indoor and outdoor air pollutants, crowding, poor nutrition, or other factors that are related to low socioeconomic status (Rabe et al. 2007; GOLD 2010b; GOLD 2013).

Nutrition

The role of nutrition as an independent risk factor for the development of COPD is unclear. Malnutrition and weight loss can reduce respiratory muscle strength and endurance, apparently by reducing both respiratory muscle and mass and the strength of the remaining muscle fibers (GOLD 2010b).

Epidemiology of COPD

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing. COPD prevalence, morbidity, and mortality vary across countries and across different groups within countries (GOLD 2013). In recent decades, COPD has become a leading global disease with a prevalence of over 10% worldwide (Van der Vlist & Janssen 2010) and its burden is projected to increase due to continued exposure to COPD risk factors (Van der Vlist & Janssen 2010; GOLD 2013). Also, changing in age structure of the world's population could affect the prevalence ratio (Rabe et al. 2007; GOLD 2013).

Prevalence

Existing COPD prevalence data show remarkable variation due to differences in survey method, diagnostic criteria and analytic approaches (GOLD 2013). Prevalence and morbidity data greatly

underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced (R. A. Pauwels et al. 2001; B.R. Celli, MacNee, et al. 2004). The lowest estimates of prevalence are those based on self-reporting of a doctor diagnosis of COPD or equivalent condition (Rabe et al. 2007; GOLD 2013). Moreover, previous imprecise and variable definitions of COPD made difficult to quantify prevalence, morbidity, and mortality (Rabe et al. 2007). Despite these complexities, several systematic reviews and meta-analysis studies highlighted that COPD prevalence is appreciably higher in smokers and ex-smokers compared to non smokers, in those older than 40 years compared with those younger than 40 years, and in men compared with women (Rabe et al. 2007; GOLD 2013). In Europe, prevalence of clinically relevant COPD varies between countries, i.e. 4-10% of the adult population, although there is a paucity of prevalence data from Central and Western countries (Figure 1.j). In the USA, more than 12 million people suffered from shortness of breath and disabling effects (Dressendorfer et al. 2002; GOLD 2013). The PLATINO investigation (2005) observed increased prevalence of COPD with ageing, from a lower value of 7.8% in Mexico city to an higher of 19.7% in Montevideo and differences in gender, i.e. appreciably higher in men than in women (Figure 1.k) (Menezes et al. 2005; GOLD 2013).

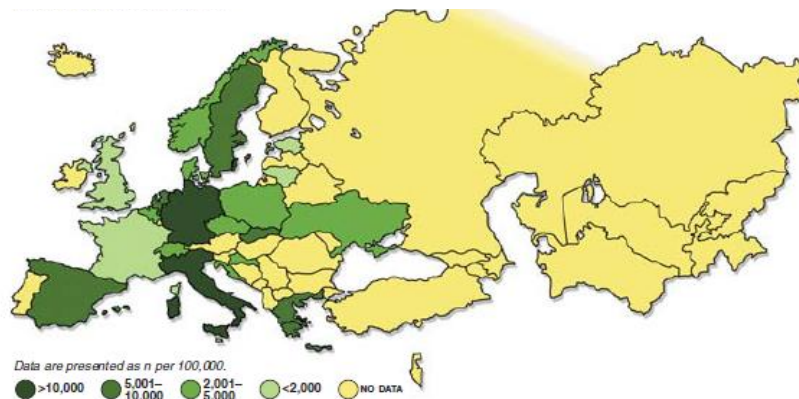


Figure 1.j – Prevalence of COPD in Europe;

(from www.oecd.org)

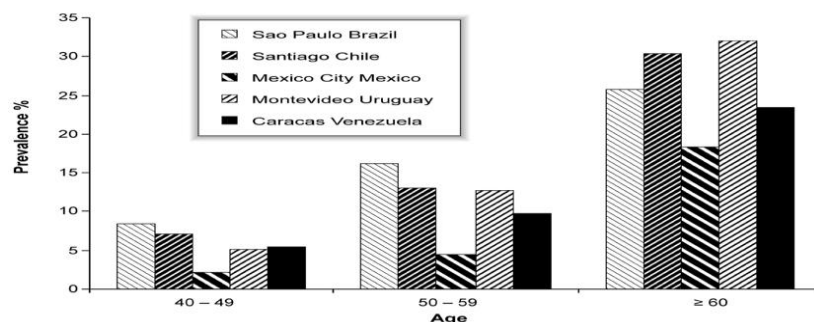


Figure 1.k – Prevalence of COPD by age in five Latin-American cities;

(adapted from Menezes et al. 2005)

Morbidity

Morbidity measures traditionally include physician visits, emergency department visits and hospitalization, but COPD databases are less readily available. The limited data available indicate morbidity related to COPD increase with age and greater, i.e. male > female (Rabe et al. 2007; GOLD 2013). In early stages COPD is usually not recognized, diagnosed, or treated, therefore may not be included as a diagnosis in a patient's medical record (Rabe et al. 2007). Moreover, in patients with more advantaged disease, COPD morbidity may be misattributed to others clinical conditions (GOLD 2013).

Mortality

Data about COPD mortality must be interpreted cautiously caused by an inconsistent use of terminology. Indeed, the 10th revision of the ICD, deaths from COPD or chronic airways obstruction are included in the broad category of "COPD and other conditions". Although COPD is often the primary cause of death, usually it is consider as a contributor. Between 1979 and 1993, mortality trend analysis in USA estimated 8% related to obstructive lung disease, among 31 million death certificates (GOLD 2013). At present, COPD is considered the fifth leading cause of death in the world and the mortality rate is expected to increase more than 30% during the next year (W.D. Reid et al. 2012). In EU, the latest data estimate COPD as the third most common cause of death (Figure 1.I) (A. D. Lopez, Mathers, et al. 2006; Niederlaender 2006).

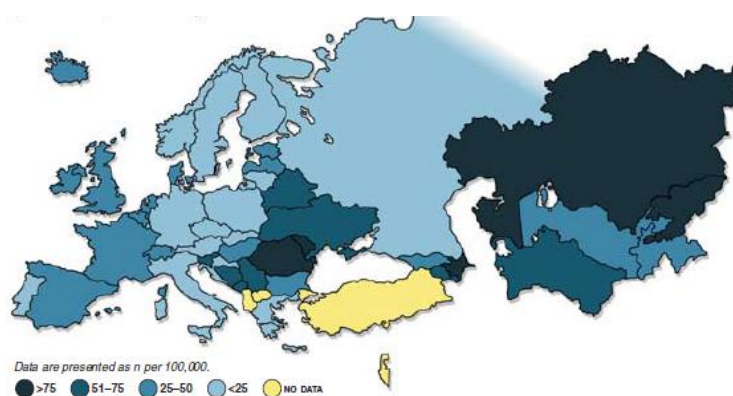


Figure 1.I – Prevalence of COPD in Europe;

(from www.oecd.org)

Economic and Social Burden of COPD

Epidemiologic data confirmed COPD as a significant public health problem which needs to be taken into account health personnel and decision-makers (B.R. Celli, MacNee, et al. 2004) because it is associated with significant economic and social burden (Rabe et al. 2007; GOLD 2013). In 2001, total direct costs in the European Union of respiratory disease were estimated to be about 6% of the total health care budget, with COPD accounting for 56%, i.e. €38.6 billion: €4.7 billion for ambulatory care, €2.7 billion for drugs, €2.9 billion for inpatient care and €28.4 billion for lost work days (Rabe et al. 2007; Viegi et al. 2007; GOLD 2013). In 2002, the USA direct costs of COPD were \$18 billion and the indirect costs totaled \$14.1 billion (Rabe et al. 2007). The latest data estimated a direct cost of COPD about \$29.5 billion and the indirect cost about \$20.4 billion. COPD exacerbations account for the greatest proportion of the total COPD burden on the health care system (GOLD 2013). However, costs per patients will vary across countries caused by differences in health care system characteristics (Rabe et al. 2007). Any estimate of direct medical expenditure for home care under-represents the true cost of home care to society, because it ignores the economic value of the care provided to those with COPD by family members. Therefore, it was designed an estimation methods, i.e. DALY, to assess disability-adjusted life year, i.e. sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disabilities. If in 1990, COPD was estimated to be the twelfth leading cause of DALYs lost worldwide, in 2030 it will be projected to become the seventh (GOLD 2013).

ENHANCING QUALITY OF LIFE IN COPD

Definition of Quality and Health-Related Quality of Life

The term QoL is difficult to define either precisely or economically. Perhaps, many people, particularly politicians, have found it to be so useful to describe the gap between that which is desired and that which is achievable. So, in the context of medicine, the term health-related QoL is used to signify the gap between desires and achievements that is specifically due to disease. The major difficulty with this topic is the requirement for standardization. Therefore, the identification of the health status or “Health Related Quality of Life measurement”, i.e. HRQL, has become a central feature of studies in COPD. Health status measurement is a means of quantifying, in a standardized and objective manner, the impact of disease on patients’ daily life, health, and wellbeing (P. W. Jones 2001) (Table 2.1).

Table 2.1 – Definition of QoL and HRQL

QOL	HRQL
Quantification of the impact of disease on daily life and well-being in a formal and standardized manner (P. W. Jones 1995).	Functional effect of an illness and its consequence therapy upon a patients, as perceived by the patients (P. W. Jones 1995; P. W. Jones 2001).

Relevance of measuring Quality of Life in COPD

COPD is a heterogeneous, multi-component disease associated with significant clinical burden. Though the presence of airflow limitation is well recognized as the pathophysiological basis, COPD as a complex disorder requires a multifaceted approach with regard to clinical assessment and response to therapy (Glaab et al. 2010). Despite the presence of the airflow limitation, in the early stages of COPD, patients appear to be symptomless and may not present to a physician until the condition is quite advanced, often only after an acute exacerbation (GOLD 2013). All that may be noticed is increasing breathlessness during leisure activities and recreational pursuits. Also, delay in recognition of the true impact of COPD may occur because the disease develops at a time of life when people generally begin to modify their leisure and recreational activity to less strenuous pursuits (P. W. Jones 1995). Instead, in advanced stages, patients show cough, excessive mucus production and feel dyspnea, not only during exercise but also at rest (GOLD 2013). The extra-effort breathlessness may cause reduction, either consciously or unconsciously,

of DPA level. This will result in a loss of cardiopulmonary fitness and some disuse atrophy of leg muscles (S. C. Lareau et al. 1996; van der Vlist & Janssen 2010). It's well known that, once FEV₁ falls below threshold of 50% predicted, essential ADL become disturbed and patients are clearly disabled (P. W. Jones 1995). Therefore, it has been suggested the model of “downward spiral of symptom-induced inactivity” in which patients with COPD may enter with the disease progression. Physical inactivity and the sedentary lifestyle lead to a physical deconditioning, resulting in a sub-consequent reduction of QoL, an increase of disability and enhanced risk of death (Figure 2.a) (B.R. Celli, MacNee, et al. 2004; M.A. Spruit et al. 2004; Pitta et al. 2005; Pitta et al. 2006; Vorrink et al. 2011). Current methods for assessing COPD progression and risk of death mainly rely on lung function tests (B.R. Celli, C. G. Cote, et al. 2004; Glaab et al. 2010), but COPD patients show systemic manifestations no-related only by FEV₁, which affected their QoL (P. W. Jones 1995; P. W. Jones 2001; Domingo-Salvany et al. 2002; B.R. Celli, C. G. Cote, et al. 2004; Duiverman et al. 2008; Glaab et al. 2010; Divo et al. 2012).

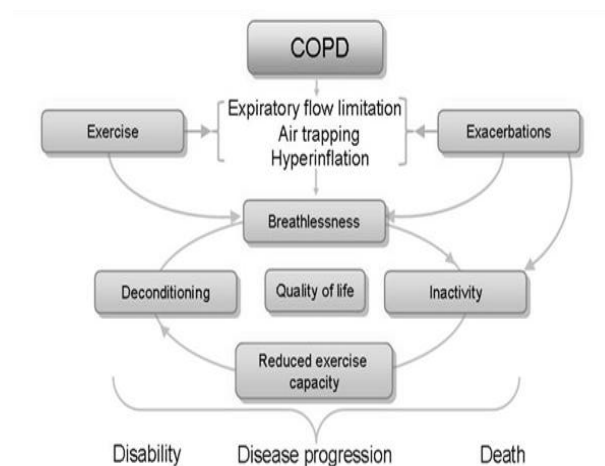


Figure 2.a - Downward spiral of COPD symptom;

(from B.R. Celli, C.G. Cote et al. 2004)

Determinants of Health-related Quality of Life in COPD

COPD has three types of effects: primary in lungs, which may be structural or mechanical, secondary in other organs, defined as systemic manifestations, and tertiary in the interaction between patients and environment. From the patients perspective, health is related to better functioning, symptom relief and longer life. Effects on pulmonary function or secondary effects on organs are important because they may reduce QoL or shorten life expectancy. Therefore,

improving in QoL is what patients want to achieve with their medical treatment. A treatment that alters a physiological parameter, such as FEV₁, but does nothing for quality of life, may not be successful (P. W. Jones & R. M. Kaplan 2003; Domingo-Salvany et al. 2002).

Systemic manifestations in COPD

Although COPD affects the lungs, the disease is associated with several systemic manifestations, which could effectively result in impaired functional capacity, worsening dyspnea, reduced HRQL and increased mortality (B.R. Celli, MacNee, et al. 2004; Barnes & B.R. Celli 2009). Indeed, at present, COPD is acknowledged as a multifactorial systemic disease in which several extrapulmonary manifestations and comorbidity factors complicate their evolution, altering prognosis and patients QoL (Kim et al. 2008; Huertas & Palange 2011). Concomitant cardiovascular compromise, malnutrition, body weight loss, dysfunction of skeletal muscles, osteoporosis, anaemia, increased gastro-esophageal reflux and clinical depression and anxiety were observed (Table 2.2).

Table 2.2 – Systemic effects of Chronic Obstructive Pulmonary Disease

Systemic inflammation
Oxidative stress
Activated inflammatory cells (neutrophils/lymphocytes)
Increased plasma levels of cytokines and acute phase proteins
Nutritional abnormalities and weight loss
Increased resting energy expenditure
Abnormal body composition
Abnormal amino acid metabolism
Skeletal muscle dysfunction
Loss of muscle mass
Abnormal structure/function
Exercise limitation
Other potential systemic effects
Cardiovascular effects
Nervous system effects
Osteoskeletal effects

(from Agusti et al. 2003)

Importantly, presence of airflow limitation greatly increase COPD patients's risk to develop lung cancer over the time. Moreover, often, patients affected by COPD are older and frequently present important comorbidities, that also required medical attention (Barnes & B.R. Celli 2009). Although these systemic manifestations have been described for years in COPD patients, it is still

unclear whether they represent consequences of the pulmonary disorder, or whether COPD should be considered as a systemic disease (Barnes & B.R. Celli 2009; Huertas & Palange 2011). However, considering that the presence of comorbidities significantly increase the patients risk of hospitalization, mortality and, consequently, the healthcare direct and indirect costs of COPD (R. A. Pauwels et al. 2001; Niederlaender 2006), there is an increasing realization that these systemic effects are clinically relevant and may contribute to better understand and manage the disease.

Systemic Inflammation in COPD

Systemic inflammation has been widely studied and considered an important key between the pulmonary disease and the related systemic manifestations (Huertas & Palange 2011). It is currently accepted that an excessive/inadequate inflammatory response of the lungs to a variety of noxious inhaled gases or particles, mostly cigarette smoke, is a key pathogenic mechanism in COPD (GOLD 2013; A. G. N. Agusti et al. 2003). Various studies have reported changes in various inflammatory cells and mediators and have shown that the lung inflammatory response is characterized by increased numbers of neutrophils, macrophages and T-lymphocytes with a CD8z predominance, augmented concentrations of pro-inflammatory cytokines, such as leukotriene B4, interleukin IL-8 and TNF- α , among others and evidence of oxidative stress caused by the inhalation of oxidants, such as tobacco smoke, and/or the activated inflammatory cells (A. G. N. Agusti et al. 2003; Huertas & Palange 2011). In Gan and colleagues' meta-analysis (2004) it highlighted that systemic inflammation is present during COPD exacerbations and stable phases of the disease (Gan et al. 2004). Furthermore, systemic inflammation has been implicated in the pathogenesis of the majority of COPD systemic effects, including weight loss, skeletal muscle dysfunction, cardiovascular diseases, and osteoporosis, although it is still controversial whether this so-called low-grade systemic inflammation represents the consequence of pulmonary inflammation into the systemic vascular bed or whether it is a systemic inflammation (A. G. N. Agusti et al. 2003; Huertas & Palange 2011). Although inflammation is certainly one of the major features of COPD, we still need to understand whether the local inflammation is sufficient to induce systemic effects, or whether a second pathogenetic event is required. Therefore, further studies are aimed to elucidate the origin of the systemic inflammation in COPD (Huertas & Palange 2011).

Abnormalities in Body Composition in COPD

Various studies described presence of nutritional and body composition abnormalities in patients with COPD, including alterations in caloric intake, basal metabolic rate, intermediate metabolism and body composition (Bolton et al. 2004; A. G. N. Agusti et al. 2003; Steuten et al. 2006). The most obvious clinical expression of these nutritional abnormalities is unexplained weight loss, which is particularly prevalent in patients with severe COPD and chronic respiratory failure. It has been estimated that weight loss occurs in ~50% of severe to very severe COPD patients, but it may be seen also in ~10–15% of patients with mild-to-moderate disease (A. G. N. Agusti et al. 2003; Bolton et al. 2004; Steuten et al. 2006; Lainscak et al. 2011). Weight loss and a low BMI are considered independent poor prognostic indicators for survival (A. G. N. Agusti et al. 2003; Steuten et al. 2006; GOLD 2013). Loss of skeletal muscle mass, i.e. FFM, is the main cause of weight loss in COPD and it is more important as a poor prognostic factor for survival, whereas loss of fat mass contributes to a lesser extent. Importantly, alterations in body composition may occur in COPD also in the absence of clinically significant weight loss. Indeed, even with a normal BMI, loss of FFM is associated with increased morbidity, poor QoL and reduced exercise tolerance (A. G. N. Agusti et al. 2003; Bolton et al. 2004). Patients with COPD may suffer from cachexia rather than malnourishment, i.e. the caloric intake of patients with COPD is normal or even greater than normal, not lower, as in malnourishment. Indeed, COPD patients metabolic rate is usually increased, whereas it is decreased in malnourished patients, and their response to nutritional support is often poor. The causes of these nutritional abnormalities are unclear and decreased caloric intake does not appear to be very prominent in these patients, except during episodes of exacerbation of their disease. In contrast, most patients with COPD exhibit an increased basal metabolic rate, which is not met by a parallel increase in caloric intake. Also causes of increased basal metabolic rate are yet unclear. Traditionally, it has been explained on the basis of an increased oxygen consumption, i.e. $\dot{V}O_2$ of the respiratory muscles due to the increased work of breathing. Recently, it has been shown that COPD patients skeletal $\dot{V}O_2$ non-respiratory muscle is higher at any given load than in age-matched HC, suggesting presence of bioenergetic abnormalities in non-respiratory muscles as contributor of increased metabolic rate in COPD. Also, several mechanisms such as drugs, systemic inflammation, tissue hypoxia and congestive heart failure, could conceivably contribute to the increased metabolic rate in COPD (A. G. N. Agusti et al. 2003). DXA or bioelectrical impedance measurements were able to assess differences in body composition (A. G. N. Agusti et al. 2003). Interestingly, by these measures, it was observed that some COPD patients show the so-called “Obesity Paradox” phenomenon defined as an inverse association of good health, survival and obesity. Overweight COPD

patients seem to have better survival rates than normal weight, a lower FEV₁ annual decline than normal BMI patients. However, this is an unknown mechanism which need further investigation (Table 2.3) (Franssen et al. 2008; Blum et al. 2011).

Table 2.3 – Prevalence of severe dyspnea, underweight, obesity and muscle wasting by COPD stages				
% (no.) of patients	GOLD 1	GOLD 2	GOLD 3	GOLD 4
	overall	overall	overall	overall
MRC≥3	9.7 (9)	28.1 (43)	53.7 (29)	82.4 (14)
BMI<21	6.5 (6)	10.5 (16)	16.7 (9)	47.1 (8)
BMI>30	16.1 (15)	23.5 (36)	9.3 (5)	5.9 (1)
FFM ≤15♀ or ≤16♂	11.8 (11)	16.3 (25)	11.1 (6)	52.9 (9)

(adapted from Steuten et al. 2006)

Skeletal Muscle Dysfunction in COPD

The extrapulmonary effects of COPD, especially the higher values of systemic inflammation, are associated with a reduced share of PA (Watz et al. 2008). Initially, given its role as the primary inspiratory muscle and considering the increased work of breathing imposed on it, the diaphragm has been the topic of most publications on respiratory muscles in COPD; Observations have highlighted that the structure and the function of the diaphragm are affected during the course of COPD (Levine et al. 1997; Kim et al. 2008; Caron et al. 2009). This topic is clinically relevant because inspiratory muscle weakness is associated with dyspnea, hypercapnic respiratory failure and even premature mortality in COPD (Caron et al. 2009). The study of limb muscle alterations linked to COPD has also been a dynamic area of research: although the association between cachexia and respiratory disease was formally reported more than 40 years ago, only during the last decade it has received more attention (Caron et al. 2009). Causes of peripheral muscle dysfunction have yet to be fully elucidated, but limb muscle dysfunction is a major concern in COPD. It is associated with decreased survival (Swallow et al. 2007; van der Vlist & Janssen 2010), poor functional status, as in VO₂max, 6MWD, inspiratory and expiratory muscle force, hand grip force (M.A. Spruit et al. 2002), a low QoL (Couillard & Prefaut 2005; Caron et al. 2009; Barreiro & Sieck 2013), and is present across all disease stages (Seymour et al. 2010), suggesting that limb muscle dysfunction is one of the main extrapulmonary manifestation affecting the exercise capacity (Table 2.4) (Mador & Bozkanat 2001).

Table 2.4 – Alterations in diaphragm and quadriceps muscles in COPD

	Diaphragm			Quadriceps		
	Presence ?	Description	Severity of airflow limitation	Presence ?	Description	Severity of airflow limitation
↓Fiber CSA	Yes	↓30% MHC content ↓40/60% CSA affected all fiber types	Mild to severe	Yes	↓25/35% CSA affected all fiber types	Mild to severe
Contractility defect	Unclear	↓Force generation of isolated skinned fibers	Mild to moderate	No	No difference in force generation of isolated fibers	Moderate to severe
Fiber shift	Yes	Type II → Type I	Mild to severe	Yes	Type I → Type II	Severe
Capillarization alterations	Yes	↑Capillary contacts with every fiber type	Mild to severe	Yes	↓Capillary contacts with type I and IIa fibers	Moderate to severe
Mitochondrial alterations	Yes	↑Respiratory chain capacity ↑Oxidative stress production	Moderate to severe	Yes	↓Mitochondrial density ↑Oxidative stress production	Mild to severe
Shift in energetic metabolism	Yes	↑Oxidative/glycolitic enzymatic ratio	Mild to severe	Yes	↓Oxidative enzymes (HADH, CS) ↓Oxidative/glycolitic enzymatic ratio	Moderate to severe

CSA, cross-sectional area; MHC, myosin heavy chain; HADH, 3-hydroxyacyl-CoA dehydrogenase; CS, citrate synthase

(from Caron et al. 2009)

Other potential systemic effects of COPD

Others organ systems might also be affected by the systemic influences of COPD. Indeed, COPD often coexists with other diseases, called comorbidities, that may have a significant impact on prognosis. Some of these arise independently of COPD whereas others may be causally related. Comorbid diseases could be increased by the sequelae of COPD and are common at any severity of COPD, so the differential diagnosis can be often difficult (Barnes & B.R. Celli 2009)

Cardiovascular disease

Cardiovascular disease is the major comorbidity in COPD and probably the most frequent disease coexisting with COPD (GOLD 2013). Usually there are features of Coronary artery disease, Ischemic heart disease, Heart failure, the Atrial Fibrillation and Hypertension (A. G. N. Agusti et al. 2003; GOLD 2013).

Nervous system effects

“ Various aspects of the nervous system may be abnormal in patients with COPD. For instance, the use of nuclear magnetic resonance spectroscopy has shown recently that the bioenergetic metabolism of the brain is altered in these patients. Whether this represents a physiological adaptation to chronic hypoxia, as occurs at altitude, or whether it may be considered another systemic effect of COPD mediated by other unknown mechanisms is unclear. Another potential systemic effect of COPD upon the central nervous system relates to the high prevalence of depression reported in these patients. It is possible that this may simply represent a physiological response to chronic debilitating disease. However, it is equally plausible that it may bear some relationship to the systemic inflammation that occurs in COPD, since TNF- α and other cytokines and molecules, such as nitric oxide, have been implicated in the pathogenesis of depression in several experimental models.” (A. G. N. Agusti et al. 2003 pp.354).

Osteoskeletal effects

Prevalence of osteoporosis is increased in patients with COPD (Figure 2.b) (Bolton et al. 2004; A. G. N. Agusti et al. 2003), is often under-diagnosed and is associated with poor health status and prognosis (GOLD 2013). Osteoporosis can have multiple causes, singly or in combination, including malnutrition, sedentary behavior, smoking, steroid treatment and systemic inflammation. Since most of them are already considered potential pathogenic factors of skeletal muscle dysfunction in COPD, they could theoretically also contribute to osteoporosis, and, in this context, excessive osteoporosis in relation to age could also be considered a systemic effect of COPD. It is interesting to note that emphysema and osteoporosis are both characterized by net loss of lung or bone tissue mass and, pictorially, an osteoporotic bone looks quite similar to an emphysematous lung, may contribute to palliating its symptoms and reducing the associated healthcare costs (A. G. N. Agusti et al. 2003; GOLD 2013).

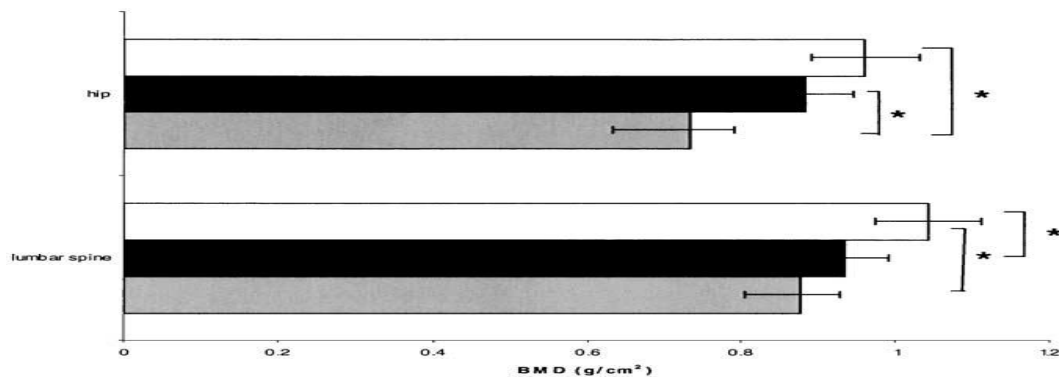


Figure 2.b – Bone mineral density at the lumbar spine and hip regions in COPD patients and healthy patients;

Data shown as means with 95% confidence interval;

(□) healthy; (■) COPD with FEV1 greater than 50% predicted; (▒) COPD with FEV1 less than 50% predicted

(from Bolton et al. 2004)

Others comorbid disease

Anxiety and Depression are common in COPD and are both associated with a poor prognosis. Also are both often associated with younger age, female gender, smoking, lower risk, cough, lower QoL and history of cardiovascular disease. Another comorbid condition is lung cancer that is frequently seen in patients with COPD and has been found the most frequent cause of death in patients with mild COPD. Moreover, studies have shown that the presence of metabolic syndrome and manifest diabetes are more frequent in COPD and the latter is likely to impact prognosis. Patients with diabetes and severe COPD are not advised to aim for a BMI less than 21 kg/m² (GOLD 2013).

Exacerbations

Exacerbation of COPD is an event in the natural course of the disease characterized by acute changes in symptoms, such as cough, dyspnea and sputum production, beyond what is considered normal variability in a patient. Patients with exacerbation often require modifications in COPD treatment regimens and hospitalization for effective management. Frequency of COPD exacerbation increases with disease severity and could affect patients ADL and QoL, increasing mortality rates. In patients with moderate to severe COPD, prospective data collection revealed that patients report only 50% of the exacerbations that they experience and have a median exacerbation rate of 3 per year with a range of 1–8. Although the cause of approximately one-third of severe COPD exacerbations is unknown, they are commonly associated with infections of the tracheobronchial tree and with air pollution. Patients who experience acute exacerbations

commonly present with increased breathlessness, wheezing, tightness in the chest, increased cough sputum production, change in color and tenacity of sputum, and fever. Also tachycardia, tachypnoea, malaise, insomnia, fatigue, depression and confusion were reported. Before the onset of an exacerbation, patients may have decreased exercise tolerance and fever (P. W. Jones 2001; B.R. Celli, MacNee, et al. 2004; Fromer & C. B. Cooper 2008; GOLD 2013).

Health Status Scale to assess Quality of Life in COPD

At the light of the multi-causal nature of COPD symptoms, it's justified the development of several health status scales that sum the effects of the different and multiple processes, in order to measure the health-related quality of life, evaluate and compare the overall effectiveness of the pulmonary rehabilitation program (Troosters et al. 2005). Indeed, the current methods for assessing clinical outcomes in COPD mainly rely on physiological tests combined with the use of questionnaires (Glaab et al. 2010).

Major outcome measures in COPD

Considered the different determinants of QoL in COPD patients, the major commonly used outcome measures regard the lung function, the health status, the exercise capacity and physical activity, the dyspnea symptoms, the number and severity of exacerbations, and the mortality (Glaab et al. 2010).

Pulmonary parameters

Lung function: FEV₁

Relevance

It is well established that patients with COPD lose lung function at a steeper rate than subjects without COPD. FEV₁ is the single most important marker to determine severity and treatment algorithms in COPD. The decline of FEV₁ over time has been traditionally used to indicate disease progression.

Measures

The diagnosis, staging and treatment of COPD in current guidelines is based on the fixed ratio of FEV₁/FVC and the percentage predicted FEV₁ value. The methodology for measuring forced expiratory maneuvers by spirometry has been standardized by ATS/ERS. Specific training to yield reproducible and reliable results is mandatory.

Strengths

FEV₁ and FVC measurements are highly reproducible if performed adequately. Reduction in lung function is a risk factor for all cause and cardiovascular mortality, and impaired health status.

Spirometry supports confirmatory detection of early stages of COPD when respiratory symptoms are often absent, thus creating the opportunity of early intervention.

Limitations

FEV₁ measurements are based on an artificial maneuver and do not always correlate with clinically relevant outcomes such as dyspnea, health status, exercise capacity, or exacerbations.

Patients with similar FEV₁ may represent different underlying phenotypes. Reference equations for lung function by European Community for Coal and Steel are disputed and limited in predicting lung function in the general population. Changes in lung volumes can occur without concomitant changes in FEV₁ and are more closely related than FEV₁ changes to exercise performance. No minimal important difference, i.e. MID, has been established yet. It was suggested that an appropriate range of values for the MID for FEV₁ might be 100-140 mL but the MID for FEV₁ remains poorly defined for COPD.

Open Questions and Outlook

FEV₁, while a crucial marker, is far from being the only measure to comprehensively characterize patients with COPD. Additional outcome measures are usually needed to assess the clinical benefit of therapeutic agents. The relationships between changes in airway structure and measures of lung function require further investigation.

Lung volumes

Relevance

Changes in absolute lung volumes can occur in COPD patients even in the absence of FEV₁ changes. Progressive hyperinflation due to airflow limitation and loss of lung elastic recoil not only increases the work required during inspiration but also profoundly decreases the ventilator reserve and increases the sense of effort and dyspnea. The assessment of absolute lung volumes has been standardized but is technically more demanding than simple spirometry. Specific training to yield reproducible and reliable results is essential.

Measures

Static lung hyperinflation and its increase during exercise, i.e. dynamic hyperinflation, are measured as elevations of total lung capacity, i.e. TLC, functional residual capacity, i.e. FRC, residual volume, i.e. RV, and as a decrease in inspiratory capacity, i.e. IC.

Strengths

Indices of dynamic hyperinflation correlate better than FEV₁ with activity limitation and exertional dyspnea and pharmacological and surgical lung volume reduction have been associated with improvements in exercise performance and dyspnea. A severely reduced IC/TLC ratio with a threshold value of 25% has been shown to predict mortality in COPD patients.

Limitations

Body plethysmography remains the gold standard for the measurement of lung volumes such as TLC, FRC and RV. Spirometrically derived assessments of lung hyperinflation are more difficult to interpret in the absence of simultaneous body plethysmographic volume measurements to rule out a concomitant restrictive ventilator disorder. The reproducibility of FRC, IC and RV in absolute values has yet to be demonstrated. Measurement of IC alone is not a reliable marker of lung hyperinflation and does not consistently reflect changes in FRC or TLC. Neither a standardized classification for the assessment of severity of hyperinflation nor a MID have been established yet. In practice, values of RV, TLC and FRC exceeding 120-130% of the predicted value are regarded to be clinically relevant, but these cut-offs are not validated. The natural course of dynamic hyperinflation in COPD is unknown and seems likely to be highly variable among COPD patients.

Open Questions and Outlook

In the absence of any consensus on the definition and/or severity of hyperinflation, it has been proposed that hyperinflation - preferentially expressed as % predicted should be specified in terms of the volume compartment referred to and the measuring method used. So far, there have been no studies aimed at exploring the longitudinal course of dynamic hyperinflation and its impact on the course of the disease in COPD patients.

Exercise Capacity and Physical Activity

Relevance

Reduced exercise capacity is considered to be a consequence of airflow obstruction, primarily because of dynamic hyperinflation occurring during exercise. Moreover, leg fatigue has been shown to be as important as breathlessness in limiting peak exercise performance. Muscle weakness is a feature of COPD, particularly of the legs but also of the arms. This may not be due entirely to disuse atrophy since nutritional depletion occurs and there is evidence of circulating inflammatory cytokines in COPD. A reduced physical activity of patients is a result of COPD, but at the same time promotes worsening and progression of the disease.

Measures

There are different approaches to determine the exercise capacity or activity levels of COPD patients. Higher exercise tolerance measured via laboratory or field tests can be translated to higher levels of activity. In addition, physical activity during daily life can be recorded directly by measuring energy expenditure or by mechanical assessment of movement.

Exercise Capacity

6-Minute Walk Test or 6MWT

Measurement of the distance walked during a 6-minute period on a level surface. The principal outcome of this self-paced test is the distance covered. The MID is estimated to be 54-80 meters.

Strengths

6MWT is relatively simple to perform and well tolerated. It reflects everyday life-like activity. It is validated and standardized. 6MWT results correlate with lung function, health status, and maximal VO₂, and have shown to be predictive for mortality.

Limitations

There are many sources of variability, e.g. patient's motivation, weight, height, age, sex, co-morbidities, and day to- day variability.

6MWT was significantly reduced only in COPD patients with GOLD stages III and IV.

Assessment of the 6MWT is associated with spatial requirements and is personnel- and time-consuming.

Standards of 6MWT are not always realizable. This might influence the results, e.g. shorter corridors reduce the distance covered because of time-consuming change in direction.

Learning effect: Walking distance is up to 17% higher for a second test performed a day later.

Shuttle Walk Test or SWT

There are two forms of assessment. In the Incremental Shuttle Walk Test, walking speed is set by the frequency of an acoustic signal. The frequency increases progressively until patients can no longer pick up the pace. The principal outcome is the distance covered. The MID is estimated to be 47.5 meters. The Endurance Shuttle Walk Test has been developed to determine sub-maximal exercise capacity with the acoustic signal frequency being constant throughout the walk. The principal outcome is the duration of exercise. No MID has yet been described.

Strengths

SWT is relatively simple to perform and well-tolerated. Learning effects are minimal. Walking pace is externally controlled.

Limitations

Instructions for SWT are time consuming. The test is less extensively validated than the 6MWT. Solid evidence for validity still has to be provided. SWT does not reflect common daily activities that require endurance and pacing.

Ergometry

To evaluate the exercise response, bicycle-ergometer or treadmill are commonly used in two different test modes. In incremental-workload tests, work-rate is increased progressively as a mild continuous ramp under computer control with the principal outcome being the distance covered. Alternatively, constant-workload tests have been performed at sub-maximal levels of exercise intensity which is typically set between 75% and 85% of the maximum workload during incremental tests. The principal outcome is the duration of workload. Reasons for break-off, e.g. leg discomfort vs. breathlessness, provide additional insights.

Strengths

For ergometry, standardized protocols are available. Treadmill walking reflects an activity of daily living. Cycle ergometer is less prone to introduce movement or noise artifacts into measurements than treadmill, and electrocardiogram and blood pressure are generally easier to measure. Additional physiological and clinical variables, such as peak O₂ uptake, CO₂ output, minute ventilation, heart rate, dyspnea, and leg discomfort can be determined in parallel.

Limitations

The workload not only depends on speed and inclination of the treadmill but also on the weight of the subject and pacing strategy. Body weight has much less effect on bicycle ergometry performance. Cycling is less closely related to the patient's activities of daily living. Resources: Ergometers are relatively expensive, treadmills require much space. No MID has been established yet.

Physical Activity

Sensors for physical activity

Relevance

The methods that are available to quantify physical activity in daily life include direct observation, assessment of energy expenditure, and the use of physical activity questionnaires or motion sensors. In particular, motion sensors are practical tools for clinical trials or practice. Accelerometers are electronic devices that record energy expenditure or mechanically assess

movement. The devices are usually worn on patients' arm or waist. Accelerometers read out stored data as movement intensity and as quantity and can also provide data on body posture.

Strength

Accelerometers generate objective data by determination of quantity and intensity of body movements. Significant limitations of physical activity can already be detected in patients with moderate COPD (GOLD stage II).

Limitation

Solid evidence for reliability, validity and responsiveness for different types of accelerometers still has to be provided. Some activity sensors are poorly accepted by patients. Variability in sensitivity among accelerometers of a given model has been detected. Accelerometers may be sensitive to artefacts like car vibrations. Activity sensors may actually fail to accurately capture the inactive life style of patients with COPD. Physical activity patterns vary from day to day and between week-days and weekend due to the patient's health, or external factors. In long-term studies, another source of variability may be seasonal climate changes, hours of daylight and weather. Observation bias: a greater level of activity may be induced during the measurement period that results in overestimation of the activity. On the other hand, underreporting bias may evolve from poor compliance. No MID has been established yet.

Open questions and outlook

Exercise capacity is an important clinical outcome in interventional trials of COPD, but it is still debatable what is the most valid, reliable, and responsive measurement of changes within subjects. Physical activity may become a key outcome measure not only in clinical trials of COPD, but also in rehabilitation programs and for patients' self-management. Even though the technical assessment of physical activity is improving rapidly, not all new techniques have been developed to the point where their clinical utility has been validated. Little is known about the agreement of exercise capacity as measured using different methods. Therefore, indirect comparisons of treatment effects on exercise capacity are obscured by different methods of assessment applied in various trials.

Dyspnea

Relevance

For patients with COPD, dyspnea is the most frequent complaint for which they seek medical attention and is the characteristic symptom of COPD. However, dyspnea is a subjective measure, i.e. there are large inter-individual differences in the perception of breathlessness for a given level

of ventilation, that poorly correlates with objective assessments of lung function, exercise capacity, and other outcomes.

Measures

Different approaches have been used to measure dyspnea in clinical trials, amongst which the BDI/TDI, Borg- Scale, and MRC are applied most often.

Baseline Dyspnea Index/Transition Dyspnea Index (BDI/ TDI)

The BDI and TDI represent one of the most commonly applied instruments for dyspnea rating in clinical trials, describing symptoms at a single point in time, i.e. BDI, and measuring changes in breathlessness from this baseline state over time, i.e. TDI.

BDI and TDI ratings are obtained in the course of an interview conducted by an experienced observer, who asks open-ended questions about the patient's experience of breathlessness during everyday activities, which are then translated into numerical values.

Strengths

BDI and TDI ratings provide multi-dimensional measurements of breathlessness, i.e. functional impairment, magnitude of task, and magnitude of effort, related to activities of daily living. In BDI/TDI, a MID with a difference of 1 unit for the mean total score being considered clinically meaningful is available though it is mainly based on retrospective data analysis.

Limitations

BDI/TDI Interviewer bias: Neither interviewer questions nor the translation of patients' answers to ratings are standardized, enforcing thorough interviewer training. BDI/TDI Recall bias: The patient has to recall BDI in order to answer questions regarding the TDI. BDI/TDI Assessment bias: Interviewer blinding to patients' clinical status is necessary to prevent assessment bias.

Medical Research Council (MRC) Scale

The MRC dyspnea scale was developed as a simple and standardized method of categorizing disability in COPD. The patient selects a grade on the self-applied 5-point instrument that describes everyday situations or activity levels provoking breathlessness and impairment. A MID has not been established.

Strengths

The MRC scale method has been widely used in the past.

Limitations

In MRC scale, a possible underestimation bias due to avoidance of exertion has to be taken into account. The MRC is relatively insensitive to change, i.e. due to therapeutic intervention. In MRC scale, there are relatively scarce clinical data on validation, responsiveness, and sensitivity.

Borg-Scale (CR-10)

The CR-10 or Borg-Scale has been developed primarily as an objective tool to measure exertional dyspnea in COPD patients. Although the 10-point category ratio scale is easy to use, concise and detailed instructions for patients are indispensable for appropriate application. Based on retrospective analysis, a MID for the Borg- Scale in the range of 1 unit has been discussed.

Open Questions and Outlook

More research is needed to optimize and validate questionnaire items including direct patient involvement in instrument generation to improve their utility in clinical trials. Little is known about the impact of concomitant disorders on outcomes, i.e. if disorders such as anxiety or depression influence perceived dyspnea and, if so, to which extent those instruments applied today reflect that influence. Furthermore, studies are needed to show which of the existing methodologies, should be ideal in the context of COPD.

Exacerbations

Relevance

Exacerbations of COPD indicate clinical instability and progression of the disease and are associated with increased morbidity, deterioration of comorbidities, reduced health status, physical and physiologic deterioration and an increased risk of mortality. The prevention or reduction of exacerbations thus constitutes a major treatment goal.

Measures

Verification by patient interview, healthcare databases or prospectively from diary cards. Endpoints: frequency of exacerbations, time to first exacerbation, severity and duration of exacerbations.

Strength

The event-based approach considers the need for systemic corticosteroids and/or antibiotics or hospitalization due to an exacerbation. This definition may be more robust and is relatively easy to record. The symptom-based definition of exacerbations considers individual patient's perception of clinical status.

Limitations

There is no standardized definition of an exacerbation, making comparative evaluations of clinical study results difficult. The symptom- and event-based approach involves subjective and recall bias, particularly because patients often have a poor understanding of exacerbation symptoms, resulting in substantial underreporting of exacerbations. The definition by use of health care resources is health system specific and affected by many other factors (social support, comorbidities, baseline health status, clinical expert behavior). Differential diagnoses to exacerbations such as pneumonia, heart failure, ischemic heart disease, pulmonary embolism have to be taken into account. Seasonal variations in exacerbation frequency usually require long-term studies of at least one year duration. No MID has been established yet.

Open questions and outlook

There is a clear need to standardize the evaluation of the onset, frequency, severity and duration of COPD exacerbations as well as to assess therapeutic effects on exacerbations in COPD. Given the potential clinical relevance of even single exacerbations it appears quite difficult to determine exactly what cut-off levels should be used in terms of MIDs. In addition, more work is needed to develop simple feasible criteria for defining exacerbations in clinical practice and to analyze the multiple factors that contribute to decisions to assess the severity stage of exacerbations. In that context, the EXACT-PRO initiative began to develop and evaluate a novel patient-reported outcome tool to measure the rate, duration and severity of exacerbations of COPD.

Mortality

Relevance

Long-term observations of large patient populations have shown an increased risk for all-cause mortality in COPD patients that rises proportionally to severity classes. Mortality can be recorded as all-cause mortality and cause-specific mortality.

Strengths

All-cause mortality is the most robust and reliable outcome of clinical trials in COPD and is relatively easy to follow-up.

Limitations

Standardized methods to accurately define the cause of death (e.g. respiratory versus cardiovascular mortality) have not been established yet. Moreover, the careful analysis of the cause of death requires substantial effort. Retrospective mortality data may be confounded by inherent statistical bias, and even prospective studies are susceptible to bias due to missing

follow-up of withdrawals. Adequately powered mortality trials require high patient numbers and extended study duration. It is as yet unclear, whether COPD-specific mortality is increased in patients with milder forms of COPD (GOLD stages I and II). Mortality tends to be lower in participants of clinical trials than is found in routine clinical care.

Open Questions and Outlook

One important issue is the statistical approach to analyze the events of death. Intent-to-treat (ITT)-analyses, aiming for complete follow-up of deaths are recommended for unbiased comparison between treatment groups and should be used preferentially as shown in major trials. For a confident, robust assessment, mortality should be the primary outcome of a prospective trial. Clinical trials evaluating death as a primary or secondary endpoint should have a data safety monitoring board and an independent adjudicating committee (P. W. Jones 2001; Glaab et al. 2010).

Multidimensional scoring systems in COPD

BODE-Index

Relevance

So far the only multidimensional scoring system that has gained broader acceptance is the BODE index which has been developed as a prognostic marker for COPD patients in an attempt to integrate not only the respiratory but also the systemic expressions of COPD in a single grading system.

Measures

It comprises the four components nutritional state, i.e. BMI, airflow limitation, i.e. Obstruction; FEV₁, breathlessness, i.e. MRC Dyspnea scale, and Exercise capacity i.e. 6MWD, distance walked in 6 min. Replacing the 6MWD with a component for exacerbation frequency, i.e. BODEx index, resulted in fully preserved power to predict the mortality risk in a prospective observational study, while expanding the BODE index with exacerbation frequency as a fifth component, i.e. e-BODE index, did not further improve its predictive power. A truncated version of the BODE index has been presented in which the exercise component is omitted (BOD index). The validity of the BODE index as a prognostic marker to predict mortality in COPD patients has recently been challenged by a study demonstrating that the risk of all cause mortality over 3 years was considerably underestimated by the BODE index in a population of severe COPD patients, while on the contrary it was overestimated in another population with milder disease, indicating that important predictors may still be missing in this index. Nevertheless, the BODE index has been

used to assess therapeutic efficacy in interventional studies investigating effects of lung volume reduction surgery, pulmonary rehabilitation, and physical training, but so far not in pharmacological intervention trials.

Strengths

The BODE index integrates different facets of COPD and the risks associated with significant comorbidities. It provides better power than that of its individual components, i.e. FEV₁, to predict mortality and future exacerbations in patient populations with severe-to-very severe COPD. Its assessment is straightforward.

Limitations

The BODE index has not primarily been developed to assess effects of therapeutic interventions and a MID has not yet been defined. The BODE index has been optimized to predict one-year mortality. The factors most critically affecting short-term survival might differ from those determining survival over a longer term. Thus, its suitability for assessment of patients with mild-to-moderate COPD is as yet less validated. The FEV₁ categories in the airway obstruction component are not consistent with the current GOLD staging system. No published experience with BODE index as a clinical outcome parameter in pharmacological intervention studies is currently available.

Open questions and outlook

More widespread application of the BODE index as an outcome parameter in clinical trials is currently hampered by the lack of experience in pharmacological intervention studies. Furthermore, its validity as a prognostic marker in a population of patients affected by mild-to-moderate COPD and its power to predict survival over longer periods of time as yet have to be proven (Glaab et al. 2010).

Questionnaires for health status in COPD

Relevance

Health-status is considered one of the main patient-related outcomes in clinical trials. It is important to make a distinction between quality of life (QoL), which is unique to the individual, and health status measurement, which is a standardized quantification of the impact of disease.

Measures

Health-status as a concept of high complexity is assessed indirectly and requires the application of specially designed questionnaires (Glaab et al. 2010). Questionnaires used for assessment of QoL may be categorized as generic or disease-specific. Generic questionnaires were designed to

make standardized comparative assessments between populations of patients (P. W. Jones 2001; Seemungal et al. 2009). Instead, disease-specific questionnaires include the Chronic Respiratory Questionnaire, i.e. CRQ, the St. George's Respiratory Questionnaire, i.e. SGRQ, the Medical Outcomes Study short-form-36, i.e. SF-36, the Severe Respiratory Insufficiency Questionnaire, i.e. SRI, and the Mageri Respiratory Failure questionnaire, i.e. MRF-26 (P. W. Jones 1995; P. W. Jones 2001; Duiverman et al. 2008; Seemungal et al. 2009; Glaab et al. 2010).

The St. George's Respiratory Questionnaire

The SGRQ was originally developed to measure health status in patients with respiratory disease, i.e. COPD or asthma. It was designed so that it may be used in long-term studies and is fully standardized (P. W. Jones 1995; Glaab et al. 2010). A COPD-specific version is available. The SGRQ covers domains of symptoms, i.e. frequency and severity of respiratory symptoms, activity, i.e. effects on and adjustment of everyday activities, and psychosocial impact, i.e. overall impact on daily life and well-being, from which a total score with a possible maximum of 100 points is calculated. The MID was assessed by various methods. Changes of 2 to 8 points were considered clinically meaningful, with a value of 4 applied most often.

Strengths

The SGRQ has been widely used in clinical trials as a secondary endpoint to assess the effects of treatment and management interventions on health status in COPD. It may be considered a standard in clinical trials. It has standardized instructions. It appeared to be similar in different countries and languages.

Limitations

The instrument is time-consuming to implement and is therefore of limited applicability in day-to-day clinical practice. There is a trend bias due to non-poled questions: first possible answer is usually "yes" and indicates worse health-status. The processing of missing answers is unsatisfactory. A missing answer is considered as if the patient had answered "no", indicating better health-status. SGRQ scores were shown to be influenced by subjects' sex, age, education, and by comorbidities. Suitability of MID for individual patients as opposed to patient group comparisons has yet to be shown. Linearity of differences between SGRQ values has not been shown, especially not in different stages of severity. Thus, it is unknown, whether a reduction in SGRQ total score by 4 points, i.e. from 44 to 40, represents a subjective improvement in health status equivalent to a reduction from 64 to 60. There is little published empiric evidence supporting the MID of four points (P. W. Jones 1995; Seemungal et al. 2009; Glaab et al. 2010).

Chronic Respiratory Disease Questionnaire

The CRQ is widely used disease-specific questionnaire that has been shown to be reliable, valid and responsive in COPD patients (Duiverman et al. 2008). It was the first disease-specific measure developed for COPD and was designed especially to detect changes following therapy (P. W. Jones 1995). The CRQ measures physical-functional and emotional limitations due to chronic lung diseases including COPD. It refers to activity-related dyspnea with results covering dyspnoea, fatigue, emotion, and mastery. The questionnaire has primarily been applied in rehabilitation trials of COPD patients. The patient is asked to recall the five most important activities that caused breathlessness over the past two weeks. A total score as well as individual subscale scores can be calculated. A difference of 0.5 for the mean domain scores is considered clinically meaningful.

Strengths and limitations

A distinctive property of this instrument is the patient-specific selection of five activities, which cause dyspnea for the individual patient. This way the instrument adapts to the specific conditions of the patient and is sensitive to treatment. On the other hand, the instrument is less suitable for inter-individual comparisons, as it mirrors individual physical limitations. The questionnaire is not interchangeable with other disease-specific instruments and has not yet been shown to be responsive to long-term disease progression. (Duiverman et al. 2008; Seemungal et al. 2009; Glaab et al. 2010).

Medical Outcomes Study Short Form-36

The SF-36 is a generic health survey. The patient is asked to complete 36 items of the questionnaire. The instrument allows the patient to self-assess psychic, physical, and social aspects of his or her quality of life.

Strengths and limitations

SF-36 is the best-known questionnaire to measure health status. The instrument has been shown to be discriminative, responsive to long-term disease progression, easy to use, and has been validated in several languages. However, as a generic measure, it is considered less responsive than disease-specific instruments in COPD and is not consistently responsive to therapeutic effects. No MID has been established yet.

The Severe Respiratory Insufficiency Questionnaire

The SRI was developed especially for patients with respiratory failure (Carone et al. 1999; Windisch et al. 2003; Duiverman et al. 2008). Questionnaire contains items on problems that patients with chronic respiratory failure experience and emphasizes different aspects of HRQL.

Strength

The SRI total score, like the CRQ total score, was most strongly related to anxiety and depression. In addition, the SRI total score was also substantially related to daily activity level. SRI contains 49 items and takes 20 min to complete. However, as answer possibilities were clearly indicated, the questionnaire is easy for the patients to complete. For the SRI, as for the CRQ, anxiety also accounted for a large part of the total variance in the summary scale.

Limitations

The SRI total score not contain items about memory, attention or concentration during daily living (Duiverman et al. 2008).

The Mageri Respiratory Failure Questionnaire

MRF-26 was developed especially for patients with respiratory failure (Carone et al. 1999; Windisch et al. 2003; Duiverman et al. 2008). Questionnaires contain items on problems that patients with chronic respiratory failure experience and emphasize different aspects of HRQL.

Strength

The MRF-26 total score was more related to activities of daily living. The MRF-26 might be more attractive in the practical sense as it contains 26 items and took the patients ~10 min to complete. However, as answer possibilities were clearly indicated, both questionnaires were easy for the patients to complete. The MRF-26 adds the cognition domain, which contains four items on the effects of impaired memory, attention and concentration on daily living but not contain psychological domain.

Limitations

The MRF-26 total score was less correlated to psychological functioning such as anxiety or depression (Duiverman et al. 2008).

Open questions and outlook

Further development of user-friendly, inexpensive instruments to enable fast and easy health status assessment in clinical trials as well as in daily practice is clearly required. Ways to involve patients in questionnaire generation should be further explored. More information is needed on the time course of health-status alterations, i.e. induced by therapeutic intervention or secondary

to COPD exacerbations and on the utility and efficacy of health status instruments in less severe COPD (Glaab et al. 2010).

Strategies to improve Quality of Life in COPD

The multi-causal nature of symptoms and determinant of QoL in COPD patients justify the development of several different strategies for disease management. Indeed, after a diagnosis of COPD has been made, the goals of treatment should include different topics, such as relief of symptoms, amelioration of disease progression, improvement of patients' exercise tolerance and health status, prevention and treatment of complications and exacerbations, and a reduction in the risk of death from by COPD (Fromer & C. B. Cooper 2008; D. E. O'Donnell et al. 2008; GOLD 2013). While there are a number of aspects of disease management that may be standard for all patients, healthcare providers and patients need to establish realistic goals and understand that these goals will vary between patients (Fromer & C. B. Cooper 2008). Therefore, a stepwise, comprehensive management approach is required to achieve these goals (B.R. Celli, MacNee, et al. 2004; D. E. O'Donnell et al. 2008; Rabe et al. 2007; GOLD 2013). At the light of the different HRQL, treatment for COPD should depend on the severity of the disease and health status of the patient, which should be evaluated based on symptom severity and impact of these symptoms on QoL and not solely on the extent of airflow limitation. Components of treatment plans should include smoking cessation strategies, pharmacologic management of the symptoms of COPD and related complications and comorbid conditions, risk factor reduction, patient counseling, mechanical bronchial hygiene, pulmonary rehabilitation, oxygen therapy and, in some cases, surgery to improve lung mechanics. A planned care management and regularly scheduled physician visits should be encouraged to monitor disease, to prevent acute care visit, to limit exacerbations experienced by patients and to improve QoL, in order to reduce economic burden of hospitalizations and emergency visits. Therefore, a support team comprised of both physician and support-service personnel should regularly follow-up with the patient to provide education, reinforce medication adherence and smoking cessation when applicable, encouraging an healthy lifestyle (B.R. Celli, MacNee, et al. 2004; Rabe et al. 2007; D. E. O'Donnell et al. 2008; Fromer & C. B. Cooper 2008; GOLD 2010b; GOLD 2013).

Pharmacologic strategy to improve QoL in COPD

Effective medications for COPD are available and all patients who are symptomatic merit a trial of drug treatment (B.R. Celli, MacNee, et al. 2004). The currently available pharmacologic therapy for COPD is used to prevent, reduce, control or abolish symptoms, reduce the frequency and severity of exacerbations and improve health status, exercise tolerance and capacity. At present, none of the existing medications for COPD has been conclusively shown to modify the rate of the long-term decline in lung function when this is tested as a primary or secondary outcome in clinical trials (B.R. Celli, MacNee, et al. 2004; Rabe et al. 2007; GOLD 2013). However, this should not preclude efforts to use medications to control symptoms (Rabe et al. 2007). The choice within each class of medication depends on the availability and cost of medications and the patient's response. Optimal pharmacotherapy of COPD and each treatment regiments need to be patient-specific as the relationship between disease and symptoms severity, airflow limitation and frequency of acute exacerbations will differ between patients (D. E. O'Donnell et al. 2008; GOLD 2013).

Non-pharmacological therapy

Although pharmacologic treatment is essential for effective management of COPD symptoms, several non-pharmacologic interventions are crucial for ensuring successful HRQL outcomes. Non-pharmacologic therapy is characterized by risk factor reducing interventions, pulmonary rehabilitation and oxygen therapy. The aims of no-pharmacologic therapy are to reduce the burden of COPD symptoms, improve QoL, and increase physical and emotional involvement in DPA. Pulmonary rehabilitation, i.e. PR, includes ExT, nutrition counseling, patient education, has been prove to be most beneficial for patients with stage II to stage IV COPD. It should address disease-specific aspects not sufficiently covered by medical therapy, such as depression, muscle wasting and social isolation. ExT should include aerobic and resistance exercises to improve aerobic capacity and muscle strength. Nutrition counseling should also be offered because nutritional status plays a key role in symptoms, disability and prognosis of COPD. Finally, patients education is important in order to better understand the disease and to improve compliance with various aspects of treatment. Adherence strategies should be developed not only for pharmacologic agents, but also for all of non-pharmacologic interventions in order to improve patients' compliance with their management plan (B.R. Celli, MacNee, et al. 2004; Nici et al. 2006; Fromer & C. B. Cooper 2008; GOLD 2010b; GOLD 2013).

PHYSICAL ACTIVITY & EXERCISE TRAINING IN COPD

Definition of Physical Activity and Exercise Training

It is important to distinguish physical activity from physical fitness, functional or exercise capacity. The latter three indicate what a person is capable of doing while physical activity reflects what someone actually does (Table 3.1).

Table 3.1 – Physical Activity and Exercise definition

PA definition	Exercise definition
Any bodily movement produced by the skeletal muscles that requires energy expenditure (Caspersen & Christenson 1985)	Any PA done on purpose and carried out in a more structured manner with the aim of improving cardio-respiratory or muscular fitness (Caspersen & Christenson 1985)

Indeed, the measurement of PA is different from the measurement of physical fitness, functional or exercise capacity. Physical Activity can be investigated by direct observation, assessment of energy expenditure, i.e. calorimetry, or doubly labeled water technique, use of diaries and self-reported questionnaires and performance-based motor sensors, such as pedometers and accelerometers (Pitta et al. 2006). The first two are time consuming and expensive and are therefore used less frequently. Performance-based motion sensors objectively quantify the amount of daily physical activity performed and is therefore more accurate as compared with questionnaires and diaries, which depend on a person's memory and interpretation (Hartman J.E. 2010). There is considerable literature supporting importance of habitual PA in primary and secondary prevention of varied chronic conditions. Routine PA is thought to be of benefit for over 25 chronic conditions. Seven chronic diseases in particular have been associated with a physically inactive lifestyle including coronary artery disease, stroke, hypertension, colon cancer, breast cancer, type 2 diabetes and osteoporosis (Warburton et al. 2010). Indeed, regular PA is well-recognized to improve body composition, automic tone, coronary blood flow, psychological wellbeing, glucose homeostasis and insulin sensivity, enhances lipid lipoprotein profiles and endothelial function, reduces blood pressure and systemic inflammation, decreases blood coagulation and augments cardiac function (Figure 3.a) (Hartman J.E. 2010; Cress et al. 2006; Warburton et al. 2010) Physical inactivity is therefore a modifiable risk factor for cardiovascular disease and a variety of other disease such diabetes mellitus, cancer, hypertension and dementia (Hartman et al. 2010).

Health issue	Benefits of physical activity
Cardiovascular health	<ul style="list-style-type: none"> Improves myocardial performance Increases peak diastolic filling Increases heart muscle contractility Reduces premature ventricular contractions Improves blood lipid profile Increases aerobic capacity Reduces systolic blood pressure Improves diastolic blood pressure Improves endurance Improves muscle capillary blood flow
Body composition	<ul style="list-style-type: none"> Decreases abdominal adipose tissue Increases muscle mass
Metabolism	<ul style="list-style-type: none"> Increases total energy expenditure Improves protein synthesis rate and amino acid uptake into the skeletal muscle Reduces low-density lipoproteins Reduces cholesterol/very low-density lipoproteins Reduces triglycerides Increases high-density lipoproteins Increases glucose tolerance
Bone health	<ul style="list-style-type: none"> Slows decline in bone mineral density Increases total body calcium, nitrogen
Psychological well-being	<ul style="list-style-type: none"> Improves perceived well-being and happiness Decreases levels of stress-related hormones Improves attention span Improves cognitive processing speed Increases slow wave and rapid eye movement sleep
Muscle weakness and functional capacity	<ul style="list-style-type: none"> Reduces risk of musculoskeletal disability Improves strength and flexibility Reduces risk of falls Improves dynamic balance Improves physical functional performance

Figure 3.a – Health benefits of regular physical activity

(from Cress et al. 2006)

An adequate physical activity program is defined as a “Well-Rounded Program” and it is an integral part of a strong, overall, health wellness and fitness program (Jones C.J. & Rose, 2005). The “well-rounded PA programs” for adults and older adults focus on the key components of endurance, strength, balance and flexibility training, and posture and maintenance of a body composition in according with ACSM position stand (M. E. Nelson et al. 2007). The recommended minimum amounts and types of physical activity that promote health and prevent disease is 30 minutes of moderately/intense aerobic physical activity at least 5 days a week or 20 minutes of vigorously intense aerobic physical activity at least 3 days a week, or an equivalent combination. Every adult should also perform muscular strength and endurance exercises at least 2 days each week (W. J. Chodzko-Zajko et al. 2009; O'Donovan et al. 2010; D.E.R. Warburton et

al. 2010). For elderly adults, i.e. age ≥ 65 , or ≥ 50 years with clinically significant chronic conditions and/or functional limitations, it is necessary to adjust the recommended intensity of aerobic activity to the elderly adult's aerobic fitness. Moreover, activities that maintain or increase flexibility are recommended next to balance exercise for elderly adults at risk to fall (Figure 3.b) (M.E. Nelson et al. 2007; Hartman et al. 2010).

Dimensions of Movement in COPD patients

A chronic condition is considered “clinically significant” if a person receives or should receive regular medical care and treatment for it. Therefore, a functional limitation is “clinically significant” if it impairs the ability to engage in physical activity (M. E. Nelson et al. 2007). Strategies to promote health are advocated for patients with long-term conditions, as well as the general population (Wilson et al. 2005). As highlighted before, breathlessness, chronic cough with or without sputum production, and chronic fatigue are the main characteristic features of COPD (Woo 2000). These clinical manifestations vary according to disease severity, with general deterioration over a period of 10 to 40 years, leading to reduced mobility, functional and social activity, and impaired quality of life (V. Williams et al. 2011). The variety of symptoms highlight the importance of a multi-faceted approach to manage COPD, integrating both pharmacological and non-pharmacological interventions (Caress et al. 2010). Many patients recognized their condition as long-term and progressive and, coupling with their family members, consider really important to improve and carry out PA in order to enhance health (Caress et al. 2010; V. Williams et al. 2011). Therefore, PR, defined as “a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy” (B.R. Celli, MacNee, et al. 2004), is recognized to be the most interventions aimed at reducing symptoms and improving well-being entail health promotion behaviors (Caress et al. 2010). The promotion of a healthy lifestyle is a key element of PR to stress therapy adherence and encouraging PA (B.R. Celli, MacNee, et al. 2004).

Psychological dimension of movement in COPD

The majority published research in relation to PA and COPD has predominantly focused on the quantitative assessment of activity, rather than the meaning of such activities for participants using qualitative methods (V. Williams et al. 2011). Instead, apart from physical impairment, patients with COPD carry substantial mental burden related to their disease and its symptoms

(G.-C. Funk et al. 2009). Rates of anxiety disorders in patients with COPD, particularly generalized anxiety disorder, i.e. GAD, panic disorder and depression, are much higher than in the general public (Brenes 2003; G.-C. Funk et al. 2009). Prevalence of GAD among COPD patients ranges from 10% to 15.8% when using standard diagnostic procedures compared with lifetime rates of 3.6% to 5.1% in the general public. Furthermore, rates of panic disorder are also higher in this population with a prevalence rate of 8%, which is 5.3-times as high as in the general population (Brenes 2003). Not only anxiety is highly common among COPD patients but the reverse is also true: the lifetime prevalence of respiratory disease is higher in people with panic disorder, ~47% than with other psychiatric diagnoses (Brenes 2003). At present, it's well known that both anxiety and depression are risk factors for re-hospitalization in COPD, poorer survival. (G.-C. Funk et al. 2009) and provide negative impact on QoL of COPD adults, i.e. greater disability, impaired functional status, physical roles, emotional roles, social functioning, bodily pain, mental health function, and vitality. Even after statistically controlling for the effects of overall health status, COPD severity, dyspnea and anxiety remain significantly associated with decreased functional status (Brenes 2003). Although, in most studies, FEV₁ and BODE index were observed as a bad predictors of anxiety and depression, on the other hand, the presence of respiratory symptoms causes substantial anxiety and depression (Figure 3.d) (G.-C. Funk et al. 2009). Anxious symptoms were explained by dyspnea, while depressive symptoms were explained by both dyspnea and reduced exercise capacity (G.-C. Funk et al. 2009).

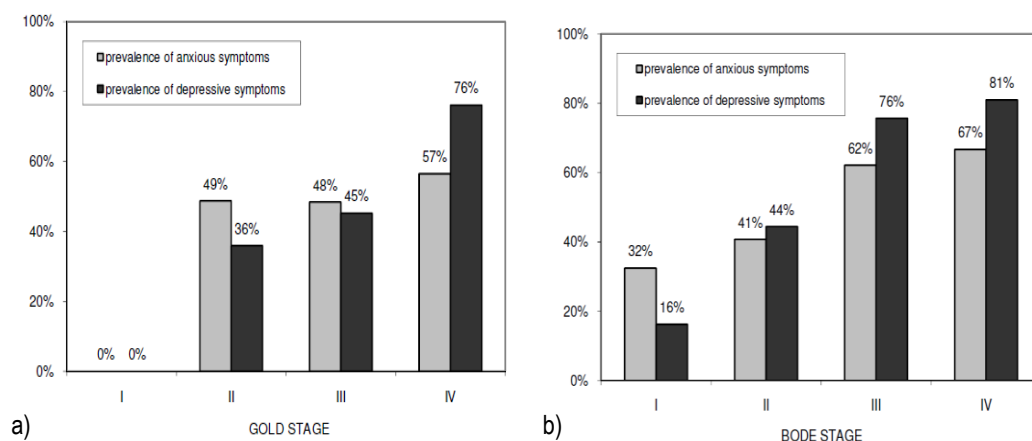


Figure 3.d – Prevalence of anxious and depressive symptoms in COPD patients according to GOLD (a) and BODE index (b);

(from Funk et al., 2009)

A limited number of qualitative studies have been published exploring various aspects of experience PA in COPD including social, physical, and psychological aspects. The major

research was made by Williams and colleagues (2011) concerning the impact of stagnation indoor air on individual perceptions of breathlessness, identified as feelings of suffocation. This study confirmed previous findings about link between emotional component of the breathlessness and feelings of vulnerability, helplessness and loss of control. The perception of suffocation, with associated feelings of anxiety, panic, helplessness, and loss of control, is not only present during acute exacerbations, but is also linked to the perception of being confined indoors when COPD is stable. Williams and colleagues developed a theoretical model showing link between environmental aspects and perception of symptoms, which in turn have an effect on the experience of activity, i.e. “Stagnation–Movement model” (Figure 3.e) (V. Williams et al. 2011).

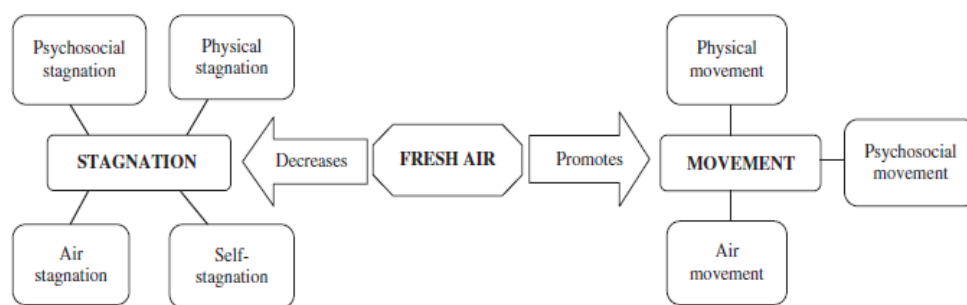


Figure 3.e – Stagnation-movement model in COPD;

(from Williams et al., 2011)

Behavioral dimension of movement in COPD

Although some discordances are present, several studies observed a positive relationship between PA, slower decline in pulmonary function and lower mortality (Cheng et al. 2003; Pelkonen et al. 2003; Prakash et al. 2007). Indeed, physical activity and non-smoking or smoking cessation are associated with a maintenance of cardiovascular and respiratory function (Figure 3.f). At present, regular PA is considered a factor to prevent or delay onset or progress of different chronic diseases (Cress et al. 2006; M. E. Nelson et al. 2007; D.E.R. Warburton et al. 2010; O'Donovan et al. 2010; Darren E.R. Warburton et al. 2011). Patients with COPD frequently report dyspnea related to everyday tasks (GOLD 2013) and may be in a downward spiral of symptom-induced inactivity, leading to deconditioning and muscle weakness (Pitta et al. 2005). The assessment of the amount and intensity of DPA is considered very important due to the close relationship between activity levels and health (Pitta et al. 2006). It is well-known that most of the patients with severe COPD are breathless even when performing simple DPA, ADL, or walking

around at home (Restrick et al. 1993), but a recent cross-sectional comparative study (Gouzi et al. 2011).

	Tertile of Physical Activity*			p Value
	Low (n = 143)	Middle (n = 143)	High (n = 143)	
Mean age, yr, SD	54.3 (5.3)	54.1 (5.6)	54.4 (5.4)	0.843
Mean FEV _{0.75} , ml, SD	2,939 (0.571)	2,939 (0.625)	2,956 (0.565)	0.963
Occupational activity, %				< 0.001
Light/moderate	29.1	12.6	12.7	
Heavy/very heavy	70.9	87.4	87.3	
Smoking category, [†] %				0.715
Never	21.7	28.7	27.3	
Quit [‡]	35.7	33.5	34.2	
Continuous	42.6	37.8	38.5	
Mean duration of smoking, yr, SD	24.3 (8.4)	24.1 (9.8)	22.9 (10.2)	0.540

* Tertile limits for baseline physical activity: less than 734 kJ/day, 734–1,361 kJ/day, and more than 1,361 kJ/day.

[†] On the basis of smoking data from the first 10 years.

[‡] Including past smokers at the baseline and smokers who gave up smoking during the first 10 years of follow-up.

Figure 3.f – Baseline characteristics of subjects by tertile of baseline physical activity

(from Pelkonen et al. 2003)
al. 2011)

assessed the lifetime pattern of PA in COPD patients and sedentary HC subjects using a PA questionnaire. Interestingly, the study showed a PA reduction in COPD patients, at 45 years old, that occurred earlier than in healthy subjects. Furthermore, Gouzi and colleagues (2011) found that this reduction becomes before any clinical signs of the disease (Figure 3.g), suggesting that PA was reduced before diagnosis and the onset of breathlessness, thus, before the disease onset.

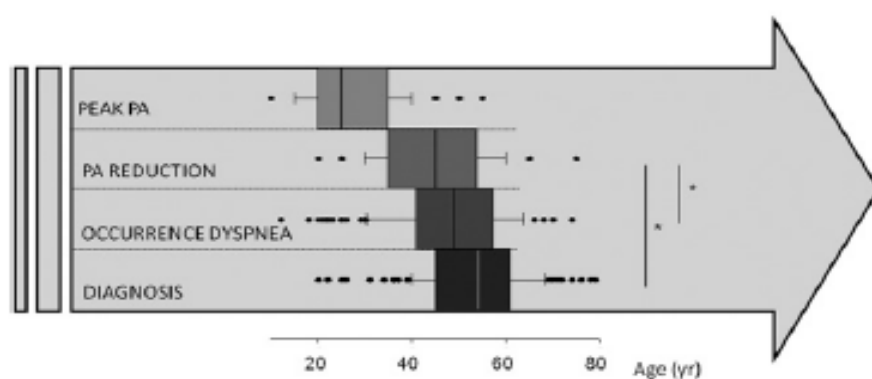


Figure 3.g – Age of occurrence of physical activity peak, reduction, breathlessness and diagnosis for COPD patients.

Box plot showing median; top and bottom edges of the box indicate 75th and 25th percentiles, respectively. The brackets above and below the boxes indicate the 90th and 10th percentiles, respectively. Additional symbols are the values that fall outside the 10th to 90th percentile range. *p<0.001.

(from Gouzi et al. 2011)

Vorrink and colleagues (2011) reviewed several studies about COPD sedentary behavior in terms of duration, intensity, and counts of DPA, compared with HC subjects. It was observed that COPD patients are physically active for significantly less time of the day than HC (Coronado et al. 2003; Pitta et al. 2005; Walker et al. 2008; Hernandez et al. 2009; Troosters et al. 2010). Pitta and colleagues (2005) showed that most COPD patients spend significantly less time walking and standing and more time sitting and lying in daily life when compared with sedentary HC elderly subjects (Figure 3.h). The degree of sedentary behavior in patients with COPD is further illustrated by the fact that they spent ~12% of the time during the day, or twice the walking time, in the lying position, as compared with ~4% in healthy elderly subjects (Pitta et al. 2005). Moreover, Hernandez et colleagues (2009) evaluated the characteristics of DPA in Brazilian COPD patients, estimating a mean walking time per day shorter than HC (55 ± 33 vs. 80 ± 28 minutes per day; $p = 0.001$). The Vorrink's review established a ratio of duration of being active for HC vs. COPD of 1:0.57 (Hernandez et al. 2009).

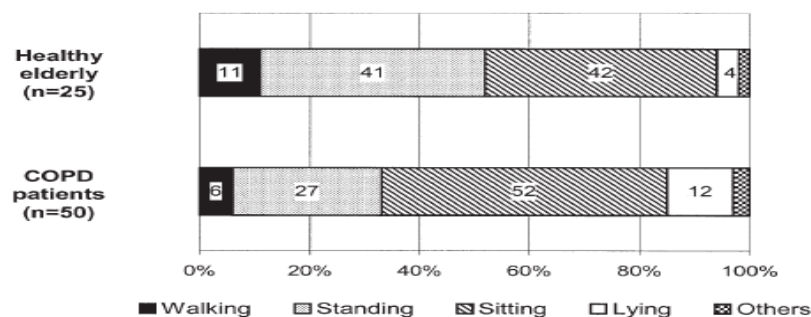


Figure 3.h – Percentages of time spent in different DPA in healthy and COPD patients; Others, cycling or undetermined activity

(from Pitta et al., 2005)

Secondly, evidences of a reduction in intensity of DPA in COPD were found (Vorrink et al. 2011). Patients with COPD walk ~25% slower, i.e., at a lower movement intensity, when compared with age-matched HC (Pitta et al. 2005; Hernandez et al. 2009; Walker et al. 2008). In addition, it was observed by Troosters (2010) that the time spent in activity with mild, moderate and high intensity was significantly reduced in COPD patients compared to HC. Same findings were described in Coronado's, Hernandez's and Singh's studies. Ratio of DPA intensity for HC versus COPD is 1:0.75 (Vorrink et al. 2011). Lower levels of daily movement counts, lower activity count, less steps per day were observed in COPD patients than the average level recorded in age- and sex-matched HC (Vorrink et al. 2011; Schonhofer et al. 1997; Walker et al. 2008; Troosters et al. 2010). Ratio of DPA counts for HC versus COPD is 1:0.56 (Vorrink et al. 2011). Regarding the relation between DPA and disease severity, several studies found a moderate correlation but

certainly not strong (Vorrink et al. 2011). Pitta and colleagues (2008) correlated FEV₁ with sedentary activities, moderate activities and vigorous activities. Only correlation with vigorous PA proved to be significant (Pitta, Takaki, et al. 2008; Vorrink et al. 2011). Hernandez (2009) and Singh & Morgan (2001) did not find correlation between FEV₁ and walking time or total activity count. Whereas, Steele found significant correlation between DPA and FEV₁ and GOLD stage (Steele et al. 2003). Finally, Pitta study (2005) indicated that, in patients with COPD, DPA are better predicted by a global or integrative test, such as 6MWD, rather than by tests focused on single components of physical functioning, such as lung function and muscle force. In fact, the study showed that 6MWD was capable of identifying patients with COPD who had low walking time during daily life: patients with a 6MWD of less than 400 m, or ~ 60% predicted, had an average walking time of less than 30 minutes/day (Figure 3.i) (Pitta et al. 2005).

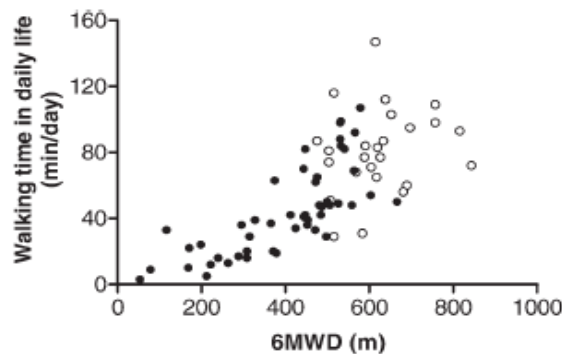


Figure 3.i – Plot of 6MWD and walking time in daily life in patients with COPD (closed circles) and healthy elderly subjects (open circles);

(from Pitta et al., 2005)

Therefore, this study showed that if the 6MWD is severely reduced, patients are markedly inactive in daily life and a 6MWD is the best surrogate marker of inactivity during daily life in patients with COPD (Pitta et al. 2006; Pitta et al. 2005). Furthermore, recently, Jehn and colleagues (2012) have evaluated the accelerometer based walking intensity as a measure of functional capacity and its association with health COPD related quality of life. They were able to demonstrate that patients with lowest accelerometer based daily walking intensity had worst outcome in terms of HRQL and highest disease severity, GOLD classification and BODE index (Jehn et al. 2012). Evidences about COPD sedentary behavior (Vorrink et al. 2011), correlation between disease severity, HRQL, and performance of usual DPA, (Pitta et al. 2005; Jehn et al. 2012), and early reduction of DPA (Gouzi et al. 2011), support potential effectiveness of ExT to break downward spiral of symptom-induced inactivity, also for at-risk populations, i.e. smokers,

which should be more fully integrated into public health care policies and for the timing of pulmonary rehabilitation (Pitta et al. 2006; Gouzi et al. 2011; GOLD 2013).

Physiological dimension of movement in COPD

Patients with COPD are disabled by their inability to carry out many ADL caused by exercise limitation. This leads to increasing social isolation, depression, and dependence. Improving physical performance is therefore an important therapeutic goal in these patients (Steiner & M. D. L. Morgan 2001). For many years it was believed that COPD patients were only limited by their ability to adequately increase ventilation to match the demands of exercise and, thus, exhibit a ventilatory limitation to exercise. Only recently, researchers have identified evidence that factors other than ventilation limitation can be very important in limiting exercise (Butcher & R. L. Jones 2006; Steiner & M. D. L. Morgan 2001). Patients with COPD exhibit several peripheral muscular, cardiac, haemodynamic and metabolic deficiencies that contribute to exercise limitation (Figure 3.j) (Bernard et al. 1998; Serres et al. 1998; Polkey 2003; Polkey 2002; W.D-C Man et al. 2009a; van der Vlist & Janssen 2010). $\dot{V}O_{2\max}$ is considered the present gold standard for measurement of cardiovascular fitness and is a useful parameter for determining aerobic capacity (I. M. Weisman et al. 2003). In patients with COPD, average $\dot{V}O_{2\max}$ ranges from 0.5 to approximately 1.6 L/min in most exercise tolerance studies with peak work rates of only 60–120W. Although $\dot{V}O_{2\max}$ is not adequately explained by measures of lung function, $\dot{V}O_{2\max}$ is typically lower in patients with more severe disease (Butcher & R. L. Jones 2006). However, there is considerable variability in $\dot{V}O_{2\max}$ and exercise performance between patients, suggesting that when comparing patients of similar severity of lung dysfunction, factors other than $\dot{V}O_{2\max}$ are more important in determining exercise performance (I. M. Weisman et al. 2003; Butcher & R. L. Jones 2006). Therefore, much attention has been given in recent literature to determining the limitations to exercise capacity in patients with COPD and several excellent reviews of traditional and contemporary views have been published.

Ventilatory limitations

Exercise ventilation in patients with COPD, as in healthy subjects, is a direct consequence of the metabolic demands of exercise. However, a greater minute ventilation, i.e. \dot{V}_E , is required to achieve a given level of alveolar ventilation. This greater ventilation is due primarily to an increase in the physiological dead space and the resulting ventilation-perfusion mismatch. The result is a reduction in the ventilatory efficiency as indicated by a high $\dot{V}_E/\dot{V}O_2$ or \dot{V}_E /work rate; however,

peak exercise ventilation is decreased. This reduction at peak exercise reflects the reduction in total work rate and has been attributed to a reduced ventilatory capacity or ceiling. There are also significant differences in the way that ventilation is achieved.

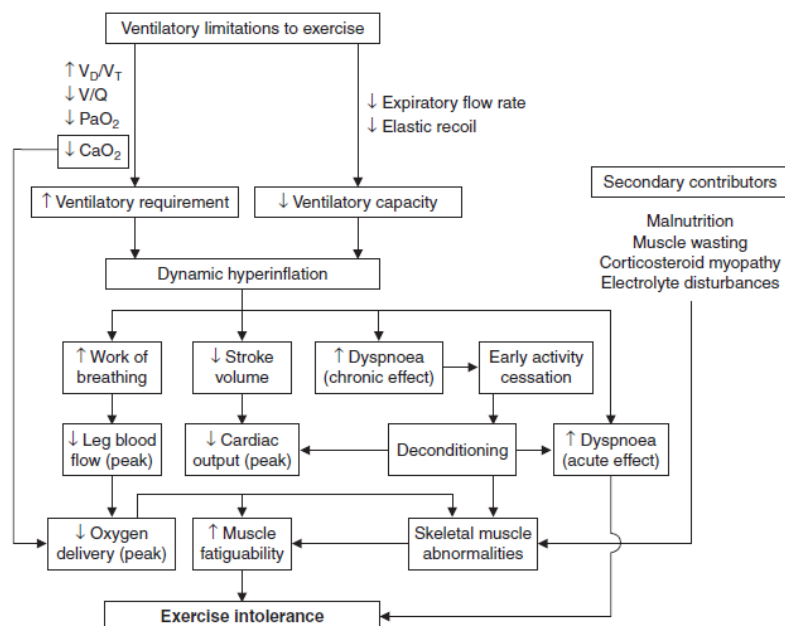


Figure 3.j – Schematic diagram of the important mechanisms of exercise intolerance in patients with COPD.

(from Butcher & R. L. Jones 2006)

Patients tend to increase tidal volume to only approximately the volume equivalent to their FEV₁ and this increase occurs early in exercise. The major increase in ventilation that occurs later in exercise is due to a disproportional increase in respiratory rate. However, because peak respiratory rate is only slightly greater than normal and there is a marked reduction in peak tidal volume, the net effect is an overall reduction of peak ventilation. The traditional view of ventilatory limitation to exercise is that a combination of a reduced ventilatory capacity and an increased ventilatory demand result in an eventual ceiling effect. That is, the inability to adequately increase ventilation to meet the metabolic demands of exercise was thought to be due to a reduced maximal potential for ventilation. Ventilatory demand is measured by an increasing V_E with exercise and ventilatory capacity is most frequently measured by maximal voluntary ventilation, i.e. MVV, or surrogates of MVV such as FEV₁ × 35 or 40. The closer V_E approaches MVV, the greater the chance of a ventilatory limitation to exercise. Problems with this approach were identified as it became apparent that measures of resting lung function do not correlate well with ventilatory patterns during exercise. Recently, other measures of ventilatory limitation have been discussed, but a consensus regarding the most appropriate measure has yet to be reached. One such measure is the determination of inspiratory capacity during exercise. Inspiratory capacity is

an easy, non-invasive method of determining the degree of dynamic hyperinflation that occurs in patients with COPD. Dynamic hyperinflation seriously affects ventilatory mechanics, inspiratory muscle function and cardiac function. As ventilation increases, end expiratory lung volume increases, i.e. dynamic hyperinflation, which, in turn, decreases the potential increases in tidal volume. As we know that total lung capacity does not increase with exercise, tidal volume can only increase to the volume that inspiratory capacity allows. Thus, a reduced ventilatory capacity is more a rising floor than a low ceiling. The degree of dynamic hyperinflation correlates very well with exercise tolerance as has been demonstrated in both maximal and sub-maximal exercise. Dynamic hyperinflation is also associated with increasing sensations of dyspnoea and an increased work of breathing. Although examination of dynamic hyperinflation is emerging as a promising method of determining ventilatory limitations to exercise, the exact measurement and interpretation of when a true limitation occurs has yet to be demonstrated (Butcher & R. L. Jones 2006; I. M. Weisman et al. 2003; Truwit 2003).

Cardiac limitations

During incremental exercise, the rise in oxygen consumption, i.e. VO_2 , with increasing work rates appears to be relatively normal; however, there is often a higher resting VO_2 in more severe patients, reflecting the increased ventilatory cost of breathing. VO_2 is determined by cardiac output, i.e. heart rate and stroke volume, and oxygen extraction at the tissue level. Systemic oxygen extraction is not normally considered to be a major limiting factor in patients with COPD, but has been found to be reduced in some patients and not in others. Cardiac output and stroke volume are reduced at peak exercise likely as a result of a reduction in peak work rate occurring because of other limitations, such as ventilatory, muscular or symptom limitations, and not because of a primary limitation in cardiac output. Peak heart rate is usually reduced, especially in studies using patients with more severe COPD. If cardiac output were the primary limiting factor to exercise, one would expect a maximal or near maximal heart rate at peak exercise. Because this does not occur, exercise ceases prior to attaining a maximal, limiting cardiac output. Sub-maximal cardiac output, on the other hand, appears to be normal, with the decreased stroke volume being offset by an increased heart rate. Reduction in stroke volume at all exercise intensities is a consistent finding in most patients with COPD. This reduction is primarily caused by reductions in right ventricular output due to lung hyperinflation, increased pulmonary vascular resistance and reduced venous return as a result of increased intrathoracic pressure. The effects of lung disease on right ventricular dysfunction also extend to the left ventricle. Increased right ventricular pressure and volume induce a septal shift, which reduces left ventricular filling. The

overall effect is reduced left ventricular stroke volume. Patients with COPD are typically able to sustain relative constant load work rates that are much higher, ~82%, than healthy subjects, ~68%, when expressed as a percentage of peak work rate obtained in an incremental test to exhaustion. The sustainable work rate achieved, i.e. critical power, in patients is directly related to measures of ventilatory function and dyspnoea. The fact that the relative critical power is much higher in patients is likely reflective of an abnormally low peak work rate during the maximal test. This fact provides further evidence that VO_{2max} , and therefore maximal cardiac output, are not likely attained in patients, and suggests that symptoms or limitations in ventilation determine both the critical power and the duration of exercise in work rates above the critical power (I. M. Weisman et al. 2003; Butcher & R. L. Jones 2006).

Peripheral Muscle Limitations

Recent evidence has pointed to skeletal muscle dysfunction as a potential limiting factor to exercise tolerance in patients. Documented skeletal muscle abnormalities that affect exercise performance in patients with COPD include decreased lower extremity skeletal muscle mass, strength, endurance, capillarity, muscle oxidative enzyme capacity and proportion of type I fibers. The net effect of these abnormalities is a greater dependence upon anaerobic metabolism, an early rise in lactate during low levels of exercise and a markedly reduced lactate threshold. There is also direct evidence that skeletal muscle strength is correlated with exercise tolerance and that skeletal muscle training increases exercise tolerance. Also, administration of a bronchodilator, which increases FEV1 and raises the potential to increase ventilation, does not improve exercise tolerance in all patients. After exhausting exercise, contractile fatigue of the quadriceps occurs in some patients limiting exercise tolerance. These findings together provide evidence that skeletal muscle abnormalities contribute to exercise limitation in certain patients and may be due to any combination of deconditioning, muscle wasting, malnutrition, corticosteroid myopathy, hypoxia or electrolyte disturbances (Gosselink et al. 1996; Bernard et al. 1998; Serres et al. 1998; ATS & ERS 1999; F. Maltais et al. 2000; W.D-C Man et al. 2009a; W.D-C Man et al. 2009b; H.R. Gosker et al. 2007; Kim et al. 2008; Couillard & Prefaut 2005; Butcher & R. L. Jones 2006).

Limitation to oxygen delivery

During exercise, respiratory muscle VO_2 required approximately ~40% of the total body peak oxygen consumption, i.e. VO_{2peak} , in patients with COPD compared with 10–15% in HC. It was hypothesized that this increased respiratory requirement would reduce available oxygen for the exercising leg muscles, leading to early exercise limitation. Recently, it has been found that

increasing respiratory muscle loads during exercise reduces exercise performance and leg blood flow at maximal exercise in healthy subjects. In some patients with COPD, a plateau in leg muscle blood flow, oxygen delivery, VO_2 and oxygen extraction occurs during incremental exercise, despite further increases in work rate and whole-body VO_2 . Although this plateau is present in HC, it occurs at a much lower work rate in patients. It was speculated that increases in work of breathing in patients who demonstrate a plateau might be a reason for reductions in exercise tolerance, due to redistribution of blood flow to the respiratory muscles during exercise. Also, when reducing the effect of central cardio-respiratory limitations during whole-body exercise, a significant metabolic reserve is demonstrated in COPD skeletal muscle. This reserve disappears when performing single limb exercise, i.e. repeated knee extension, with heliox and hyperoxia. It is likely that this finding demonstrates that skeletal muscle may not be the cause of exercise limitation, but that a deficiency in the oxygen delivery system is. Also, it is quite possible that a limitation in oxygen delivery is partly responsible for some of the skeletal muscle abnormalities demonstrated in these patients. Although the exact mechanisms of exercise intolerance vary across individuals, most patients with COPD come very close to reaching, if not reach, their pulmonary mechanical limits during heavy exercise. Other limitations, such as peripheral muscle fatigue may occur prior to reaching a ventilatory limitation; however, ventilation is usually close to maximal. Importantly, however, these limitations appear to be different than healthy age matched control subjects in type and magnitude, making exercise prescription much more complex (Bernard et al. 1998; Butcher & R. L. Jones 2006).

Exercise training in pulmonary rehabilitation

Movement is an important aspect of COPD patients daily life despite their limitations (V. Williams et al. 2011). In fact, patient's satisfaction with physical functioning, i.e. SPF, is considered a component of HRQL. More specifically, decreased satisfaction with physical abilities is associated with greater physical impairment, greater disability in valued activities, and depressive symptoms (Katula et al. 2004). Therefore, encouragement to be more active in daily life to improve the level of DPA is a major goal in the care of COPD patients and should be an important part of the management of patients with COPD because inactivity may influence their clinical evolution (Roche 2009). In fact, the GOLD guidelines (2013) indicates pulmonary rehabilitation as a recommended standard of care and management for COPD patients. A comprehensive pulmonary rehabilitation program is a multi-component intervention which include patient

assessment, exercise training, education, and psychosocial support (Nici et al. 2006; Ries et al. 2007). Its definition focuses on three important features of successful rehabilitation:

- Multidisciplinary: Pulmonary rehabilitation programs utilize expertise from various healthcare disciplines that is integrated into a comprehensive, cohesive program tailored to the needs of each patient.
- Individual: Patients with disabling lung disease require individual assessment of needs, individual attention, and a program designed to meet realistic individual goals.
- Attention to physical and social function: To be successful, pulmonary rehabilitation pays attention to psychological, emotional, and social problems as well as physical disability, and helps to optimize medical therapy to improve lung function and exercise tolerance (Nici et al. 2006).

At current, of all the pulmonary rehabilitation programs topics, ExT is the major component and is considered an established safe and effective intervention for improving physical capacity and quality of life in COPD patients (Dressendorfer et al. 2002). Any patient with moderate to severe COPD and exercise or activity limitation who lacks contraindications should undergo ExT, particularly of the lower limbs (Ries et al. 2007). However, some studies highlighted importance of ExT also in the early stages of COPD in order to improve fitness of patients with mild to moderate COPD (Chavannes N.H. et al., 2001). Persons who lack access to formal comprehensive PR or supervised ExT should be given a home-based exercise program to follow (Thomas et al. 2010). Evidence suggests that expected gains in endurance are less when patients are given only education and verbal advice and guidance about exercise, as compared to participating in a supervised exercise program (C. L. Rochester 2003). Although exercise and education sessions are conducted twice weekly in many outpatient programs, one recent study highlighted that twice weekly exercise may not be sufficient to achieve gains in walking distance and health status (Ringbaek et al. 2010). The recommendations for exercise training in the above-noted current clinical guidelines are summarized in the Figure 3.k.

Clinical benefits of Exercise Training in Pulmonary Rehabilitation

Many physiological and psychological benefits have been reported in COPD patients after participation in randomized controlled trials of prescribed exercise involving upper and lower body endurance and/or resistance training. Major benefits include increased physical capacity, decreased anxiety about breathlessness, greater independence in ADL, reduced fatigue and

Training/Candidacy	ACCP/AACVPR*	ATS†	BTS‡
Lower-Limb Training	Recommended as part of PR: optimal specific prescription not defined	Endurance and strength training recommended: • 20–30 min • 2–5× per week • intensity 60% VO ₂ max where possible	Endurance and strength training recommended: • 20–30 min • 3–5× per week • intensity 60–70% VO ₂ max where possible • maintain O ₂ saturation >90%
Upper-Limb Training	Strength and endurance training recommended as part of PR	Strength and endurance training recommended as part of PR	Strength and endurance training may be included in PR
VM Training	Evidence does not support routine use in PR; may be considered in some patients with decreased respiratory muscle strength and breathlessness	Role in PR unclear	Nonessential
Patient Candidacy	Any patient with stable disease of the respiratory system and disabling symptoms	Patients with chronic respiratory impairment who are dyspneic or have decreased exercise tolerance or experience restriction in activities	All patients with chronic lung disease whose medical management is optimized and whose lifestyle is adversely affected by chronic breathlessness

ACCP = American College of Chest Physicians
 AACVPR = American Association of Cardiovascular and Pulmonary Rehabilitation
 ATS = American Thoracic Society
 BTS = British Thoracic Society
 VM = ventilatory muscle
 PR = pulmonary rehabilitation
 VO₂max = maximal oxygen consumption

*American College of Chest Physicians and American Association for Cardiovascular and Pulmonary Rehabilitation. Pulmonary rehabilitation: joint ACCP and AACVPR evidence-based guidelines. Chest 1997;112(5):1363–96.
 †American Thoracic Society Statement. Pulmonary rehabilitation—1999. Am J Respir Crit Care Med 1999;159:1666–82.
 ‡British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation. Pulmonary rehabilitation. Thorax 2001;56:827–34.

Figure 3.k – Evidence-based guidelines for ExT in COPD.

(C. L. Rochester 2003).

improved QoL (C. L. Rochester 2003; N. H. Chavannes et al. 2002; Dressendorfer et al. 2002; Butcher & R. L. Jones 2006). These positive outcomes occur even though impaired lung function continues to persist after ExT (Dressendorfer et al. 2002) despite discordance about benefits duration and maintenance over the time (C. L. Rochester 2003). However, regular ExT thus enables COPD patients to do more recreational and vocational activities despite their lung disease (Dressendorfer et al. 2002). Finally, since both aerobic fitness/endurance training and weight training can be beneficial and are safe for patients with COPD most rehabilitation programs currently use both types of training (C. L. Rochester 2003; Butcher & R. L. Jones 2006).

Effects of Endurance Training in COPD patients

In general, endurance ExT improves one's ability to sustain an exercise task at a given work load. Walking, running, cycling, stair climbing and swimming are examples of endurance training exercise (C. L. Rochester 2003). Recently, it was suggested that also Nordic Walking could be an effective ExT to improve endurance capacity of COPD patients (Breyer et al. 2010). Endurance training is regarded as a fundamentally important component of any pulmonary rehabilitation program (C. B. Cooper 2001). Evidence-based guidelines for PR, published jointly by ACCP and AACVPR, identified two modalities of treatment that have been shown by well-designed, prospective, placebo-controlled, clinical trials to be of value in pulmonary rehabilitation (Ries

2008; Ries et al. 2007). These modalities are endurance training, using large muscle groups and strategies to assist with the mastery of dyspnea. Interestingly, aerobic exercise *per se* might be one of the most efficacious and time-efficient means of achieving mastery of dyspnea (C. B. Cooper 2001). There is little doubt that endurance training, especially for lower extremities, is beneficial and an important components of PA programs for COPD patients (Butcher & R. L. Jones 2006; B.R. Celli, MacNee, et al. 2004). As breathless and fatigue are the major limiting symptoms, improvements in endurance may contribute to greater sustainability of task performance, and lower levels of perceived fatigue, which, clinically, have been associated with improved functional performance, exercise tolerance and health status (Casaburi et al. 1997; C. B. Cooper 2001; Salman et al. 2003; Langer et al. 2009). Randomized controlled trials about endurance ExT effectiveness reported significant improvements in maximal exercise capacity, walking distance and endurance capacity after respiratory rehabilitation (Troosters et al. 2000; Casaburi et al. 1997; M.A. Spruit et al. 2004; van Helvoort et al. 2010). Bicycle ergometry training at workloads of at least 60% of maximal workload, showed improvements in maximal workload, ~30%, and endurance time, ~70% (M.A. Spruit et al. 2004). Moreover, increases in endurance time and in time to fatigue at identical pre- and post- training work rates were observed, with a range from 70% to 100% (M.A. Spruit et al. 2004; Butcher & R. L. Jones 2006). Similar improvements were observed in ExT program incorporating both treadmill and walking exercise or combined walking and cycling programs (Casaburi et al. 1997; Nici et al. 2006; Lacasse et al. 2006; Troosters et al. 2000; M.A. Spruit et al. 2004). Improvements in 6MWD by 10–25%, in HRQOL, in activities of daily living and reduced symptoms of dyspnea and fatigue were observed (Troosters et al. 2000; M.A. Spruit et al. 2004; Butcher & R. L. Jones 2006). Increases in VO_{2peak} are not as commonly observed (Butcher & R. L. Jones 2006).

Intensity Training in COPD patients

Many low- and moderate intensity show non-significant increases in VO_{2peak} after training (Butcher & R. L. Jones 2006) although gains in exercise tolerance were demonstrated (C. L. Rochester 2003). Striking gains in treadmill endurance were observed without increases in VO_{2max} (Ries 2008). Low-intensity multimodality ExT also led to increased exercise tolerance for patients undergoing inpatient PR. The mechanisms by which exercise tolerance/endurance improves following low-intensity exercise, where in no specific improvements in aerobic fitness are noted, are not fully elucidated. However, gains in peripheral or respiratory muscle strength, increased mechanical efficiency of performing exercise due to improved neuromuscular coupling and coordination, reduction in hyperinflation/ improved lung emptying, reduced anxiety and

dyspnea, and improved motivation may all play a role. Different combinations of mechanisms likely result in the improvements noted in individual persons. In general, high-intensity exercise is considered to be that which takes place at greater than 60 percent of the patient's $VO_{2\max}$ or W_{\max} , whereas lower intensity exercise is conducted at lower work rates (C. L. Rochester 2003; Butcher & R. L. Jones 2006). High to near maximal intensity studies tend to show more consistent increases in $VO_{2\text{peak}}$. Interestingly, peak ventilation also increase with training, 6-11%, with slightly greater change likely after higher intensities of training, 9-11%, compared with lower intensities, 6-8%, although this is not consistent across all studies. Greater peak of ventilation may be explained by reductions in dynamic hyperinflation and by increases in ventilator efficiency that occur as a result of training (Butcher & R. L. Jones 2006). Characteristic physiologic changes provided by high intensity training indicating improvements in aerobic fitness following ExT include increased muscle fiber capillarization, mitochondrial density and oxidative capacity of muscle fibers, and delay of the onset of anaerobic metabolism during exercise, i.e., ability to exercise to a higher work rate before reaching the anaerobic/lactate threshold. These factors in turn lead to reduced ventilatory requirement for a given exercise task, increased $VO_{2\max}$ and decreased HR for a VO_2 . The demonstration of improvements in one or more of these variables following exercise training in patients with COPD is evidence of physiologic improvement in aerobic fitness (C. L. Rochester 2003; Casaburi et al. 1997; C. B. Cooper 2001; Butcher & R. L. Jones 2006).

Guidelines for Endurance Training

“ The evidence-based guidelines for pulmonary rehabilitation indicate scientific support in favor of aerobic exercise training using the large muscle groups of the legs. Arm endurance training is less effective than leg endurance training in improving functional capacity. Furthermore, when time for supervised endurance training is limited, it is clearly advantageous to focus on leg exercise. [...] Treadmill exercise is usually preferred by patients and rehabilitation therapists because of the readiness with which patients adapt to treadmill exercise and with which it translates to activities of daily living. Cycle ergometry can be used as a means of varying the exercise mode, provided intensity criteria are matched between the treadmill and cycle. In some cases, such as patients with arthritis, joint deformities, or morbid obesity, the cycle ergometer will be preferred because of its low impact on the musculoskeletal system. Cycle ergometry might also be chosen if therapists find difficulty with monitoring, such as pulse oximetry or electrocardiography during treadmill exercise. [...] Pulmonary rehabilitation should aim for an accumulation of 30 min of aerobic exercise on at least 3 d/wk for at least 6–8 wk. [...] Perhaps the most contentious of all issues regarding exercise prescription in chronic pulmonary disease is the

question of an appropriate exercise intensity. Several studies have indicated, as with normal subjects, that higher exercise intensity results in better training responses [...]. Despite these and similar findings, it has never been proven that there is a threshold exercise intensity above which it is necessary to train in order to obtain benefit. By contrast, low-intensity training induces worthwhile training responses both in asthmatic subjects and in those with COPD. Notwithstanding this knowledge, in order to obtain the most favorable response, patients in pulmonary rehabilitation should be encouraged to train at as high an intensity as tolerated with due consideration for various safety aspects. The obvious concern is that unsupervised training is less likely to achieve and sustain the exercise intensity required to elicit a clinically meaningful improvement in functional capacity. Determination of the optimal exercise intensity is the essence of the aerobic exercise prescription. An arbitrary approach (i.e., guessing the exercise intensity and making empirical adjustments) is unlikely to be the most effective strategy. However, unfortunately this is how many pulmonary rehabilitation programs operate. In order to advance the discipline of pulmonary rehabilitation and in order to optimize outcomes, the aerobic exercise prescription needs a firmer scientific basis. [...] First, exercise intensity should have a “target” that represents the minimum intensity needed to produce a clinically meaningful response. This does not imply that exercise intensities below the target are ineffective but rather that any such effect would be insufficient to translate into clinical benefit. Second, exercise intensity should have a “range,” the upper limit of which is typically defined by patient acceptance and safety considerations. Third, an effective exercise prescription must take into account “progression,” necessitating careful adjustment of the exercise prescription to maintain the desired intensity in the presence of training adaptations. Again, it is self-evident that in order to attain these goals with any degree of precision requires some physiological measurement or monitoring. [...] Patients with COPD are known to be able to achieve greater than 80% of their initial maximum work rate as a training intensity. [...] The diverse nature of limitation in COPD is likely to make it more difficult to predict what percentage of achieved maximum work rate constitutes an appropriate exercise prescription. Similar considerations are likely to apply to a percentage of measured $\dot{V} \text{ O}_2\text{max}$. The traditional and probably the commonest approach to aerobic exercise prescription for normal subjects uses a percentage of predicted maximum heart rate or heart rate range calculated from measured or predicted maximum heart rate. Again, in patients with chronic pulmonary disease, measured heart rate often does not bear the same relationship to exercise intensity that one expects with normal subjects. Furthermore, predictions of maximum heart rate are subject to errors. [...] One way around these difficulties is to use RPE rather than heart rate as a measure of exercise intensity. When using the RPE scale, it is helpful to establish some idea

of the relationship between RPE and heart rate for a given individual. For a given subject in pulmonary rehabilitation, this can be achieved simply by making paired observations of heart rate and RPE during submaximal exercise. Also, the RPE scale (range, 6–20) is preferred to the CR-10 (range, 1–10) scale [...]. Regular use of the RPE scale in the manner Borg intended leads to an appreciation of the appropriateness of RPE compared with the cardiovascular response to exercise. [...] When RPE is used to determine the aerobic exercise prescription for pulmonary rehabilitation, the desired threshold is likely to be 12 and the upper limit 16. Many rehabilitation programs use a rating of breathlessness rather than perceived exertion as an intensity target for patients with chronic pulmonary disease. This approach seems understandable on the basis of the fact that breathlessness is often the dominant limiting factor in these patients [...]” (C. B. Cooper 2001, pp. 673-674). Finally, current knowledge supports prescription of low to moderate endurance intensity training to increase COPD patients ability to sustain tasks currently able to perform, and High endurance intensity training in order to enhance ability to perform tasks that are above the current level (C. B. Cooper 2001; C. L. Rochester 2003; Butcher & R. L. Jones 2006)

Effects of Resistance Training in COPD patients

Resistance training is an exercise modality in which small muscle groups are trained by repetitively lifting heavy weights. This training modality has been successfully used in the rehabilitation of elderly subjects and in patients with chronic heart failure to improve peripheral muscle force, exercise capacity and ambulation (Spruit et al. 2004; C. L. Rochester 2003). A recent review (2009), O’Shea and colleagues analyzed the results from 18 controlled clinical trials and confirmed progressive resistance exercise with isotonic and/or free weight as an appreciable modality of training in order to improve several important COPD patients PR therapy outcomes, such as muscle strength, 6MWD and mass. Despite these findings, improvements in body composition, psychological function, societal participation and maximal exercise capacity remained inconclusive (O’Shea et al. 2009) confirming previous studies (Bernard et al. 1999). “Progressive resistance exercise can lead to appreciable increases in arm and leg muscle strength for people with COPD. Given that muscle weakness is a common problem in this population, progressive resistance exercise represents a beneficial treatment for improving muscle strength. Moreover, improvements in muscle strength can be obtained when progressive resistance exercise is conducted alone or in combination with aerobic training, indicating that it can be successfully performed in conjunction with other training modalities during pulmonary rehabilitation. Despite improvements in muscle strength after progressive resistance exercise,

inconclusive evidence was found for changes in skeletal muscle structure. Minor structural adaptations may reflect the small number of investigations, small sample sizes, or variations in training type and intensity utilized. Furthermore, disease-related factors, such as chronic hypoxia, long-term corticosteroid use, altered endocrine hormone concentrations, systemic inflammation, or nutritional status, may influence the rate or degree of muscle remodeling occurring during progressive resistance exercise for people with COPD. A primary goal of rehabilitation interventions for people with COPD is to optimize function. Therefore, it is important to determine whether increases in muscle strength after progressive resistance exercise translate into meaningful changes in activity performance and societal participation. Improved endurance in healthy young persons, and older adults has been reported after progressive resistance exercise. As fatigue is a major symptom identified by people with COPD, improvements in endurance may contribute to greater sustainability of task performance, and lower levels of perceived fatigue, which, clinically, have been associated with improved functional performance. When compared with no intervention, the findings [...] suggest an apparent trend toward improved endurance after progressive resistance exercise for people with COPD. However, when progressive resistance exercise is compared with aerobic training, improvements in cycling endurance favor aerobic training; highlighting the importance of aerobic training modalities for increasing endurance in people with COPD. Moreover, no additional benefit was demonstrated by adding progressive resistance exercise to a program of aerobic training. Concurrent progressive resistance exercise and aerobic training has been recommended during pulmonary rehabilitation for people with COPD; but it remains unclear which participants and which outcomes will benefit most and how combined training is best implemented in the clinical setting. [...] Improvements in muscle strength may carry over to improved daily task performance, such as stair-climbing, sit-to-stand, and arm elevation activities. [...] However, it has been reported [...] that participants reported improvements in measures of impairment, *i.e.* muscle strength, in the context of activity performance, despite no change being detected with quantitative measures of activity. Future investigations of rehabilitation interventions, such as progressive resistance exercise, should place greater emphasis on measures of activity and participation, as clinically meaningful benefits for people with COPD are likely to be associated with improvements in tasks and roles that are important in the context of daily life [...]” (O’Shea et al. 2009).

Intensity and Modality Training in COPD patients

Fewer studies have evaluated the impact of strength training as a sole exercise modality for persons with COPD. The relative advantages and disadvantages of high- versus low-intensity

strength training for persons with COPD are as yet unknown (C. L. Rochester 2003). The typical progressive resistance exercise protocols used in PR were similar to guidelines for healthy adults and those that have been applied to healthy older adult populations (M. E. Nelson et al. 2007; W. J. Chodzko-Zajko et al. 2009; Haskell et al. 2007) and very few adverse events were reported, suggesting that progressive resistance exercise is generally safe and appropriate for people with COPD (O'Shea et al. 2009). However, prevention of muscle tears is of paramount importance, particularly for persons on chronic steroid treatment who may be at risk for muscle rupture, i.e. biceps, when exposed to a high-intensity load. Clearly, such rupture can lead to prolonged, if not permanent, additional functional disability (C. L. Rochester 2003). Despite moderate withdrawal rates from trials, high levels of training adherence were reported with short-term interventions (O'Shea et al. 2009).

Effects of Eccentric Exercise Training in COPD patients

Many COPD patients do not tolerate high exercise intensities during whole body exercise because of breathlessness (C. B. Cooper 2001). Dynamic exercise can be accomplished by either concentric, i.e. positive work, or eccentric muscle contractions, i.e. negative work. During eccentric exercise, such as lowering a weight or walking downstairs, the contracting muscle lengthens in a controlled way, whereas during concentric exercise, i.e. lifting a weight and walking upstairs, the muscle shortens (Asmussen E. 1953). It was observed that eccentric exercise is associated with a reduced oxygen cost and ventilator requirement both in HC subjects and patients with COPD (Rooyackers et al. 2003) compared to concentric exercise at the same absolute workload (Roig et al. 2008; Rooyackers et al. 2003). It is generally accepted that exercise protocols in which eccentric actions are emphasized produce more important gains in strength (Hilliard-Robertson et al. 2003) muscle mass (Seeger et al. 1998) and neural adaptations (Hortobagyi et al. 1996) than regimens consisting of concentric actions only. Moreover, when eccentric and concentric contractions are performed at the same metabolic level eccentric-biased interventions result in greater strength gains and muscle fiber hypertrophy (LaStayo et al. 2000). The lower metabolic, neural, and cardio-respiratory cost of eccentric actions (Hortobagyi et al. 2000) combined with the relative preservation of eccentric force expression during ageing (Hortobagyi et al. 1995) has led to the prescription of this type of training program for individuals with reduced tolerance for physical activity (Krishnathasan et al. 2000). Despite evidences of musculoskeletal dysfunction in COPD patients (Couillard & Prefaut 2005; Kim et al. 2008; W.D-C Man et al. 2009b; W.D-C Man et al. 2009a), only one study explored the use of eccentric-biased programs in exercise COPD patients' prescription (Roig et al. 2008). Rooyackers and colleagues

(2003) applied eccentric training in a COPD patients PR trial, establishing that eccentric exercise training is enabled the patients to achieve high intensities in terms of strength and endurance without being short of breath and while maintaining S_{aO_2} above 90%. Moreover, they found that non-contractile components of the muscle and elastic elements contribute to the force generation during eccentric contractions and higher forces were generated during negative work as compared to positive work. Also, at similar work-loads, electromyographic activity and perceived exertion were lower, whereas mechanical efficiency was higher during negative work. Finally, despite all patients experienced some muscle soreness during the first 4 weeks of eccentric ExT, due to muscle damage provided by the negative work, this was well tolerated, did not influence the exercise intensity achieved during the training, reporting patients enjoyment to perform this type of exercise because of the low impact of exercise-limited symptoms, i.e. dyspnea and breathlessness during a conversation (Rooyackers et al. 2003). In conclusion, the relative conservation of eccentric force in older individuals (Hortobagyi et al. 1995) and in COPD patients (Mathur et al. 2007) by comparison to either isometric or concentric force makes this contraction a potential tool for restoring muscle function in COPD patients, also because the great capacity of eccentric contractions to induce muscle gains and neural adaptations (LaStayo et al. 2000) at a reduced metabolic level has been demonstrated (Roig et al. 2008).

Effects of Exercise Training on Balance in COPD patients

Impairments in peripheral muscle function, mobility, and exercise capacity are well established in COPD patients (ATS & ERS 1999; Bernard et al. 1998). However, emerging evidence also suggests that older adults with COPD show important reductions in balance control that may be associated with an increased fall risk in this population (Roig, Eng, D. L. Macintyre, J. D. Road, et al. 2010; Beauchamp et al. 2011). Although information regarding postural control in persons with lung disease is limited, evidence suggests that balance deficits constitute an important secondary impairment in older adults with COPD (Beauchamp et al. 2010). Two studies have shown reduced balance performance and coordination in subjects with COPD compared with healthy controls (Eisner et al. 2008; Butcher et al. 2004). One study examining the impact of fatigue on physiologic measures of postural sway found that patients with COPD showed impaired static postural control after a 6MWT in the absence of visual input, i.e. eyes-closed condition (Chang et al. 2008). In addition, it was reported that standard clinical balance measures discriminated between fallers and non-fallers with COPD, despite similar pulmonary function and 6MWT distances in the 2 groups (Beauchamp et al. 2009). ACSM recommends exercise with balance training as an essential component of a multifactorial falls intervention strategy for community-

dwelling older adults who are at risk for falling (M. E. Nelson et al. 2007). Although the exercise component of PR is considered the cornerstone of rehabilitation for patients with COPD, it is directed predominately to training peripheral muscles. Balance training and fall prevention strategies are not included in international guidelines for PR, and very few programs include standardized balance assessment (Ries et al. 2007). Beauchamp and colleagues (2010) described effects PR on balance in persons with chronic obstructive pulmonary disease (COPD) in order to determine whether any observed changes in balance were associated with change in exercise tolerance or health-related quality of life. They observed that PR was associated with minor changes in results of standard clinical tests of balance, without effects on balance confidence in patients with COPD. Also, they highlighted that measures of exercise tolerance and HRQL could not be used as surrogate measures to derive balance information. Finally, they emphasized the value of including a balance assessment and specific balance training in PR program, especially in patients with moderate and severe COPD, particularly if they have a history of falling (Beauchamp et al. 2010; Beauchamp et al. 2011).

SEDENTARY BEHAVIOR, EXERCISE & MUSCLE WASTING IN COPD

Evidence of Skeletal Muscle Dysfunction in COPD patients

DPA, HRQL, muscle strength and performance are likely intimately interlinked. At present, skeletal muscle weakness is recognized to contribute to poor health status, increased health utilization and even mortality. Therefore muscles seems to represent a potential site to improve COPD patients level of function and their QoL, in contrast with the irreversible lungs impairment (W.D-C Man et al. 2009b). Initially, this dysfunction has been tried to be explain by the sedentary lifestyle commonly observed in COPD patients. Then, in light of the most recent research, evidence has suggested that a sedentary lifestyle is unlikely to be the only explanation for this muscle weakness. Therefore, it was assumed that an intrinsic muscle disease, i.e. myopathy, may play an important role in reducing muscle strength performances of COPD patients (M. P. Engelen et al. 2000; Couillard & Prefaut 2005; Kim et al. 2008). Myopathy is defined as a “disease of the muscle unrelated to any disorder of innervations or the neuromuscular junction”, implying that muscle is affected by a pathological condition and couldn't function normally. There are different forms of myopathy, such as hereditary, metabolic, inflammatory, endocrine, and toxic causes. Whatever its form, myopathy is usually characterized by several metabolic, morphological and/or structural muscle abnormalities that lead to dysfunction (Couillard & Prefaut 2005). Literature indicates that corticosteroids, inflammation, hypoxemia and oxidative stress are the major factors contributing to COPD muscle dysfunction, although their relative contributions have not been fully elucidated (Couillard & Prefaut 2005; Kim et al. 2008).

Functional characteristics of Skeletal Muscle Dysfunction

In patients with COPD, peripheral muscle dysfunction is clearly evidenced by a significant reduction in both strength and endurance in the patients ambulatory muscles compared with healthy subjects (Couillard & Prefaut 2005; Kim et al. 2008; van der Vlist & Janssen 2010; W.D-C Man et al. 2009a)

Depressed muscle strenght

Muscle strength is the muscle capacity to develop maximal force. Alterations in muscle strength performances of COPD patients are not homogenous between various muscle groups (Mador &

Bozkanat 2001; Kim et al. 2008). Gosselink and colleagues (1996) have found that COPD upper limb strength was relatively preserved when compared to lower limbs (Mador & Bozkanat 2001). Diaphragm, adductor pollicis and abdominal muscles are relatively preserved in COPD patients compared with age-matched healthy control (Gosselink et al. 1996; Bernard et al. 1998; ATS & ERS 1999; Kim et al. 2008; W.D-C Man et al. 2009b) (Figure 4.a). Reasons behind differences between various skeletal muscles remain unclear, although many investigators have proposed daily muscle recruitment and activation as determinant factors (Kim et al. 2008). In general, depressed muscle strength appears to be particularly localized in to lower arms or, however, seems to involve primarily the lower limbs (Mador & Bozkanat 2001). The amount of the decrease was estimated about 20-30%, than compared with age-matched HC (Gosselink et al. 1996; Bernard et al. 1998; Serres et al. 1998; van der Vlist & Janssen 2010), although these differences disappear when quadriceps strength is normalized to the mid-thigh cross-sectional area (Bernard et al. 1998; W.D-C Man et al. 2009b). The degree of the strength decrease seems to be correlated with the disease stage severity (Bernard et al. 1998; Mador & Bozkanat 2001). Depressed muscle strength in COPD lower limbs is an important topic of research because it seems to be a relatively predictor of mortality, affecting the exercise capacity, increasing symptoms as dyspnea and deteriorating patients QoL (Gosselink et al. 1996; Swallow et al. 2007; Kim et al. 2008)

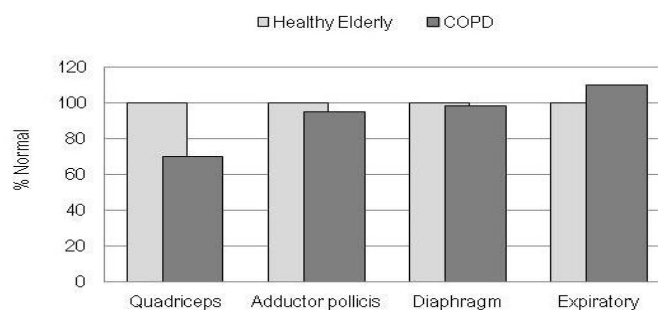


Figure 4.a – Localization of skeletal muscle weakness in COPD patients

(from W.D-C Man et al. 2009)

Reduction in muscle endurance

Muscle endurance is defined as the muscle capacity to maintain a certain force over the time and, together with the muscle strength, it's a determinant of the strength performance in COPD patients (Couillard & Prefaut 2005; Kim et al. 2008; W.D-C Man et al. 2009a). Information about the limb muscle endurance in patients affected by COPD is still conflicting (Mador & Bozkanat 2001). No homogenous reduction was observed in endurance COPD patients muscle capacity:

for instance, ventilatory muscles, particularly diaphragm, present different workloads than do the lower limb muscles. Caused by an increased work of breathing brought on by airflow obstruction and hyperinflation, ventilatory muscles are in a chronically overload state. Instead, lower extremity muscles are in a chronically underloaded state due to a chronic inactivity and disuse (Kim et al. 2008). Comparison between quadriceps and diaphragm showed the latter is relatively fatigue-resistant to exhaustive exercise; also it has been shown that COPD diaphragm fibers are metabolically more efficient than those from HC (W.D-C Man et al. 2009b). These findings suggest that dissimilar loading patterns could be the likely cause of biochemical and structural adaptations in ventilatory muscles, not present in lower limb muscles (Kim et al. 2008). Newell and colleagues (1989) did not find any changes in endurance capacity of the elbow flexors, but in Zattara-Hartmann study (1995) it was observed a significant reduction in adductor pollicis endurance (W.D-C Man et al. 2009b). However, several studies have confirmed the presence of alterations in endurance capacity of the lower limb skeletal muscle of COPD, due by a morphological and enzymatic deficiencies (Maltais, 1996; Whittom, 1998) and a change in mitochondrial oxidative capacity (Allaire et al. 2004; Kim et al. 2008). These alterations reduce endurance approximately of 30/50%, in patients with moderate COPD (Serres et al. 1998; ATS & ERS 1999; Kim et al. 2008) and increase quadriceps fatigability for equivalent workload (Mador et al. 2003; W.D-C Man et al. 2009b). Finally, this impairment seems to be positively correlated with physical activity index, FEV₁, and resting PaO₂ (Serres et al. 1998; Mador et al. 2003; Kim et al. 2008).

Structural characteristics of skeletal muscle dysfunction

In addition to the functional skeletal muscle abnormalities, loss of muscle performance is due also by a muscle structure changes, i.e. muscle atrophy, and a dysfunction of the remaining muscle tissue, as changes in fiber type size, fiber type distribution, muscle section, type of fiber oxidative capacity and metabolic capillary distribution (Couillard & Prefaut 2005; Kim et al. 2008; van der Vlist & Janssen 2010).

Muscle fiber atrophy

As in other chronic inflammatory condition, it has long been observed that a proportion of severe COPD patients develop a “cachexic” state with significant weight and muscle mass loss (E. F. M. Wouters 2002; W.D-C Man et al. 2009b). In 1993, Shols and colleagues demonstrated that about

of the 45% of stable COPD patients were either underweight or have a depletion in FFM, mainly in muscle mass (W.D-C Man et al. 2009b). Although there aren't results regarding the direct measurement of muscle mass of individual muscles, in several studies, radiological techniques have demonstrated that the lower limb muscles of COPD patients show a significant muscle atrophy, characterized by a reductions in mass, in mid-thigh and in calf muscle cross sectional area compared with matched HC (Wuyam et al. 1992; H.R. Gosker et al. 2000; H.R. Gosker et al. 2003; Hopkinson et al. 2007; W.D-C Man et al. 2009b; Mador & Bozkanat 2001). The amount of thigh muscle mass loss is relatively greater than the whole body weight, indicating a preferential loss of muscle tissue over other body tissues in COPD (Bernard et al. 1998; Kim et al. 2008). The degree to which fiber atrophy contributes to reduce the lower muscle strength in this patients remains yet unclear and is still on debate.

Fiber type shift

The latest results in research suggest that besides atrophy, dysfunction of the remaining muscle also contributes to the loss in COPD muscle function (Van der Vlist & Janssen 2010). The diaphragms of patients in severe disease stage showed an increased proportions of type I fibers as compared with HC. This was documented firstly by Levine and colleagues (1997), reporting that the proportion of type I fibers averages 64% of total fibers whereas the proportion of these fibers averages only 45% in control diaphragms (Levine et al. 1997). This rise in proportion of type I fibers in the diaphragm is evident only in severe COPD (Kim et al. 2008). Moreover, fiber type switching toward an increase in proportion of type I fibers can also be observed in other inspiratory muscles, such as parasternal intercostals (Kim et al. 2008). Instead, several studies about quadriceps muscles of patients with severe COPD found a significant redistribution of fiber type ratios, with a reduction in the proportion of the type I, i.e. slow-twitch oxidative, and an increase of the proportion of type IIb, i.e. fast-twitch glycolytic, fibers (H.R. Gosker et al. 2003; Mador & Bozkanat 2001). Whittom's study (1998) showed a 20% of decrease in fiber type I and an increase of 10% in fibers type IIb of COPD patients compared to healthy subjects (ATS & ERS 1999). Several studies reported oxidative fibres averaged at ~23% (even down to 19%) in the patients, whereas they average, as expected, 44% in the healthy sedentary subjects (Allaire et al. 2004; Remels et al. 2007; H.R. Gosker, van Mameren, et al. 2002; Couillard et al. 2003; Couillard & Prefaut 2005). These results clearly indicate a two-thirds reduction in the proportion of type I fibres in the peripheral muscles of COPD patients, which is unlikely to be accounted for by muscle disuse alone (Figure 4.b) (Couillard & Prefaut 2005; Mador & Bozkanat 2001).

Studies about histochemical composition of the vastus lateralis muscle in patients with moderate to severe COPD, found correlation between proportion of type I fibers, lung function and BMI. In addition, several investigators reported also an atrophy of the type I, IIa and IIx fibres (H.R. Gosker, M. P. K. J. Engelen, et al. 2002; W.D-C Man et al. 2009b). The findings suggest an increase in early fatigable type II fibers proportion leading to an increased muscle fatigue, with a consequently reduction in lower arms endurance performances (H.R. Gosker et al. 2000). Moreover, a lower oxidative enzyme activity (H.R. Gosker, Van Mameren, et al. 2002; F. Maltais et al. 2000; Wuyam et al. 1992) and mitochondrial density (Picard et al. 2008) have been shown in the vastus lateralis muscle of COPD patients comparing with HC (H.R. Gosker et al. 2007).

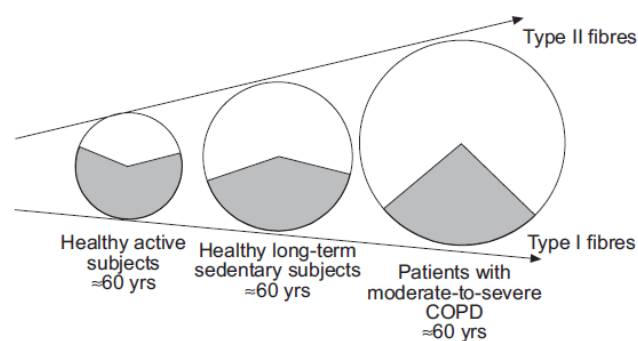


Figure 4.b – Histochemical proportion of type I (■) and type II (□) fibres observed in vastus lateralis of healthy active, long-term sedentary and COPD subjects.

(Couillard & Prefaut 2005)

Changes in fibre type distribution, low levels of oxidative enzyme activities and a low mitochondrial density suggest a reduced oxidative capacity of skeletal muscle in COPD, which is associated with an early increase in intracellular acidosis occurring at lower work rates when compared to HC (Van der Vlist & Janssen 2010). Lower capillary to muscle fiber ratio in vastus lateralis were found on COPD patients compared to HC (Eliason et al. 2010). In conclusion, the lower limb skeletal muscle of people affected by COPD do not function appropriately (Table 4.1).

Consequences of skeletal muscle dysfunction in patients with COPD

Exercise intolerance and dyspnea on exertion are considered the most common symptoms in patients with COPD (Kim et al. 2008), which reduced the QoL and increased the risk of premature death (Mador & Bozkanat 2001; Kim et al. 2008). These complaints cannot be explained entirely on the basis of a decline function and impaired gas exchanged: in fact, lung function impairments

Table 4.1 – Quadriceps muscle abnormalities in COPD

Abnormality	
Clinical	Reduced strength
	Increased fatigability
	Reduced endurance
	Reduced mid-thigh CSA
Structural	Reduced fiber type I proportion and increased fiber type IIx proportion
	Reduced fiber CSA
	Reduced capillary contacts to fiber CSA
Metabolic	Reduced oxidative enzyme capacity and increased glycolytic enzyme activity
	Increased intracellular acidosis
	Increased lactic acid
	Reduced PCr/P _i ratio

(from W.D-C Man et al. 2009b)

shows only a weak relation to exercise capacity, suggesting that other factors could play an important role in exercise tolerance in these patients (M.A. Spruit et al. 2004; Kim et al. 2008). Indeed, association between skeletal muscle function, FFM and exercise capacity (E. F. M. Wouters 2002; W.D-C Man et al. 2009b), improvements in muscle function and exercise tolerance (M.A. Spruit et al. 2004; Kim et al. 2008), and significant relationship between mid-thigh cross sectional area and mortality (Marquis 2002) suggest that muscle wasting may play important roles in exercise capacity in COPD patients. Decramer et colleagues (1997) shown also that a reduction in exercise capacity and the quadriceps weakness lead to disability and correlate with higher utilization of health care resources (Kim et al. 2008).

Mechanisms of skeletal muscle dysfunction in COPD patients

Skeletal muscle dysfunction in COPD patients can be attributed to a set of complex interactions between many factors, both systemic and local (Figure 4.c).

Inflammation

At present, it is clearly established the association between COPD and both systemic and local inflammation, characterised by an enhanced activation of circulating inflammatory cells, i.e. neutrophils and lymphocytes, a greater expression of surface adhesion molecules in circulating neutrophils, and an increased plasma level of cytokines, including tumor necrosis factor- α (TNF α), interleukin-8 (IL8), IL6 and its receptors tumour necrosis factor, as sTNF-R55 and sTNF-

R75, and C-reactive protein. This increased circulating levels of inflammatory cells induces a systemic oxidative stress (Couillard & Prefaut 2005; Kim et al. 2008; van der Vlist & Janssen 2010).

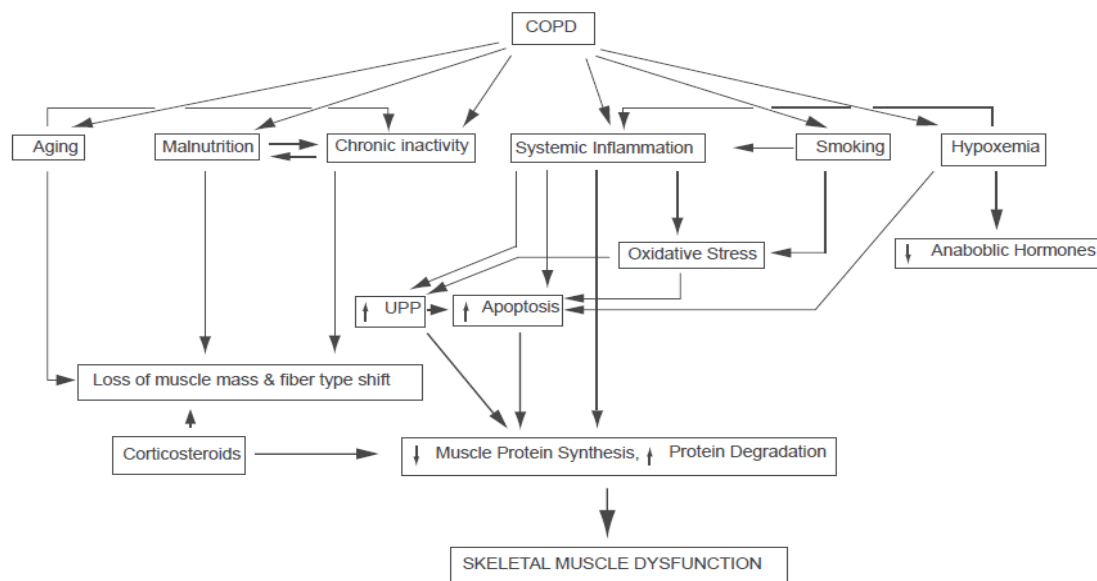


Figure 4.c – Potential mechanisms of skeletal muscle dysfunction in COPD patients
UPP, ubiquitin/proteosomal pathway

(from Kim et al. 2008)

One likely source of inflammation is the lungs, but no direct correlations have been found between sputum and plasma concentrations of inflammation markers in patients with mild to moderate COPD, suggesting contribution provided by other organs, such as the skeletal muscle. Some studies indicated association between systemic inflammation, abnormal body composition and muscle dysfunction, observing that serum levels of TNF α seem to be higher in COPD patients with reduced body mass, BMI and FFM (Van der Vlist & Janssen 2010). Moreover, several studies confirmed both ventilatory muscle, i.e. diaphragm and intercostal muscles, and lower limb muscle, such quadriceps, as sources of systemic inflammation. Inflammatory mediators involvement in skeletal muscle dysfunction is suggested by the observation that systemic inflammation markers correlate with poor muscle contractile performance in COPD patients. In Spruit's study (2003), quadriceps muscle strength correlates negatively with serum IL8 levels in COPD patients during exacerbations and with IL6 and TNF- α in aged COPD patients (Kim et al. 2008). Although the exact mechanisms have not yet been completely elucidated, the muscle dysfunction in COPD seems to be caused by alterations in both degradation and the synthesis rate of muscle proteins (Figure 4.d).

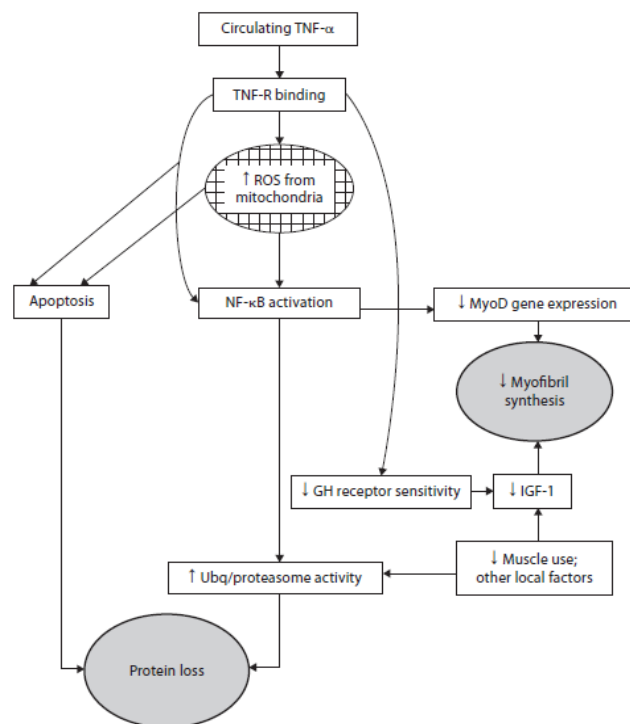


Figure 4.d – The possible effects of inflammation on muscle protein degradation and synthesis.

(from Van der Vlist & Janssen 2010)

Several studies shown that systemic inflammation may trigger a catabolic/anabolic imbalance that results in skeletal muscle wasting and reduced strength (Jagoe & M. P. K. J. Engelen 2003; Couillard & Prefaut 2005). Therefore, inflammation seems to have a negative impact on muscle protein catabolism, affecting the growth and the contractile muscle performances of patients with COPD, via different cytokine-mediated pathways, particularly TNF- α (Couillard & Prefaut 2005). In fact, TNF- α promotes muscle wasting by enhancing the activity of the ubiquitin proteasome pathway and inducing apoptosis and muscle atrophy. Moreover, TNF- α might also reduce the oxidative capacity of the muscles through the inhibition of mitochondrial biogenesis and exerts acute inhibitory effects on acute muscle contractility, depressing sensitivity of myofilament proteins to Ca^{++} and to enhanced generation of ROS and RNS (Kim et al. 2008; van der Vlist & Janssen 2010). Although the involvement of systemic inflammation in peripheral muscle wasting and weakness of COPD has never been directly demonstrated, all the findings highlighted before strongly support a causal relationship.

Malnutrition

Reduction in BMI and a loss of FFM significantly correlate with an increased morbidity, a poor QoL, a reduced exercise performance and an high mortality in COPD patients (Bolton et al.

2004). It was established that over 30% of COPD patients undergoing pulmonary rehabilitation experience nutritional depletion. Whereas malnutrition is the result of an imbalance between energy intake and energy expenditure, nutritional status could be an important systemic factor that may affect the exercise performance and skeletal muscle dysfunction in COPD patients. A reduced dietary intake in these patients has been attributed to symptoms such as postprandial dyspnea, early satiety, fatigue and loss of appetite. Instead, elevated energy expenditure has been attributed to increased work of breathing, thermogenic effects of bronchodilators and systemic inflammation. An impairment of nutritional status could affect the skeletal muscle structure and contractile performance, as seen in patients with anorexia nervosa (Kim et al. 2008).

Corticosteroid use

Patients affected by COPD are usually treated with corticosteroids either as “short-burst” therapy, for acute exacerbations, or as long-term low-dose “maintenance” therapy, for controlling chronic symptoms. Therefore, several authors have investigated the possibility that COPD peripheral muscles experience a toxic myopathy, i.e. “steroid-induced myopathy”. Firstly it was observed that a long-term high doses of steroids mediate detrimental effects on the structure and function of COPD peripheral muscle, reducing strength and atrophy of both ventilator and limb muscles of COPD patients (Kim et al. 2008). In subsequent studies, others studies reported a significant reduction in quadriceps strength, strongly associated with quadriceps atrophy (Bernard et al. 1998; Couillard & Prefaut 2005; Kim et al. 2008). Deleterious effects of corticosteroids on skeletal muscle function have been attributed to inhibition of signaling pathways involved in protein synthesis, as well as to augmented protein degradation, which itself is a result of increased expression and activity of the ubiquitin proteasome pathway, including upregulation of pathway regulators known as “Forkhead transcription factors” (Kim et al. 2008). However, it was established that a short-term corticosteroid treatment did not affect quadriceps muscle strength or metabolic parameters during exercise, suggesting that this treatment does not in and of itself cause skeletal muscle weakness in COPD patients (Hopkinson et al. 2004; Couillard & Prefaut 2005; Kim et al. 2008).

Inactivity

PA is an important clinical parameter related to lung function, hospitalization and mortality in COPD patients (W.D-C Man et al. 2009a). In fact, active COPD people have lower risk of both COPD-related hospital admissions and mortality (Garcia-Aymerich et al. 2006; Watz et al. 2008). Several studies confirmed that both current PA level, i.e. planned and structured regular ExT performed deliberately, and DPA, i.e. workplace and household physical activity, in COPD are lower than those in sedentary healthy subjects control group (Mador M.J., 2011; Gouzi et al. 2011). The fact that a great proportion of COPD patients show a sedentary lifestyle (Chapter 3) led many investigators to attribute skeletal muscle dysfunction in these patients to physical deconditioning (Pitta et al. 2005; Couillard & Prefaut 2005; Kim et al. 2008; W.D-C Man et al. 2009a; van der Vlist & Janssen 2010). This concept was supported by observations that a longer duration of inactivity (Serres et al. 1998) in COPD causes greater alterations due to the dose-response effect of PA (Steele et al. 2000). Physical inactivity induces adaptive changes in skeletal muscles, including reduction in proportions of type I fibers, attenuation of oxidative enzyme capacity, regulators of mitochondrial biogenesis (PPARs and PGC-1 α), fiber atrophy, reduction of antioxidant enzyme levels and lower capillary density (Kim et al. 2008). However, recent trials suggested that physical inactivity alone does not sufficiently to explain COPD skeletal muscle dysfunction. First of all, these muscle alterations are more severe in COPD patients than sedentary HC (Pitta, Troosters, et al. 2008; Gouzi et al. 2011). Secondly, reductions in quadriceps muscle endurance was observed between COPD and HC with similar level of PA (Kim et al. 2008). Indeed, while sedentary lifestyle is associated with reduction of quadriceps muscle type I fiber proportion, from 60%–65% in healthy active control subjects to about 40% in inactive subjects (Proctor et al 1995; Houmard et al 1998), the proportion of type I fibers in quadriceps muscles of COPD patients reaches as low as 19% (H.R. Gosker, Van Mameren, et al. 2002; Allaire et al. 2004; Couillard & Prefaut 2005; Kim et al. 2008; Richardson et al 2004). Moreover, it has been shown that prolonged periods of ExT exerts a relatively small influence on the proportion of type I fibers in quadriceps muscles of COPD patients, and only partially reverses reductions in oxidative enzyme activities in the muscle (F. Maltais et al. 2000). Finally, several studies found contradictory results regarding relationship between PA and limb muscle endurance in COPD. Serres and colleagues (1998) described a positive correlation while Gosker and colleagues (2003) did not observe any relationship between these parameters (Kim et al. 2008). Therefore, physical inactivity is almost certainly an important factor in skeletal muscle dysfunction of COPD patients, but the most recent data indicate that disuse only partly explains

the severe morphological, metabolic and functional abnormalities observed in COPD peripheral muscle (Couillard & Prefaut 2005; Kim et al. 2008; van der Vlist & Janssen 2010).

Aging

The well-recognized presence of a systemic inflammation may be considered as a contributor to the development of comorbid conditions and these disorders can be seen as manifestations of COPD or vice versa. Moreover, aging is characterized by a progressive, generalized impairment of function and amplification of the inflammatory response that results in an increased vulnerability to environmental challenge and an increased risk of disease. Therefore, an accelerated aging is a further process that could account for both the local lung effects of COPD and its comorbidities (Han et al. 2010). In fact, Lopez and colleagues (2006) have reported the importance of aging in relative risks of COPD-related mortality (Figure 4.f) (A. D. Lopez, Shibuya, et al. 2006)

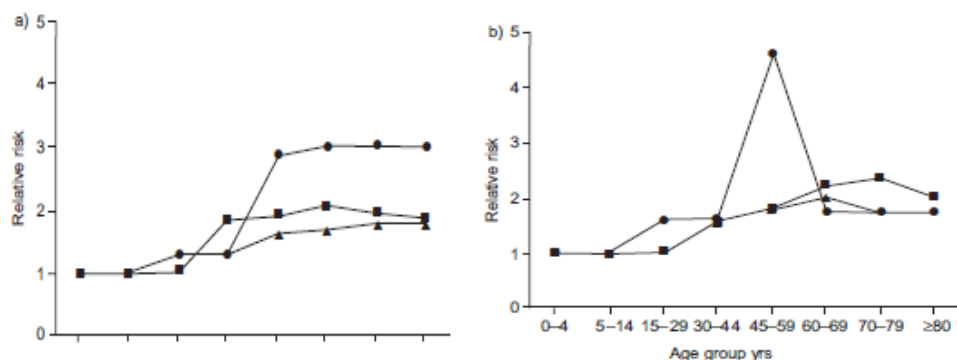


Figure 4.f – Comparison of relative risk of COPD-related mortality by age in different gender for a) males and b) females.
 ▲ USA burden of disease study; ● Global Burden of Disease Study; ■ Model estimates

(from Lopez et al. 2006)

“It has been well established that limb muscles of older individuals are significantly smaller and have significantly more fat and connective tissues than those of younger individuals. In addition, limb muscle strength, particularly that of the quadriceps muscle, has been reported to be about 39% lower in men in their seventies as compared to men in their twenties. Furthermore, declines in muscle strength with aging correlate with the degree of atrophy of type II fibers and are not limited to limb muscles. Indeed, maximum transdiaphragmatic pressure ($P_{di_{max}}$) measured at various lung volumes is reportedly to be approximately 25% lower in elderly subjects as compared to that measured in young subjects. Similarly, 13% and 23% reductions in sniff P_{di} and twitch P_{di} (generated by phrenic stimulation) have been observed in elderly subjects, as

compared to young subjects. These studies clearly indicate that aging contributes to poor skeletal muscle contractile performance in COPD patients.” (Kim et al. 2008, pag. 645).

Hypoxemia

Several studies about healthy subjects have established that exposure to high altitude hypoxia over a few months is associated with significant detrimental effects on specific skeletal muscle properties: functional, i.e. reduced strength and endurance (Caqueland et al. 2000), morphological, i.e. atrophy, and metabolic, i.e. reduced Krebs cycle enzyme activity. Many COPD patients develop chronic moderate-to-severe hypoxemia or may present repeated episodes of hypoxemia due to exercise-induced desaturation or sleep apnoea (Couillard & Prefaut 2005; Kim et al. 2008). Although there is no direct proof of hypoxemia involvement in reducing skeletal muscle functionality, there are circumstantial evidences suggesting the role of hypoxemia as a contributor factor in deterioration of COPD skeletal muscle performance. For instance, the proportion of type I fibers in quadriceps muscles of COPD patients was reported to be significantly lower in hypoxemic as compared with non-hypoxemic patients (H.R. Gosker, Van Mameren, et al. 2002) and strongly correlated with their resting Pa,O₂ (Jakobsson et al. 1990). Serres et colleagues (1998) confirmed correlation between quadriceps endurance capacity and resting Pa,O₂ in COPD patients (Serres et al. 1998; Couillard & Prefaut 2005; Kim et al. 2008). Greater levels of exercise-induced lipid peroxidation and oxidized proteins in hypoxemic COPD patients quadriceps muscles than non-hypoxemic (Koechlin et al. 2005). Also maximum diaphragm force and diaphragm endurance are both significantly reduced in COPD patients with chronic hypoxemia, although inhalation of O₂ for 15min elicits an increase in diaphragm strength and endurance (Couillard & Prefaut 2005; Kim et al. 2008). Despite molecular and cellular mechanisms underlying hypoxemia deleterious effects on skeletal muscle still need to be elucidated, literature data strongly indicate hypoxemia as a direct and indirect factor on contractile processes, eliciting skeletal muscle dysfunctions (Couillard & Prefaut 2005; Kim et al. 2008).

Smoking

“ Most COPD patients are current or previous smokers, making smoking the main risk factor for COPD. However, the potential effects of smoking on skeletal muscle function remain unclear. A recent study by Montes de Oca and colleagues (2008) suggests that smoking *per se*,

independent of the presence of COPD, elicits skeletal muscle atrophy, as indicated by a reduction in the cross-sectional areas of both type I and II fibers, a reduction in the expression of constitutive nitric oxide synthases and augmentation of the number of low oxidative and highly glycolytic muscle fibers. The deleterious effects of smoking on muscle metabolism have been further analyzed by Petersen and colleagues (2007), who have reported that heavy smoking (≥ 20 cigarettes/day for ≥ 20 years) elicits no change in whole body protein breakdown but significantly attenuates quadriceps muscle protein synthesis and augments the expression of both myostatin (inhibitor of muscle growth) and atrogin-1 (E3 ligase). These results suggest that smoking induces skeletal muscle fiber atrophy as a result of inhibition of protein synthesis, rather than as a result of increased protein degradation. These deleterious effects of smoking on skeletal muscle function may be mediated directly by nicotine or by other toxic byproducts of cigarette smoke, or indirectly as a result of changes in lifestyle and physical activity ” (Kim et al. 2008, pag.646).

Local factors

Skeletal muscle dysfunction in COPD patients has also been attributed to local factors within skeletal muscle fibers. These local factors include oxidative and nitrosative stress of muscle fibers and changes in balance between protein synthesis and degradation, eliciting changes in protein expression, protein function, reduction of muscle mass and depression of contractile functions (Couillard & Prefaut 2005; Kim et al. 2008).

Oxidative stress

There is now considerable evidence of both local and systemic oxidative stress in COPD patients, which is involved in the pathogenesis of local lung inflammation as well as in systemic phenomena, such as skeletal muscle dysfunction, increasing cardiovascular risk of mortality (MacNee 2005). Cachexia and loss of FFM of COPD patients may involve oxidative stress. Skeletal muscle is exposed continuously to changes in the redox environment as occurs during exercise (MacNee 2005). Although in normal skeletal muscle fibers, ROS are produced at relatively low levels and play a positive role in maintaining muscle contractility, patients affected by COPD show a significant higher level production of ROS and RNS (MacNee 2005; Couillard & Prefaut 2005; Kim et al. 2008). Development of oxidative and nitrosative stress has been documented in COPD skeletal muscles both at rest, in DPA and after ExT (Couillard et al. 2002; Couillard et al. 2003; Couillard & Prefaut 2005; Kim et al. 2008). In resting quadriceps muscles of severe COPD, disturbed redox homeostasis was observed, i.e. glutathione levels and

concentrations of glutamate are reduced whereas the levels of lipid peroxidation products are significantly higher than those detected in control subjects. The impairment of glutathione metabolism and the increased lipid peroxidation suggest an oxidative damage in skeletal muscle of COPD patients (MacNee 2005; Kim et al. 2008). Moderate to severe COPD patients show elevated ROS-induced DNA damage in peripheral blood mononuclear cells, plasma uric acid, blood oxidized glutathione and lipid peroxides levels at the end of whole body ExT. These evidences suggest systemic oxidative stress in COPD patients, even during DPA (Kim et al. 2008). The excessive ROS and/or NOS produced within muscle fiber lead to develop oxidative stress state, affecting mitochondrial and myofilaments, leading to apoptosis, mitochondrial respiratory chain dysfunction, and/or an alteration in myofilament contractile properties (Figure 4.g) (MacNee 2005; Couillard & Prefaut 2005; Kim et al. 2008).

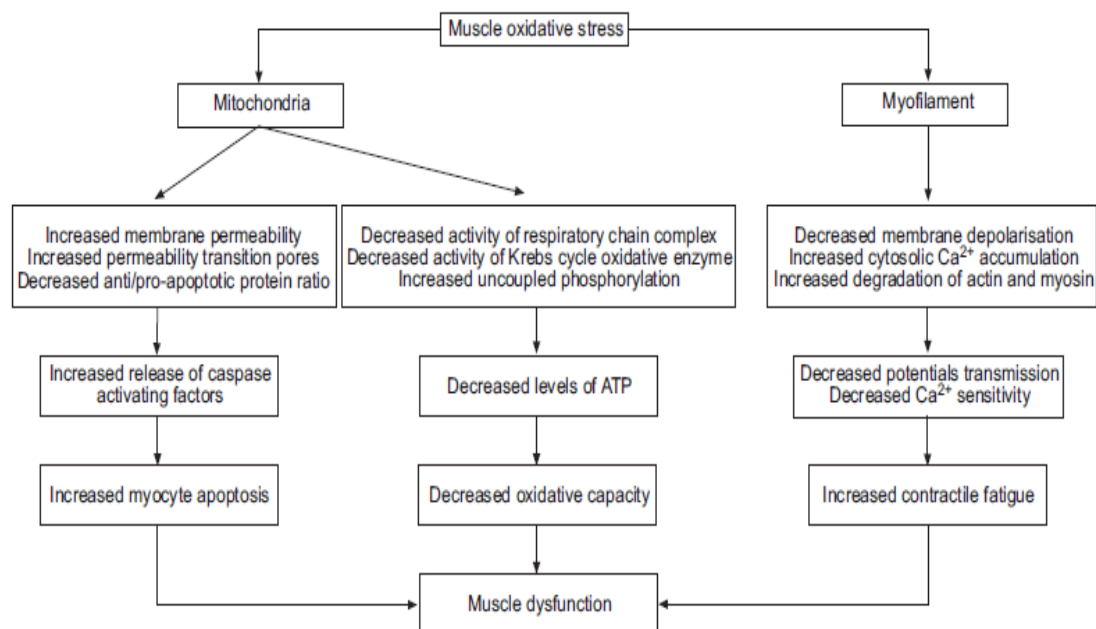


Figure 4.g – Molecular mechanisms that may underlie oxidative stress-induced peripheral muscle dysfunction.

(from Couillard & Prefaut 2005)

Regulation of protein synthesis/degradation

Regulation of muscle mass is a dynamic process involving a delicate balance between hypertrophic, i.e. protein synthesis, and atrophic, i.e. degradation, signaling pathways. Generally it is assumed that COPD peripheral muscle atrophy is due to imbalance between protein synthesis and degradation, in favor of the latter (Kim et al. 2008). Increased protein degradation activated by inflammatory factors seems to be partly responsible for muscle wasting in COPD, although some studies suggest also a role of inflammatory cytokines to affect protein synthesis (Van der Vlist

& Janssen 2010). “ Debigare and colleagues (2003) have shown that limb muscle atrophy in COPD patients may be due to an increase in the ratio of catabolic factors, such as IL6 and cortisol, to anabolic factors, i.e. testosterone, dehydroepiandrosterone and insulin-like growth factor-1 [IGF-I]. Increased IL6, ROS and RNS levels are expected to upregulate the ubiquitin-proteasome components, while increased anabolic factors are expected to downregulate these components. [...] Debigare and colleagues (2008) employed microarray technology to compare gene expression profiles in quadriceps muscles of four patients with moderate or severe COPD to those of control subjects. They reported significant upregulation of FoxO1 and FoxO3 transcription factors in quadriceps muscles of COPD patients. Both transcription factors promote muscle atrophy through inhibition of IGF-I-mediated muscle growth and by upregulating the expression of atrogin-1 and MuRF-1 [...]. Activation of the ubiquitin-proteasomal pathway is not limited to the limb muscles of COPD patients. Activity of the 20S proteasome and atrogin-1 expression have recently been shown to be upregulated by 3-fold in the diaphragms of patients with mild to moderate COPD (Ottenheijm et al. 2006). While these studies imply that the proteasomal pathway contributes to proteolysis of skeletal muscle proteins in COPD patients, no information is as yet available about the relative contributions of the lysosomal, calpain and caspase pathways to the atrophy process. Systematic and thorough investigations of how, where, and when these pathways are activated, and thus contribute to muscle protein degradation, are clearly needed in relation to patients with COPD. ” (Kim et al. 2008, pag. 651).

Vascular density and capillarization

An adequate capillarization is essential for maintenance of adequate oxygen supply required for normal muscle function (Eliason et al. 2010). However, little information is available about changes in capillary density in skeletal muscles of COPD patients. Some studies reported a lower capillarity to muscle fiber ratio in COPD patients vastus lateralis muscle compared to HC. Decreased capillarity was estimated about ~47% lower than those measured in the same muscle of age-matched HC (Kim et al. 2008). Additionally, Eliason and colleagues (2010) highlighted a positive correlation between degree of muscle capillarization and degree of airflow obstruction. Considered evidences of increased proportion of type IIa fibers, decreased proportion of type I in tibialis anterior muscle, attenuation of oxidative enzymes activities, and presence of hypoxemia, the reduction of muscle capillarization seems to be due to a rearrangements of capillary fiber geometry which affect the exercise capacity in COPD patients (Eliason et al. 2010). Reduction in skeletal muscle mitochondrial density and volume are also been observed in vastus lateralis muscle of COPD patients (H.R. Gosker et al. 2007). In conclusion, both capillary and

mitochondrial densities reduction in COPD skeletal muscles seem to provide deleterious effects on muscle oxidative capacity since it is associated with augmentation of serum and muscle lactic acid levels during exercise and an early onset of contractile fatigue (Kim et al. 2008).

PROMOTING ACTIVE LIFESTYLE & CHANGE BEHAVIOR IN COPD

Promotion of Active Change Behavior in Adults and Elderly people

Considering the evidences about the benefits of PA in order to improve health and QoL in several target populations, the PA on prescription has attracted attention in recent years (US Preventive Services Task Force, 2002; Sørensen et al., 2006; Kallings 2008) and the role of community-based interventions to promote physical activity has emerged as a critical piece of an overall strategy to increase active behaviors among worldwide populations (Kahn et al. 2002). Indeed, in 1995, the Centers for Disease Control and Prevention, i.e. CDC, and the American College of Sports Medicine, i.e. ACSM, published a preventive recommendation that every adult should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week (Pate et al. 1995). Subsequently, in 2007, ACSM and the American Heart Association, i.e. AHA, provide an update to this recommendation (Haskell et al. 2007). The update was more inclusive and provided recommendations for moderate-intensity aerobic activity, vigorous-intensity aerobic activity, and muscle-strengthening activity. Moreover, it was highlighted that many adults should exceed the minimum recommended amount of activity. Furthermore, ACSM deemed that it would appropriate to issue a separate recommendation between adults and older adults. Therefore, specific guidelines for men and women age ≥ 65 years and adults age 50 to 64 years with clinically significant chronic conditions and/or functional limitations were provided (M. E. Nelson et al. 2007). Differences between adults and older adults PA recommendation were highlighted before, i.e. chapter 3. However, as recommended by ACSM guidelines, the promotion of physical activity in adults, older adults and people with chronic diseases should avoid ageism that discourages from reaching their potential in order to become more physically active (M.E. Nelson et al. 2007; Haskell et al. 2007). Considering also that adults and older adults with a medical condition for which PA is therapeutic should engage in ExT in order to treat their conditions and reduce risk of developing other comorbidities, several interventions that promote the adoption and maintenance of lifestyle physical activity are being developed (M. E. Nelson et al. 2007; Haskell et al. 2007; Heesch et al. 2003).

Motivations to engaging in a physical activity

Although physical activity is a primary factor that contributes to health and to an healthy aging (Haskell et al. 2007; M. E. Nelson et al. 2007), the majority of adults and elderly people do not meet current recommendations of moderate activity for 30 minutes on most days of the week (AARP et al. 2001; Heesch et al. 2003; Rhodes et al. 2009). Given the aging demographics, an examination of the adults and elderly people motivational aspects to engage in a PA is required to implement the interventions effectiveness on behavior change (Dacey et al. 2008). Indeed, motivation represents one of the most important analyzed variables in the assessment of the behavior change. Motivation has been the subject of attention from a host of individual, including philosopher and psychologist. Psychologist, in particular, have provided some general definitions of the construct. A widely accepted definitions of motivation is that it represents the hypothetical construct used to describe the internal and/or external forces that lead to the initiation, direction, intensity and persistence of behavior. Thus motivation leads to actions (Vallerand 2004). One of the difficulties in defining motivations is that it is not directly observable. Over the year, psychologists have come to realize the experience of different type of motivation. Self-determination theory, i.e. SDT (Ryan & Deci 2002) provides an excellent framework for examining physical activity motivation: SDT posits that motivation exists along a continuum that includes Amotivation, Nonself-determined Extrinsic Motivation, Self-determined Extrinsic Motivation, and Intrinsic Motivation (Vallerand 2004; Dacey et al. 2008). Research studies with younger adults reported that Self-determined Extrinsic and Intrinsic forms of motivation distinguish those who are regularly active from individuals who are sedentary or less active (Mullan et al. 1997; Ingledew et al., 1998). In terms of gender, studies with younger adults suggest that women are more likely to report higher levels of Nonself-determined Extrinsic motives to body image and appearance (Frederick et al. 1996; Ryan et al. 1997) as well as self-determined extrinsic motives of fitness and social affiliation (Gill et al. 1996). In older adults, an increase of intrinsic and self-determined extrinsic motives seems to be positively associated with more physical activity behavior (Dacey et al. 2008).

Intrinsic Motivation

Intrinsic motivation is represented in behaviors that are performed for their inherent interest and enjoyment of the activity itself. Indeed, it refers to engaging in an activity for itself and for the pleasure and satisfaction derived from participation. Therefore, more an individual will be likely to

engage a particular activity, more that behavior will be persisted. It was proposed three types of intrinsic motivation:

- Intrinsic motivation to know, i.e. engaging in the activity for the pleasure of learning;
- Intrinsic motivation toward accomplishments, i.e. engaging in the activity for pleasure to trying to surpass oneself;
- Intrinsic motivation to experience stimulation, i.e. engaging in the activity out of sensory and aesthetic pleasure (Vallerand 2004; Dacey et al. 2008).

Extrinsic Motivation

When extrinsically motivated, individuals do not engage in the activity out of pleasure but rather do so to derive some kind of reward that are external to the activity itself. Avoiding punishment also pertains to extrinsic motivation. In 1985, Deci and Ryan proposed the existence of a number of types of extrinsic motivation that vary in terms of their inherent levels of self determination. Nonself-determined Extrinsic Motivation is characterized by controlled behavior that is performed to avoid immediate negative consequences or to obtain ego enhancements. Self-determined Extrinsic Motivation is present when an individual performs a behavior for an extrinsic reason, but for personally valued and endorsed outcomes. Therefore, from the lowest to the highest level of self determination, these types of extrinsic motivation are:

- External regulation, i.e. regulated through external means such as obtaining rewards and avoiding constraints;
- Introjected regulation, i.e. referred to start to internalize the reasons of the action;
- Identified regulation, i.e. referred to identification of extrinsic motives;
- Integrated regulation, i.e. referred to engaging in an activity from an extrinsic perspective in a “choiceful” manner (Vallerand 2004; Dacey et al. 2008).

Amotivation

Besides intrinsic and extrinsic motivation, Deci and Ryan (1985) have proposed a third motivational concept namely, Amotivation, to fully understand human behavior. When amotivated, individuals experience a lack of contingency between their behaviors and outcomes. Their behaviors are neither intrinsically nor extrinsically motivated. Amotivated behaviors are the least self-determined because there is no sense of purpose and no expectations of reward or possibility of changing the course of events. Amotivation can thus be seen as similar to learned

helplessness where the individual experiences feelings of incompetence and expectancies of uncontrollability (Guay et al. 2000; Dacey et al. 2008).

Determinants of Intrinsic and Extrinsic Motivation

Motivation is present in people at the three levels of generality, i.e. global, contextual and situational level. Research reveals that several types of variables produce important effects onto the levels of generality. These variables could be identified in Individual, Environmental and Task variables (Vallerand 2004; Hemmingsson et al. 2001).

Individual Variables

Individual variables could be subdivided into several subcategories, i.e. intrapersonal, interpersonal and socio-cultural determinants. The intrapersonal determinants are influenced by biologic, i.e. genetic differences, health status, chronic diseases, obesity, demographic, i.e. age, gender, education, occupation, ethnicity, cognitive, i.e. self-efficacy, self-health perception, stress, enjoyment, perceived benefits, expectations, attitude, perceived barriers and risk, and behavioral, i.e. successful chance and transferability, factors (Vallerand 2004; Schutzer & Graves 2010; Stiggelbout et al. 2006). Indeed, the elderly most frequently cite poor health as the leading barrier to both physical activity and exercise: perceived health problems, illness, injuries and pain emerged as the most common barriers to exercise. Also, lack of knowledge and understanding of the relationship between moderate exercise activity and health is an especially relevant barrier (Schutzer & Graves 2010). One of the most potent and frequently mentioned psychological mediators of successful behavior change is self-efficacy. Self-efficacy is highly situational, i.e. one can have high self-efficacy for weight training and, conversely, low self-efficacy for aerobic dance. McAuley and colleagues (1994) found that previously sedentary middle-aged adults significantly improved adherence to a 20-week walking program with a relatively simple information program, specifically aimed at increasing self-efficacy. Also it was found that self-efficacy enhancement was particularly important in the early phases of behavior change, and less important as physical activity become less psychologically demanding. Interpersonal determinants are influenced by emotional, instrumental, informational and appraisal support. Receiving support and encouragement from other people, such as family members, general practitioner and specialist could be reduced anxiety and enhanced motivation (Hemmingsson et al. 2001; Cress et al. 2004; Cress et al. 2006; Kahn et al. 2002; Vallerand 2004). Moreover, it was observed that a

prescription of PA in primary care seems to increase patients' behavior change (N. H. Williams et al. 2007; Kallings et al. 2008) and that the attitude and knowledge of general practitioners, specialists and nurses on health and PA promotion could influence the acquisition process of an healthy lifestyle (Geense et al. 2013; Schutzer & Graves 2010). Therefore, according to Deci and Ryan's self-determination theory, social factors influence motivation through their impact on one's perceptions of competence, autonomy and relatedness. Because individuals experience the needs to feel competent, autonomous, and related to significant others in their interaction, activity that allow people to satisfy these needs will be engaged in choicefully and on a regular basis. Variables that nurture those needs help intrinsic motivation and identified regulation to flourish. Variables that thwart those needs produce negative effects on the latter types of motivation and facilitate the development of external and introjected regulation and amotivation (Vallerand 2004)

Environmental Variables

The physical environment can also present as a potential barrier to exercise adherence. Environmental variables could be influenced by both by climatic and seasonal influences, available PA structures, and socio structural context (Vallerand 2004). Environments with available and convenient resources used both for exercise and physical activity performance, such as sidewalks, parks, recreation centers, and fitness facilities, make it easier for people to be exercise. Conversely, environments with high crime decrease the likelihood of people becoming more active (Schutzer & Graves 2010). Several studies, investigating the adherence at ExT programs of obese people (Jakicic et al. 1999 ; Perri et al. 1997) found that a more easily access to PA equipment and structures improved significantly the activity levels, the weight loss maintenance and/or loss, recordering also a lower drop-out rate (Hemmingsson et al. 2001).

Task Variables

A part from the many psychological, behavioral, social and environmental influences of physical activity, there is also research indicating that activity bout adaptations of volume, type, intensity, duration and frequency may influence behavior change. Indeed, task differ in terms of their intrinsic properties in that certain task are more enjoyable than others. Thus, it is not surprising that certain tasks generate higher levels of situational intrinsic motivation than do others. Moreover, individual differences and environmental variables may affect perceptions of task in such a way that even dull task may, at times, be experienced as enjoyable.

For example, Chao and colleagues (2000) pointed out that many elderly deem the adoption of moderate physical activity as time consuming. Time commitments include the time needed to perform activity and the time required for travel to an exercise facility. This time commitment increases substantially for those who rely on public transportation. Furthermore, these investigators maintained older adults tended to view exercise as a recreational pursuit instead of necessary medical therapy (Schutzer & Graves 2010). Therefore, incorporating a comprehensive and individualized behavioral management strategy in physical activity interventions can help maximize recruitment, increase motivation for exercise progression, and minimize attrition (Hemmingsson et al. 2001; Vallerand 2004; Cress et al. 2006; Rhodes et al. 2009).

Models of Behavior Change

Encouraging and supporting patients to embark on PA lifestyle changes is an everyday challenge faced by many health professionals. Although many public health intervention are developed without explicit reference to theory, evidence suggests that the explicit use of theory will significantly improve chances of effectiveness (Hutchison et al. 2009). During the years, several theory were developed in order to lead interventions to be more effective in changing physical activity behavior, such as the Health belief model, i.e. HBM (Houchbaum, 1958), the Theory of Reasoned Action, i.e. TRA, and the Theory of Planned Behavior, i.e. TPB, (Ajzen 1975; Ajzen, 1991), the Precaution Adoption Process Model, i.e. PAPM, (Weistein, 1988), the Socio-cognitive theory, i.e. STC, (Bandura 1986) and the Ecologic model (Sallis & Owen, 1996). However, the most commonly adopted theoretical frameworks for PA behavior change interventions are the Transtheoretical Model, i.e. TTM (Prochaska & DiClemente, 1983) and the Stages of Motivational Readiness for Change Model, i.e. SOC (Marcus, Rossi, Selby et al. 1992).

The Transtheoretical Model

The TTM is an integrative model of behavior developed from a comparative analysis of leading theories of psychotherapy and behavior change (Lowther et al. 2007; Hutchison et al. 2009). Since its conception, the model has been applied to a variety of behavior change contexts such as substance abuse, diet and PA (Hutchison et al. 2009). In 1983, Prochaska and DiClemente reported that smokers who 'self-changed' their behavior used the processes to progress through a series of stages. Initially it was thought that progress through these 'stages of change' was linear, but subsequently a spiral pattern of change has been reported, recognizing that people

may relapse on several occasions while trying to change behavior. The TTM evolved to encompass two further constructs: decisional balance and self-efficacy. Decisional balance relates to individuals weighing up of the benefits and costs of changing behavior. The benefits and costs appear to be particularly relevant for understanding and predicting movement in the first three stages, but during the action and maintenance stages, these decisional balance measures are far less prominent predictors. Self-efficacy is the situation-specific confidence people have that they can maintain a behavior change. This construct was integrated into the TTM from Bandura's (1977, 1982) self-efficacy theory. In general, as progression is made through the stages of change, self-efficacy is seen to increase (Prochaska & Marcus, 1994). (Lowther et al. 2007). Therefore, the TTM has evolved in a multidimensional design model including the facets of the stages of change, the processes of change, self-efficacy, and decisional balance. When applying the TTM as a theoretical framework to develop behavior change interventions, a good understanding of each dimension and how they interact with one another needs to be demonstrated (Hutchison et al. 2009).

The Stages of Motivational Readiness for Change Model

The stages of change identified by the TTM have been applied to physical activity to form the Stages of Motivational Readiness for Change Model (Marcus, Rossi, Selby et al. 1992). Specifically the stages include Precontemplation, Contemplation, Preparation, Action and Maintenance (Marcus et al. 2003). In the Precontemplation stage, individuals are sedentary and have no intention of becoming more active in the next six months. In Contemplation, individuals are also sedentary but are considering being more active in the next six months. The Preparation stage signifies that the person is intending to become more active in the very near future, usually the next month. They may also have actually started some activity but not enough to meet current recommendations (Pate et al., 1995). Individuals in the Action stage are physically active to recommended levels but only in the last six months. Action is the least stable stage and is also when people are at most risk from relapse (Prochaska & Marcus, 1994). The Maintenance stage occurs when the individual has been active to recommended levels for longer than six months. In comparison to action, maintenance is stable, but there is still risk of relapse (Lowther et al. 2007; Marcus et al. 2003). Marcus and Simkin (1993) have developed a four-item self-report questionnaire that categorizes individuals into one of the five stages of change (Figure 5.1). Moreover, as with the stages of change, Marcus and colleagues (1992) showed that the 10 processes of change, i.e. five behavioral processes and five cognitive processes, could be

generalized to exercise behavior and suggested that these processes can be organized in a hierarchical manner consisting of two higher-order constructs, experiential and behavioral (Figure 5.2). Marcus and colleagues (1992) went on to show that the experiential processes are more important in understanding and predicting progress in the early stages of change but the behavioral processes appear to be more important in the latter stages. Thus it was argued that successful behavior change depends upon engaging the right process at the right stage and if the key processes of change can be identified that facilitate movement from one stage to the next, interventions can be designed to target those key processes (Lowther et al. 2007; Marcus et al. 2003; Marcus, Simkin, Rossi & Pinto, 1996).

For each of the following questions, please circle Yes or No. Please be sure to read the questions carefully.

Physical activity or exercise includes activities such as walking briskly, jogging, bicycling, swimming, or any other activity in which the exertion is at least as intense as these activities.

1) I am currently physically active. **NO** **YES**

2) I intend to become more physically active in the next 6 months. **NO** **YES**

For activity to be regular, it must add up to a total of 30 minutes or more per day and be done at least 5 days per week. For example, you could take one 30-minute walk or take three 10-minute walks for a daily total of 30 minutes.

3) I currently engage in regular physical activity. **NO** **YES**

4) I have been regularly physically active for the past 6 months. **NO** **YES**

Scoring Algorithm:

Precontemplation: Question One = No; Question Two = No

Contemplation: Question One = No; Question Two = Yes

Preparation: Question One = Yes and Question Three = No

Action: Question One = Yes; Question Three = Yes; and Question Four = No

Maintenance: Question One = Yes; Question Three = Yes; Question Four = Yes

Figure 5.2 –The Physical Activity Stages of Changes Questionnaire, i.e. PASC-q

(from Marcus et al. 2003)

Cognitive strategies	Behavioral strategies
Increasing knowledge Encourage your client to read and think about physical activity.	Substituting alternatives Encourage your client to participate in physical activity when she is tired, stressed, or unlikely to want to be physically active.
Being aware of risks Provide your client with the message that being inactive is very unhealthy.	Enlisting social support Encourage your client to find a family member, friend, or co-worker who is willing and able to provide support for being active.
Caring about consequences to others Encourage your client to recognize how his inactivity affects his family, friends, and co-workers.	Rewarding yourself Encourage your client to praise himself and reward himself for being physically active.
Comprehending benefits Help your client to understand the personal benefits of being physically active.	Committing yourself Encourage your client to make promises, plans, and commitments to be active.
Increasing healthy opportunities Help your client to increase her awareness of opportunities to be physically active.	Reminding yourself Teach your client how to set up reminders to be active, such as keeping comfortable shoes in the car and at the office, ready to be used at any time.

Figure 5.3 –The process of Change

(from Marcus et al. 2003)

Criticisms to Transtheoretical and Stages of Motivational Readiness for Change models

Despite the popularity of the TTM as a theoretical framework used to develop and guide PA behavior change interventions, previous reviews have questioned the effectiveness of TTM-based health promotion and PA interventions (Hutchison et al. 2009). Adams and White (2003) produced evidence to suggest that TTM-based PA promotion interventions are reasonably effective in promoting PA adoption but have little influence on long-term adherence to increased activity levels. Bridle and colleagues (2005) included seven PA behavior change interventions in their review, and in only one of these did the effect favor the TTM-based intervention compared to usual care. On the basis of these findings, it was concluded that TTM-based activity promotion interventions may be less effective than originally proposed. A number of arguments have been presented to explain the lack of support for TTM-based interventions (Hutchison et al. 2009). First, it has been suggested that PA behavior is more complex than single behaviors such as smoking and that individuals could be in a number of different stages of change depending on the type of activity being considered (Adams & White, 2005). Second, the importance of accurately determining current stage of change was highlighted, and it was demonstrated that many of the

previously reviewed interventions lacked validated algorithms to assess this (Adams & White, 2005; Bunton et al., 2000). Third, it was suggested that exercise behavior may be influenced by a number of factors not considered by the TTM. Finally, it has been suggested that many of the previously reviewed interventions may not have been complex enough to do justice to the multidimensional nature of the TTM (Adams & White, 2005). Moreover, regarding the Stages of Motivational Readiness for Change model, a meta-analysis by Marshall and Biddle (2001) questioned the relevance of the processes of change in physical activity. Although the meta-analysis found that, in general, individuals use all 10 processes when trying to modify exercise behavior and that the predictions for the higher order constructs were partially supported, it also found similar patterns of change for individual process use across all stage transitions, which argues against a stage by process interaction. Marshall and Biddle (2001) call for further work in this area, particularly studies employing a longitudinal (as opposed to cross-sectional) design (Lowther et al. 2007)

Behavioral measures of motivation

Situational measures of motivation were developed to assess participants' immediate or current reactions toward a specific activity in which they were engaged. For two decades, two types of measures have been used: behavioral and self-report indices.

The Behavioral Measure of Intrinsic Motivation

“ The behavioral measure, namely the free-choice measure, has been extensively used in laboratory research in psychology. [...] Free-choice measure consists of calculating the time spent on the activity when external contingencies are no longer operative. More precisely, the experimenter declares that the experiment is officially over and presents a pretext for leaving the participant alone for a period of time (typically 8 minutes). During that period, the participant is surreptitiously observed through a one-way mirror. The participant then has the opportunity to work on the experimental task, to read some magazines, or to do something else. The rationale underlying the free choice measure is that the more an individual persists at the experimental activity, the more he or she should be intrinsically motivated. This operationalization of the measure is in line with the usual definition of intrinsic motivation, which states that intrinsically motivated behavior typically occurs in the absence of any apparent external rewards. [...] Although this measure is useful for laboratory research it nevertheless has two important

limitations. First, this measure is unidimensional and consequently cannot assess other important motivational concepts derived from self-determination theory, namely identified regulation, external regulation, and amotivation. Second, the free-choice measure can hardly be used in field settings. This seriously limits the type of research that can be conducted with this measure” (Guay et al. 2000, pp.178-179).

Self-Report Measures of Intrinsic Motivation

“ In addition to the free-choice measure, self-report measures have also been used to assess intrinsic motivation at the situational level. A review of the literature reveals that two main scales were developed and validated: The Mayo Task Reaction Questionnaire (TRQ; Mayo, 1977) and the Intrinsic Motivation Inventory (IMI; McAuley, Duncan, & Tammen, 1989). We will also briefly discuss a third one that has been developed by Conti, Amabile, and Pollack (1995). The TRQ is formed of 23 items assessing different aspects of intrinsic motivation (i.e., concentration, interest/enjoyment, achievement, challenge, competence, and autonomy), which are rated on a 7-point Likert scale. Although the scale measures many conceptual aspects of intrinsic motivation (e.g., challenge, enjoyment, etc.), the TRQ has been constructed in a way to capture overall intrinsic motivation (i.e., the scale is unidimensional). The psychometric properties of the TRQ have been supported in some studies. [...] Evidence for the construct validity of the TRQ has emerged in line with predictions stemming from self-determination theory. [...] It should be noted that although the TRQ has some interesting psychometric properties, there are some problems with this measure. First, the scale is relatively long (23 items) for a situational measure. Second, no evidence has been reported on the factor structure of the scale. It is thus difficult to determine if the TRQ is unidimensional or multidimensional. Third, the TRQ does not assess different types of motivation postulated by self-determination theory, namely identified regulation, external regulation, and amotivation. Finally, as pointed out by Vallerand and Fortier (1998), the TRQ includes items that refer to some determinants (e.g., perceived competence) and consequences of intrinsic motivation (e.g., concentration). Inferring motivation from motivational determinants and consequences seriously compromises the construct validity of the scale. [...] The Intrinsic Motivation Inventory (IMI; McAuley et al., 1989) represents another self-report instrument that was developed to assess situational intrinsic motivation. This scale was designed to assess four underlying dimensions of intrinsic motivation in a specific situation, namely interest-enjoyment, perceived competence, effort-importance, and pressure-tension. Studies have revealed high level of internal consistency for the subscales. Moreover, the construct validity of the scale has been

supported by results in line with existing theories. However, data on the factorial validity of the IMI are much less impressive. [...] In addition, the IMI displays some of the limitations found with the TRQ. More specifically, the instrument does not assess other forms of motivation besides intrinsic motivation. Further, it also evaluates determinants (e.g., perceived competence) and consequences of intrinsic motivation (e.g., effort) rather than motivation per se. [...] Conti et al. (1995) have developed a scale that measures two types of intrinsic motivation: (1) interest, (2) willingness to partake in future activities like the experimental task for intrinsic reasons; and three types of extrinsic motivation: (1) concern with the performance, (2) pressure and tension, and (3) concern with the experimenter's opinion. However, these subscales have not been fully validated and have low levels of internal consistency. [...] In sum, although some of these traditional measures of situational motivation have provided results in line with hypotheses derived from existing theories, none of them assesses the types of extrinsic motivation proposed by Deci and Ryan (1985) as well as amotivation. Furthermore, the free-choice measure is difficult to use in field studies." (Guay et al. 2000, pp.179-180).

The Situational Motivation Scale

The Situational Motivation Scale, i.e. SIMS, was developed and validated as a measure of situational motivation that overcomes the limitations of the free-choice measure and self-report questionnaires. This measure scale was designed to assess a more diverse range of the types of motivation postulated by self-determination theory, namely intrinsic motivation, identified regulation, external regulation, and amotivation. This measure would thus represent a multidimensional measure of ongoing self-regulatory processes that could be used in laboratory and field settings, offering the possibility to address questions related to other types of regulation (i.e., identified regulation and external regulation) (Figure 5.4) (Guay et al. 2000).

The Exercise Motivation Inventory

The Exercise Motivation Inventory-2, i.e. EMI-2, was developed by Markland & Hardy (1997) in order to assess a range of physical activity motives. It was based upon self-determination theory and was used to study younger adults' physical activity motivation. Although Guay and colleagues (2000) has criticized that a self-report measure of motivation could not assess determinants and consequences of intrinsic motivation, a Dacey's study (2008) examined the feasibility of using with older adults a modified version of the EMI-2 to assess a range of physical activity motives based upon self-determination theory. The resultant factor structure

demonstrated a good psychometrics, with an high alpha reliability and good predictive validity based on concepts from self-determination theory.

Directions: Read each item carefully. Using the scale below, please circle the number that best describes the reason why you are currently engaged in this activity. Answer each item according to the following scale: 1: *corresponds not all*; 2: *corresponds a very little*; 3: *corresponds a little*; 4: *corresponds moderately*; 5: *corresponds enough*; 6: *corresponds a lot*; 7: *corresponds exactly*.

Why are you currently engaged in this activity?							
1. Because I think that this activity is interesting	1	2	3	4	5	6	7
2. Because I am doing it for my own good	1	2	3	4	5	6	7
3. Because I am supposed to do it	1	2	3	4	5	6	7
4. There may be good reasons to do this activity, but personally I don't see any	1	2	3	4	5	6	7
5. Because I think that this activity is pleasant	1	2	3	4	5	6	7
6. Because I think that this activity is good for me	1	2	3	4	5	6	7
7. Because it is something that I have to do	1	2	3	4	5	6	7
8. I do this activity but I am not sure if it is worth it	1	2	3	4	5	6	7
9. Because this activity is fun	1	2	3	4	5	6	7
10. By personal decision	1	2	3	4	5	6	7
11. Because I don't have any choice	1	2	3	4	5	6	7
12. I don't know; I don't see what this activity brings me	1	2	3	4	5	6	7
13. Because I feel good when doing this activity	1	2	3	4	5	6	7
14. Because I believe that this activity is important for me	1	2	3	4	5	6	7
15. Because I feel that I have to do it	1	2	3	4	5	6	7
16. I do this activity, but I am not sure it is a good thing to pursue it	1	2	3	4	5	6	7

Codification key: Intrinsic motivation: Items 1, 5, 9, 13; Identified regulation: Items 2, 6, 10, 14; External regulation: Items 3, 7, 11, 15; Amotivation: Items 4, 8, 12, 16.

Figure 5.4 –The Situational Motivation Scale questionnaire
(from Guay et al. 2000)

Psychometrics also accounted for gender invariance and an assessment of a range of physical activity behaviors, from sedentary to regularly active for over a year. This revised instrument was used as a measure of intrinsic motivation and certain forms of self-determined and nonself-determined extrinsic motivation toward physical activity participation in older adults. Results demonstrated that motivation differentiates activity levels and that an increase of intrinsic and

self-determined extrinsic motives is positively associated with more physical activity behavior in older adults (Dacey et al. 2008; Markland & Ingledew 1997).

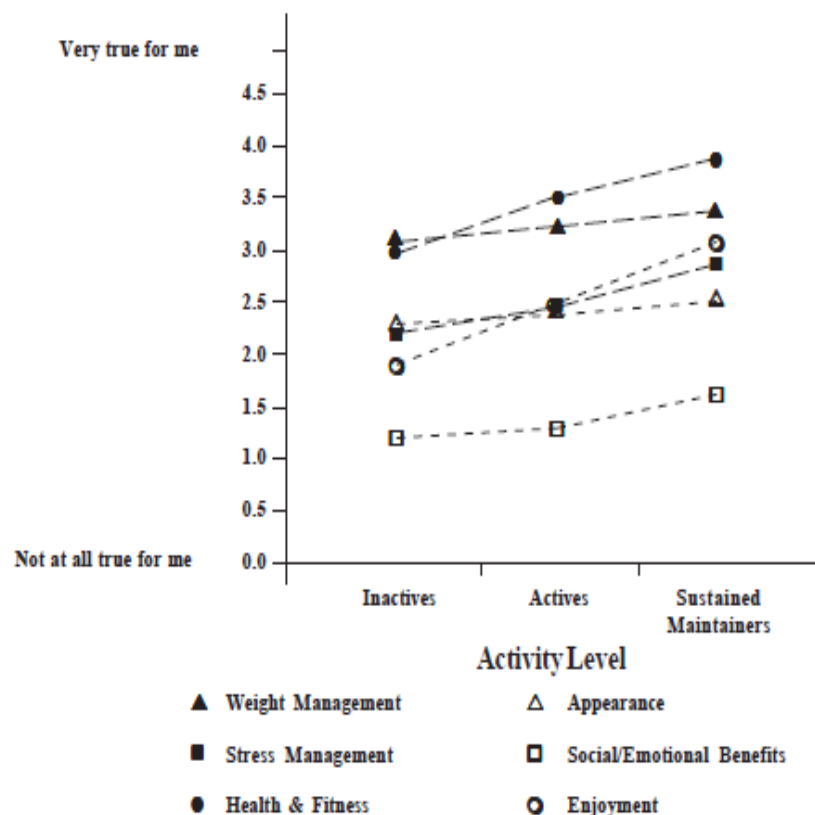


Figure 5.5 –Adjusted means of motive measures as a function of exercise activity levels, controlling for gender and age category (N=632)

(from Dacey et al. 2008)

Strategies to increase physical activity behaviors

The role of community-based interventions to promote physical activity has emerged as a critical piece of an overall strategy to increase physical activity behaviors among population. Therefore, several organizations, associations, and agencies, with expertise in health, medicine, social and behavioral sciences, epidemiology, gerontology/geriatrics, clinical science, public policy, marketing, medical systems, community organization, and environmental issues, developed guides, such as The National Blueprint (2001), to plan strategies in order to help adults and elderly people to increase their physical activity (AARP et al. 2001). An independent, nonfederal Task Force on Community Preventive Services, i.e. the Task Force, developed in 2002 The Guide to Community Preventive Services (the Community Guide) with the support of the U.S.

Department of Health and Human Services, of the Centers for Disease Control and Prevention, and in collaboration with other public and private partners (Kahn et al. 2002). This guide highlighted three categories of interventions in order to increase physical activity behavior:

- Informational approaches to change knowledge and attitudes about the benefits of and opportunities for physical activity within a community;
- Behavioral and social approaches to teach people the behavioral management skills necessary both for successful adoption and maintenance of behavior change and for creating social environments that facilitate and enhance behavioral change;
- Environmental and policy approaches to change the structure of physical and organizational environments to provide safe, attractive, and convenient places for physical activity (Kahn et al. 2002).

Promoting Active Lifestyle and Change Behavior in COPD patients

The variety of symptoms and comorbidities, the functional impairment caused by the disease, and the high level of sedentary behavior, reported by COPD patients, and described in the chapters before, enforce the need to find realistic and effectiveness long-term strategies to promote health and active lifestyle in these patients, as well as the general population (Wilson et al. 2005; Caress et al. 2010). A large body of evidence shows that PR programs and ExT are beneficial to patients with COPD in order to improve exercise capacity, muscle force, symptoms, and health-related quality of life (GOLD 2013; Lacasse et al. 2006; Troosters et al. 2005). Moreover, it well recognizes that a comprehensive PR should include elements of an healthy lifestyle promotions in order to stress adherence to therapy, encourage behavior change, engage physical activity in daily routine and prevent patients from re-entering the vicious circle of inactivity (B.R. Celli, MacNee, et al. 2004; M.A. Spruit et al. 2004). Considered that it has been shown that COPD patients who perform some level of regular physical activity have a lower risk of both COPD admission and mortality (GOLD 2013), an active lifestyle should be considered as a therapeutic priority in this populations. Indeed, making the patients more active in daily lifestyle should be a goal of PR programs, and strategies specifically aimed at improving active time, i.e. behavior strategies, should be considered as components to be added to the program (Pitta, Troosters, et al. 2008; Nici et al. 2006; Ferreira et al. 2009; Lacasse et al. 2006; Ries et al. 2007).

Recruitment and Adherence of COPD patients in Exercise Training Programs

Encouraging and supporting adults, elderly and chronic disease patients to embark on PA lifestyle changes is an everyday challenge faced by many health professionals (Hutchison et al. 2009). In fact, health promoters find it challenging to recruit people into ExT and PA programs (Hildebrand & Neufeld 2009). However, several guides and behavior change programs were established worldwide in the last years, for example “Get fit for Active Living” by Canadian Center for Activity and Aging (CCAA) and “The Rural Route to active Aging” by Alberta Center for Active Living (for more details and program see ACSM 2002). These programs approached to meeting the challenge of promoting physical activity in adults and elderly people, also with chronic condition, including evidenced-based strategies of behavior change (Hildebrand & Neufeld 2009). With regard on the recruitment of COPD patients in ExT and PA programs, the situations is more challenging than that observed for healthy adults, elderly and/or people with others chronic disease. Indeed, it is well documented that a considerable proportion of eligible patients decline participation and/or drop out from PR (Keating et al. 2011; Faulkner et al. 2010; Fischer et al. 2007; Goldstein et al. 1994), especially if these initiative are clinical trials (Bell-Syer at al. 2000). It has been estimated that in the United Kingdom, less than 1.5% of patients with COPD access into PR each year (Yohannes & Connolly 2004). In a recently Faulkner’s study (2010) it was established that to recruit 100 patients it would be necessary to approach approximately 7000 patients on a COPD register. Moreover, an high rate of drop out to COPD rehabilitation program was often observed (Faulkner et al. 2010; Fischer et al. 2007; Young et al. 1999). In the prospective controlled study of Goldstein and colleagues (1994) it was recorded an adherence to complete PR program rate of ~34%, confirmed by than recorded in Ries and colleagues (1995) of ~36%. More recent trials showed the same trend: 29.26% Pitta’s study (2008), 27.92% Steele’s study (2008), 46.87% Ringbaek’s study (2010). Furthermore, considered that the positive effects of exercise decline over the time (Ries et al. 1995; Berry et al., 2003), the long-term adherence to an exercise prescription is critically important (Donesky-Cuenca et al. 2007; M.A. Spruit et al. 2004). In healthy adults it was estimated a rate of ~50% adherence to an exercise prescription (Dunbar-Jacob et al. 2000). In the available studies about adherence to an exercise training and prescription in COPD, data vary considerably due to differences in definition of adherence, units of measurement and data analysis strategies. However, Berry and colleagues (2003) estimated a rate of ~55% of COPD patients who continued to attend prescribed exercise maintenance sessions after pulmonary rehabilitation at 12 months. The ACSM states that individuals of all ages should maintain a minimum of 30 minutes of moderate exercise, i.e. walking, per day to

maintain or develop fitness (Pate et al. 1995). Pitta and colleagues (2005) showed objective data on PDA of COPD patients and highlighted that ~30% of patients involved in the study did not reach the recommended amount of walking time per day, whilst all the healthy group subjects met these goals. In addition, even in those patients with walking time exceeding 30 minutes per day, the movement intensity was ~17% significant lower than the movement intensity observed in healthy elderly subjects. This finding shows that even the most active patients with COPD probably walk at an intensity insufficient to bring benefits in terms of fitness maintenance. Furthermore, considered that inactivity is a risk factor for hospital readmission in COPD, according to the threshold, i.e. walking at least 60 minutes/day every day, ~74% of the patients included in the Pitta's study can be considered "at risk" (Pitta et al. 2005). Subsequently, in another study, Pitta and colleagues (2008) investigated the effects of 3 and 6 months of PR on the time spent by COPD patients in different activities and body postures in daily life and examined whether PR leads to a change in the duration of bouts of continuous walking. In this study it was observed that changes in PA in daily life were limited only to an improvement in movement intensity during walking in daily life, suggesting that more time was needed to introduce important lifestyle changes. Also it was observed that an improve in functional exercise capacity and functional status seems to not suffice to introduce a more active lifestyle (Pitta, Troosters, et al. 2008). This results are according with previous findings observed by Spruit and colleagues (2004). This study reported that short programs, i.e. 2-3 months, might not be able to permanently change physical behavior in COPD patients, suggesting the need to emphasize general training principles into aftercare programs (M.A. Spruit et al. 2004).

Predictor of Non-adherence in COPD patients

Considered that a careful exercise prescription and a close supervision of patients during exercise training are important to elicit training effects, it seems of great importance to offer COPD patients an extensive PR that is linked up perfectly with an aftercare program to preserve the brought about changes in physical behavior and to prevent patients to revert again to a sedentary lifestyle (M.A. Spruit et al. 2004). Although several studies focused their attention to understand the predictor of adherence to ExT and PA program among adults and elderly people (Hemmingsson et al. 2001; Kahn et al. 2002; Heesch et al. 2003; Stiggelbout et al. 2006; Bergman et al. 2008; Dacey et al. 2008; Schutzer & Graves 2010; Geense et al. 2013), the reasons for non-attendance of COPD patients at PR and ExT programs are not well-documented. Most studies are small and may be influenced by local health system characteristics and program

organization, as much as by individual patient characteristics. Moreover, the factors that influence whether people choose to attend their initial appointment may be different to the factors that influence program completion (Young et al. 1999; Fischer et al. 2007; Keating et al. 2011). In a recent review of Keating and colleagues (2011) it was highlighted that patients with COPD have difficulty attending and completing pulmonary rehabilitation programs. This review found that patients who fail to attend pulmonary rehabilitation at all may do so because of personal perceptions such as disruption to routine, influence of their doctor and inconvenient timing. In contrast, failure to complete a program is related to illness, depression and current smoking. Travel to the pulmonary rehabilitation centre, difficulties with transportation, mobility, distance and location of programs influenced both attendance and completion (Keating et al. 2011). The standard recommended PR program runs over a period of 8-12 weeks and people are required to attend at least twice weekly (Nici et al. 2006). Accessing the program may be a significant burden for this group of people who have limited mobility and financial resources. At present, pulmonary rehabilitation guidelines do not make strong recommendations regarding transport. Whilst it is stated that transport may make programs more accessible, its impact on the cost of the service is also recognized (BTS 2010). Moreover, also lack of perceived benefit influences both failure to attend and failure to complete PR programs. Limited data were available to assess the reasons that people with COPD fail to attend pulmonary rehabilitation at all. The small studies that were available (N= 11) suggest that negative perceptions of pulmonary rehabilitation from the patients themselves or medical professionals are important factors influencing the decision to attend. (Keating et al. 2011). These findings are according with results observed in others study among general population (Karapolat et al. 2012; Geense et al. 2013). Pulmonary rehabilitation was not perceived as important enough to warrant disruptions to important personal routines (Fischer et al. 2007; Keating et al. 2011). This is consistent with other literature suggesting that if participants cannot perceive the benefit of an intervention, they will be less likely to adhere (Keating et al. 2011). Young and colleagues (1999) observed that divorced or widow, and living alone were also predictive of non-adherence (Young et al. 1999). Illness related to lung disease or comorbid conditions was linked to non-completion PR. Considered these findings, a qualitative study by Fischer (2007) about patients' pretreatment beliefs and goals with regard to participation in pulmonary rehabilitation proposed an explanation model about reasons for drop out or decline PR (Figure 5.6).

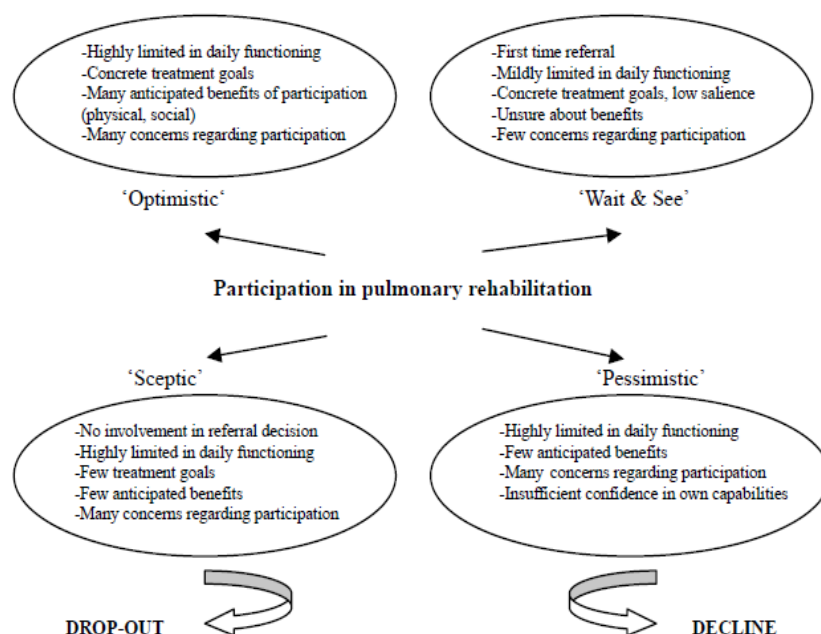


Figure 5.6 - Attitudes of referred patients with COPD towards participation in a pulmonary rehabilitation program.

(from Fischer et al. 2007)

Although quantitative data did not indicate a greater non-completion rate in patients who experienced an exacerbation during their program, it did increase the risk of dropout in at-risk groups such as smokers. This is also reflected in qualitative studies analyzed by the review, where patients consistently identified exacerbations as important contributors to non completion. Comorbid conditions are present in over half of COPD patients who undergo pulmonary rehabilitation (Crisafulli et al. 2008) and are associated with increased mortality and social isolation (GOLD 2013). Given the common nature of both comorbidities and exacerbations, strategies to support completion in this large group of patients should be considered. These findings are well related to previous studies' results in which non-adherence was strongly associated with deficient disease-specific social support. Management programs should be to provide support persons with the skill to provide better quality disease-specific support and should be regarded to improve social activity (Young et al. 1999). Current smoking and depression were the only two baseline demographic factors that clearly increased the odds of non-completion (Young et al. 1999; Keating et al. 2011). Commonly used measures of disease severity such as lung function, dyspnea and BMI were not consistently related to uptake or completion (Keating et al. 2011). In conclusion, COPD patients non-adherence in PR is not homogeneous and the factors affecting patient's decision and ability to engage in pulmonary rehabilitation are a complex mix of physical and personal factors. Differences in barriers to uptake and completion suggest that different strategies may be needed to enhance program attendance

in these two groups of patients (Young et al. 1999; Fischer et al. 2007; Caress et al. 2010; Keating et al. 2011).

Supporting health behavior change in COPD

As highlighted before, permanent lifestyle changes are needed to ensure long-term maintenance of treatment effects. Therefore, in order to improving compliance with therapy and encouraging permanent changes in PA behavior, several specific COPD strategies in the PR field were individuated.

Maintenance and follow-up

There is currently debate concerning the follow-up care that should be provided to patients with COPD after graduation from pulmonary rehabilitation programs. However, after a 6-month program, Troosters and colleagues (2000) observed prolonged i.e. more than 1 year after stopping the program, benefits without rigorous maintenance programs. After shorter programs, more intensive follow-up care seems important (Troosters et al. 2005). Usual care, regular telephone support, and once-monthly follow-up visits were insufficient to maintain benefits of an 8-week outpatient or 6-week inpatient rehabilitation program (Ries et al. 2007; Ries 2008; Troosters et al. 2005; Langer et al. 2009). Brooks' study (2002) showed that compliance with maintenance home exercise therapy was relatively low. Continued three-times weekly outpatient rehabilitation up to 15 months after graduation was superior to exercise advice during the follow-up (Berry et al. 2003). However, the current knowledge advise once-weekly high-intensity maintenance exercise training sessions (M.A. Spruit et al. 2004; Troosters et al. 2005).

Patient education interventions to increase physical activity

Atkins and colleagues (1984) investigated the effects of strategies to improve adherence to a home-based walking program. Despite their promising findings little attention has been paid so far to the incorporation of behavior modification strategies into the treatment plan for patients with chronic obstructive pulmonary disease. A pilot study by de Blok (2006) looked into the effects of lifestyle physical activity counseling, using physical activity self-monitoring, with pedometers, as an adjunct to pulmonary rehabilitation. They found a non-significant increase in daily steps in comparison to a control group at the end of a nine-week pulmonary rehabilitation program. Two recent trials using feasible, alternative, cheap and easy accessible physical training modalities, based on Nordic Walking activity (Breyer et al. 2010) and use of a metronome in order to

maintain the rate of walking during home ExT (Pomidori et al. 2012), resulted effective PA training modalities to impact the DPA pattern of COPD patients under short- and long-term observation.

Other considerations

Several studies showed that intense physical exercise training as part of a multidisciplinary rehabilitation program had only modest effects on participation in physical activities in daily life (Pitta, Troosters, et al. 2008; Steele et al. 2003). Simply advising patients to do more physical activity without more specific assistance and follow-up seems to be ineffective (Langer et al. 2009). COPD education requires a physical activity intervention that is feasible, acceptable and effective in a variety of settings. Studies with successful results in chronically ill adults had in common that they used physical activity self-monitoring, i.e. with pedometers or diaries, and applied behavioral strategies to increase patient's self efficacy and self-regulatory skills (Conn et al. 2008). A systematic review of randomized controlled trials on physical activity self-monitoring with pedometers showed an average increase of 2491 steps per day, i.e. 95% confidence interval: 1098–3885 steps, above control interventions (Bravata et al. 2007). Many of these interventions used two or more interventions; i.e. self-monitoring, goal setting, diaries or counseling. A recent trials, using a metronome in order to maintain the rate of walking during home ExT (Pomidori et al. 2012), resulted an effective PA training modality to achieve and sustain an optimal exercise intensity. Although both classical training techniques of walking, i.e. walk a known distance in a given period, and alternative metronome method resulted in improved daily MET expenditure, peak MET level, and duration of PA more than 3 METS after 6 months, only the alternative techniques showed to maintain the results over the time, i.e. 12 months. Current knowledge recommended to implement interventions to initiate and maintain change of physical activity behavior. Short questionnaires or pedometers can be used during these interventions to facilitate follow-up assessment and self-monitoring of behavior change (Langer et al. 2009).

Study 1

University of Verona



Master School of Translational and Biomedical Sciences

**Doctorate Course in Science of Physical Exercise
and Human Movement**

RECRUITMENT OF MILD TO SEVERE COPD PATIENTS INTO EXERCISE TRAINING PROGRAMS: ANALYSIS OF THE FEASIBILITY

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Background

Despite lung function parameters don't improve after PR, extensive knowledge reports positive effects of ExT on symptoms, physical capacity and HRQL in COPD patients (Ries 2008; D. E. O'Donnell et al. 2008; GOLD 2013). Unfortunately, there are few health-care structured programs of PA and ExT available (Valero et al. 2009; Dourado et al. 2009) and a considerable proportion of eligible COPD patients decline participation or drop out from the programs (Faulkner et al. 2010). Reasons for decline and drop-out in PR and ExT have seldom been investigated systematically (Keating et al. 2011; Fischer et al. 2007).

Purpose

The aim of this study is to outline motivation and barriers which reduced COPD patients recruitment in ExT and hindered an active lifestyle acquisition.

Design

A single-centre, multi-practice, randomized, parallel-group clinical trial was designed and recruitment steps (Glaser & Strauss in 1969) were recorded in order to assess patients' motivation of decline or drop out.

Subjects

A total of 269 males COPD patients were established from the Respiratory Division of ULSS 20, but only 132 were considered eligible according to study inclusion criteria. Patients were contacted and invited to take part at 6 months of ExT program; participants were randomized and assigned to one of the three evaluation groups: Fitness Center based group (FC), Educational PA group (EDU) and Control group (CG). Ethical approval by Department of Neurological, Neuropsychological, Morphological and Movement Sciences, University of Verona, Medical Hospital Management approval of ULSS20, and informed consent by patients were obtained.

Measures

The qualitative study was based on administration of a semi-structured interview and the EMI-2 structured questionnaire (Markland & Hardy 1997). One way ANOVA was used to detect significant differences between groups and between variables.

Results

A total of 132 COPD males patients was established eligible to the ExT program but only the 70% (n=92) was possible contacted. Only the 59.8% of patients (n=55) demonstrated interest regarding the initiative and attended the initial meeting. The remaining 40.2% (n=37) reported immediately intention to not-participate caused by no-interest in practice ExT and PA (n=21), instable clinical conditions (n=11), difficulties in transportation (n=3) and lack of available time (n=2). After the initial meeting, the 69.1% (n=38) of subjects provided informed consent, while the 30.9% (n=17) decline participation due to lack of available time (n=17), recently onset of clinical condition (n=2) and difficulties in transportation (n=1). At the end of the 6-months ExT program, the 89.5% of patients (n=34) concluded the trial, instead the 10.5% of subjects (n=4) dropped out caused by onset of instable clinical conditions. Analysis of recruited COPD patients' motivation of COPD recorded a low score (mean 81.69pt \pm 48.08; 44.27% of maximum total score). No significant differences were found at baseline between the 3 evaluations group. After 3 months of ExT and at the end of the 6-months of PA program only the FC group showed a significant improvement in total score motivation (3 months= +43.99%, $p<0.05$; +47.42%, $p<0.05$). After 3 months of ExT, FC subjects showed significant increases in Socio/Emotional aspects ($p<0.01$), in Weight management ($p<0.05$) and Enjoyment items ($p<0.01$). At the end of the 6 months of ExT significant improvement in FC groups were observed in Socio/Emotional aspects ($p<0.01$) and in Enjoyment items ($p<0.05$).

Conclusion

Recruitment of COPD patients is very challenging and the major cause of not-participation are related to mismatched inclusion criteria. (65.53%) according to difficulties of recruitment in clinical trials reported by literature (Bell-Syer S. 2000). No-interest in ExT (8.94%), lack of available time (6.81%) and inability to access at the PA structures (1.7%) were the most commonly cited reasons to decline participation confirming previous literature's findings (Keating et al. 2011). Compared to the literature, the study's recruitment showed higher score (25.7% vs 6.5% of Faulkner's study, 2009), and lower number of drop out after 6 months of PA program (10.52% vs. 29.26% Pitta F. 2008, 27.92% Steel, 2008, 25%, 46.87% Ringbaek, 2010) suggesting that a great effort practice of recruitment, managed by Exercise Specialist, characterized by persistence and flexibility strategies, seems to be more effective Improving level of liaison between Specialist Physicians and Exercise Specialist should be empathize. At baseline low total scores of motivation to practice PA were recorded in COPD patients. Significant short and long-term motivation items improvements, suggest that a, structured and constantly supervised PA program could positively influence COPD patients' intrinsic and self-determined extrinsic motives to ExT. Analysis of subscales highlighted importance to design COPD ExT programs focused on patients' needs and interests.

Key words: COPD; recruitment; motivation; feasibility; exercise training; physical activity

Background

At present, exercise training and physical activity are commonly recognized components of an healthy lifestyle and several professional societies and governmental agencies recommend that all adults and elderly people should participate in a regular and moderate exercise program. (Darren E.R. Warburton et al. 2011; Cress et al. 2006). Moreover, considering the positive effects of exercise and physical activity, people affected by chronic disease condition should be addressed to an healthy behavior changes in order to match international guidelines (M. E. Nelson et al. 2007; Harman J.E. 2010). COPD is one of a major global public health problem and it is one of main cause of worldwide morbidity and mortality (GOLD 2013; Viegi et al. 2007). It is characterized by a progressive airflow limitation, not fully reversible, due to an abnormal lungs inflammatory response (B.R. Celli, MacNee, et al. 2004; GOLD 2013). Extra-pulmonary manifestations and several co-morbidities are present in more than 50% of COPD patients (Divo et al. 2012; Barnes & B.R. Celli 2009) who undergo in pulmonary rehabilitation (Crisafulli et al. 2008) and they are associated with increased mortality (Sin et al. 2006). Indeed exercise intolerance and symptoms such as dyspnea and skeletal muscle wasting may contribute to increase patients disabilities, affecting their quality of life and reducing the maintenance of an active lifestyle (Kim et al. 2008; Caress et al. 2010; Glaab et al. 2010; Huertas & Palange 2011; Vorrink et al. 2011). Therefore, the financial cost of COPD is very high for the health system and there is a large impact on individuals, with loss of productive healthy years of life (GOLD 2013; Rabe et al. 2007). To attacking the problem of COPD, several international efforts (GOLD 2013) and a number of management approaches alongside conventional medical interventions have been deployed in order to reduce the COPD disease burden (Walters et al. 2012). Despite lung function parameters don't improve, physical activity is considered the cornerstone of a comprehensive pulmonary rehabilitation (Nici et al. 2006) and the most effective non-pharmacological intervention to improve COPD patients health, quality of life and exercise capacity (B.R. Celli, MacNee, et al. 2004; D. E. O'Donnell et al. 2008; Fromer & C. B. Cooper 2008; GOLD 2013). Unfortunately, there are few health-care structured programs of physical activity for COPD (Valero et al. 2009; Dourado et al. 2009) and a considerable proportion of eligible patients declined participation or dropped out from pulmonary rehabilitation (Faulkner et al. 2010; Keating et al. 2011). Reasons for declining and dropping-out from pulmonary rehabilitation and exercise training programs have seldom been investigated systematically (Fischer et al. 2007; Keating et al. 2011). Therefore primary aim of this study is to describe every steps of recruitment patients into an ExT program in order to outline which motivations and

barriers reduced COPD patients participation in a PA initiative. Through this analysis and together with data about COPD patients' adherence and drop out from the ExT program, the second purpose of the study is to assess which motivation variables hindered an active lifestyle acquisition for these chronic patients.

Methods

Design

This study is a single-centre, multi-practice, randomized, parallel-group clinical trial. It was designed to assess every recruitment steps according with the Grounded Theory (Glaser & Strauss 1969) and to record the different COPD patients' motivation to participate, decline and/or drop out from a secondary study, i.e. a 6-months longitudinal randomized controlled trial investigating the effects of two models of exercise training. Moreover, subsequently, the study analyzed the score obtained by the baseline administration of the Motivation Inventory-2 questionnaire, i.e. EMI-2 (Markland & Hardy 1997), which is a validated instrument to assess a range of physical activity motives based upon Self-Determination Theory, i.e. SDT (Ryan et al. 2002). The individual EMI-2 total score obtained by COPD patients was used as one of the three randomization criteria for the secondary longitudinal study and re-administration was performed after 3 and 6 months of exercise training. Ethical approval by Department of Neurological, Neuropsychological, Morphological and Movement Sciences, University of Verona, Medical Hospital Management approval of ULSS20, and informed consent by participant patients were obtained (Figure S1.a).

Procedures

The data were obtained during the periods between September 2011 and February 2012, in which were singled out, contacted and recruited participants from eligible COPD patients, and between March and September 2012, in which COPD recruited patients were randomized in a 6 months, longitudinal, controlled trial of the differential effects of varying type of supervised exercise prescription. Evaluation sessions were provided at baseline, after 14 weeks and after 28 weeks

Sample

The convenience sample of 132 eligible patients enrolled in the clinical trial had the following criteria (Figure S1.a).

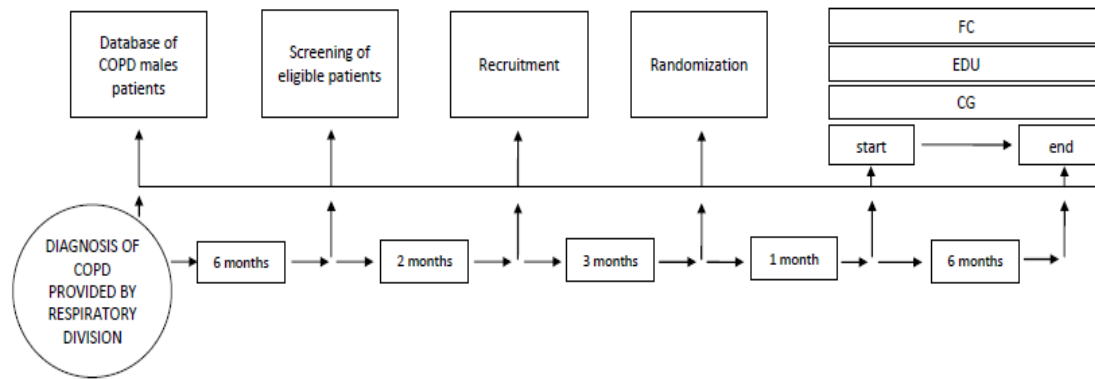


Figure S1.a – Study 1 procedures

Participants were recruited from the Cardiovascular and Thoracic Department, Respiratory Division, of ULSS 20, Verona, Italy. Over 6 months, i.e. March-August 2011, a database of 269 COPD males patients, assessed by the Respiratory Division of the Cardiovascular and Thoracic Department, ULSS 20, was created. Subsequently, between the period of September and October 2011, 132 eligible patients, which matched the inclusion criteria (Table S1.b) were singled out and advised about the initiative with an introduction mail at their home. Then, we were able to contact by telephone 92 subjects and we invited them at first introducing meeting at the Faculty of Science Sports of the University of Verona. During the meeting, COPD characteristics' disease, positive effects of ExT and PA programs to improve health, quality of life and exercise capacity, and research's purpose and details were provided to participants. After one week, patients were contacted a second time by telephone to verify their participation and to set another individual meeting in order to provide informed consent and to administrate questionnaires. As a result of this screening process, 17 subjects were excluded, 2 who did not meet clinically stable condition criteria and 15 who were dropped after the meeting because lack of available time to take part at the study (N=14), and difficulties with transportations (N=1). The remaining 38 patients were randomized in three different groups: Fitness Center based group (FC=13), Educational PA group (EDU=12) and Control group (CG=13).

Table S1.b – Study 1 participant inclusion and exclusion criteria	
Inclusion	Exclusion
65 years \pm 5	4 stage of COPD
males	Instable cardiac disease
Stage 1 to 3 GOLD classification	Pneumonia, pulmonary embolism, pulmonary vascular disease, respiratory infections
Clinical stability for at least 1 months	Lung cancer, thoracic malignancy, malignancies
	Bone fractures, fractures

Randomization parameters were disease stage, according to GOLD classification (GOLD 2013), total recorded score motivation, assessed by EMI-2 and the share of practiced physical activity calculated by administration of the International Physical Activity Questionnaire-short form (IPAQ 2005). COPD patients randomized into the FC group attended 3 time/wk, 90-minute of supervised APA, delivered by a qualified exercise practitioner, for 6 months, i.e. period between March and October 2012. Subjects of the EDU group were involved in 14 weeks of low progressive supervised ExT, in which they practiced different types of PA, and subsequently 14 weeks of self-selected PA. CG patients were not involved in any type of treatment but only in evaluation sessions.. At the end of the 6 months 4 patients from FC (N=1) and CONT (N=3) groups dropped out caused by instable onset clinically conditions (Figure S1.c).

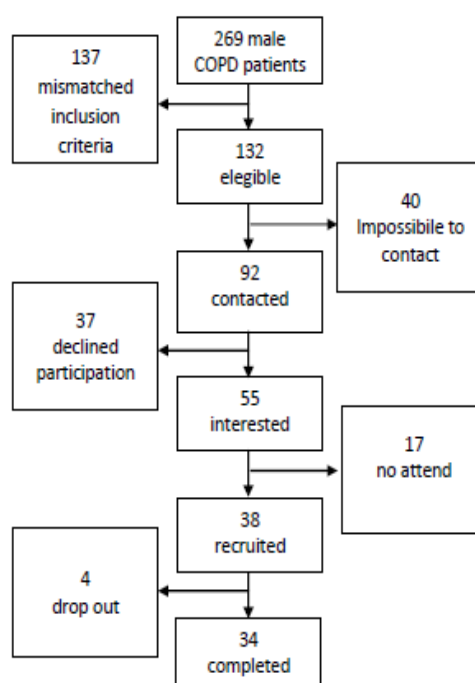


Figure S1.c – Patients recruitment to the Study 1

Measurements

Database information

Through the analysis of all the physical examinations and pulmonary function evaluations performed by the clinicians of the Respiratory Division of ULSS 20, between March and August 2011, all COPD males patients were collected in a database. Personal data, such as name, surname and date of birth were recorded. Also home address, telephone, mobile and eventually e-mail were included. Moreover, information about clinical conditions, i.e. last available %FEV₁ and %FEV₁/FVC post-bronchodilator evaluation, disease stage diagnosis, co-morbidities and MRC scale were reported in the database, in order to acquire as much details as possible for the subsequent screening processes.

First mail and telephone records

After first screening process, COPD males eligible patients were contacted by mail. Then telephone contact was based on a semi-structured interview, for investigating their interest and their willingness to participate at subsequent introducing meeting. In such meeting, we provide more specific informations about training and its locations. All the answers and details provided by the subjects were collected and recorded in the database.

First introducing meeting

First meeting lasted about 90 minutes, and it was attended by 15-20 patients per time.. Patients family members, such as wife or sons, were invited at the meeting. Between December 2011 and February 2012, five introducing meetings were performed at the Faculty of Science Sports of the University of Verona. During each meeting, COPD subjects and family members could visit the University Fitness Center structures and they were involved in a presentation regarding the trial. Characteristics' disease, positive effects of ExT and PA programs to improve health, quality of life and exercise capacity, and research's purpose and details were provide to participants. The information model about trial details was delivered to each participants. Adherences to the meeting, questions and answers provided by or to the subjects were collected and recorded in the database.

Second telephone records

After one week from the meeting, patients were contacted a second time by phone call. Even this second telephone contact was based on a semi-structured interview to verify their willingness to participate at the study and to set another individual meeting in order to provide informed consent and administrate questionnaires. All the answers and details provided by the subjects were collected and recorded in the database.

Individual meeting

Subsequent individual meeting was required to each patients that did show interest to the research project. During this meetings, that lasted 60 minutes, family members were invited. COPD patients were involved in the administration of the some questionnaires: the IPAQ short form, to assess the share of DPA, the EMI-2 questionnaire, to record the motivations to practice PA, and the Physical Activity Readiness questionnaire, i.e. rPAR-q (Thomas et al. 1992), to evaluate onset changes in clinical conditions from the evaluation made by the Respiratory division of ULSS 20. Scores of all questionnaires were collected and recorded in the database.

Adherence, drop out and EMI-2 administration during the longitudinal randomized trial

Adherence and/or drop out motivations from the secondary 6-months longitudinal randomized controlled trial were collected and recorded in the database. Moreover, EMI-2 re-administration were performed after 3 months and at the end of research in order to assess changes in the total and items PA motivation scores obtained by the different patients groups.

Statistical methods

To address the purpose of this analysis, we calculated descriptive statistics, such as means, proportions, and standard deviations for EMI-2 total score and each EMI-2 items score, i.e. Health and Fitness, Social/Emotional benefits, Weight management, Stress management, Enjoyment and Apparence, separated by treatment group, using routines in the Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, IL). The statistical analysis plan for this study was developed together with the data analysis of the secondary 6-months longitudinal randomized controlled trial. Therefore, a two-way repeated measures ANOVA was

performed. Then, post hoc analysis using Bonferroni correction was used to compare difference among testing sessions and groups.

Results

Patients recruitment

Preliminary records identified 269 males patients with COPD. 132 COPD (49%) patients appeared to match study inclusion criteria after inspection of patients record by the researchers, and they were established eligible to the ExT program. We were able to contact by mail 92 patients the (70%). After the first telephone contact 55 patients (59.8%) demonstrated interest regarding the initiative and attended to the initial meeting to present details. Instead, the remaining 37 patients (40.2%) reported immediately intention to not-participate caused by no-interest in practice ExT and PA (n=21), instable clinical conditions (n=11), difficulties with transportation, mobility, distance and location of PA structures (n=3) and lack of available time to take part at the study (n=2). At the second telephone contact, after one week from the introducing meeting, 38 subjects (69.1%) provided the informed consent, while the 17 (30.9%) decided to not-participate caused by lack of available time (n=14), which was considered too much challenging, recently onset of instable clinical condition (n=2) and inability to access easily at the PA structures (n=1). At baseline assessment no subject mismatch the inclusion criteria by the PAR-q analysis. During the 6-months ExT program, the 89.5% of patients (n=34) concluded the trial, instead the 10.5% of subjects (n=4) dropped out caused by onset of instable clinical conditions (Table S1.d).

Motivation towards physical activity

The analysis about the motivation of COPD recruited patients towards PA and ExT recorded a low score (mean 81.69pt \pm 48.08; 44.27% of maximum total score), although improving health (mean 32.5pt \pm 15.88; 59.09% of maximum item score), management of body weight (mean 13.49pt \pm 6.65; 58% of maximum item score) and decreasing stress (mean 17.06pt \pm 7.24; 58.52% of maximum item score) resulted the main reasons (Table S1.e and Figure S1.f). No significant differences were found at baseline between the 3 evaluations groups.

Table S1.d – Study 1 recorded variables of decline, no-attendance and drop out (tot N subject = 92)

	<i>N</i>	<i>%</i>
<i>Decline participation</i>	37	40.2
No interest	21	22.8
Instable clinical condition	11	11.9
Difficulties in transportation	3	3.4
Lack of available time	2	2.2
<i>No-attendance</i>	17	18.5
No interest	-	-
Instable clinical condition	2	2.17
Difficulties in transportation	1	1.08
Lack of available time	14	15.21
<i>Drop out</i>	4	4.3
No interest	-	-
Instable clinical condition	4	4.34
Difficulties in transportation	-	-
Lack of available time	-	-

Table S1.e – EMI-2 recorded score at baseline

<i>Variable</i>	<i>Tot max score</i>	<i>COPD score</i>	<i>SD</i>
<i>Total EMI-2</i>	185	81.69	48.08
<i>Health</i>	55	32.5	15.88
<i>Socio/Emotional</i>	50	15.17	12.09
<i>Weight</i>	20	11.6	12.09
<i>Stress</i>	52	14.63	8.82
<i>Enjoyment</i>	20	10.57	6.48
<i>Appearance</i>	15	2.76	3.49

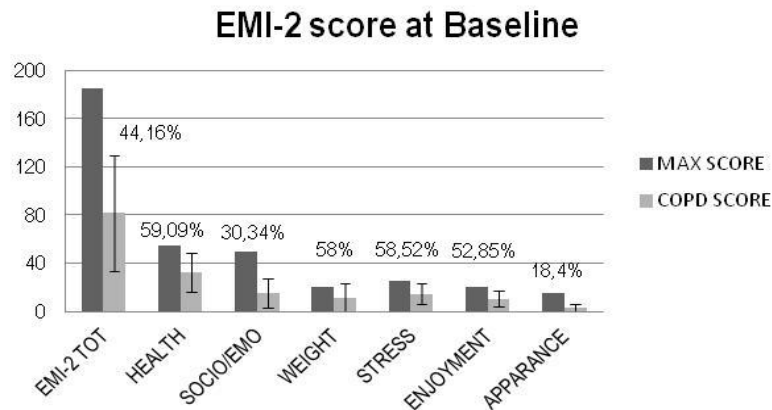


Figure S1.f – % of EMI-2 total score recorded and % of each variables recorded.

After 3 months of ExT and the end of the 6-months longitudinal randomized controlled trial only the FC group showed significant improvement in total score motivation (3 months = +43.99%, $p < 0.05$; 6 months = +47.42%, $p = 0.05$) (Table S1.g). After 3 months of ExT FC subjects showed significant increases in Socio/Emotional aspects ($p < 0.01$), in Weight management ($p < 0.05$) and Enjoyment items ($p < 0.01$). At the end of the 6 months of ExT significant improvement in FC groups were observed in Socio/Emotional aspects ($p < 0.01$) and in Enjoyment items ($p < 0.05$) (Table S1.h).

Table S1.g – EMI-2 total score in different ExT group

mean (SD); * $p < 0.05$; # $p = 0.05$			
Groups	baseline score	at 3 months	at 6 months
FC	85.75 (52.45)	117.55 (35.39) *	123.67 (39.87) #
EDU	85.18 (35.42)	111.17 (23.34)	117.33 (29.12)
CG	72.00 (58.79)	85.86 (40.39)	105.00 (44.85)

Table S1.h – Changes in 6 months of EMI-2 total score and variables (FC group)

mean (SD); * $p < 0.05$; # $p = 0.05$; § $p < 0.01$;			
Variable	baseline score	at 3 months	at 6 months
Total EMI-2	85.75 (52.45)	117.55 (35.39) *	123.67 (39.87) #
Health	33.83 (14.75)	40.63 (7.49)	40.08 (10.46)
Socio/Emotional	20.42 (13.49)	27.45 (11.68) §	31.33 (14.50) §
Weight	11.25 (6.74)	13.72 (5.87) *	13.75 (7.25)
Stress	15.58 (8.91)	16.36 (5.55)	17.75 (8.40)
Enjoyment	11.25 (6.25)	13.63 (5.5) §	15.50 (5.84) *
Appearance	3.33 (4.14)	5.72 (5.29)	5.25 (5.07)

Discussion

It was observed that the recruitment of COPD patients becomes very challenging especially if ExT and PA programs are complex or have restrictive entry criteria (Bell-Syer et al. 2000). As expected, also this study have recorded difficulties to recruit high number of COPD patients. Our rate of recruitment, based on the number of eligible patients (132, i.e. 25.75%), and the major cause of not-participation into the ExT program was related to mismatched inclusion criteria by COPD patients, i.e. 137 patients at the first screening process and 13 patients during the recruitment. Figure S1.i summarizes all the several motivation recorded to decline participation or drop out from the study. The recruitment of COPD patients in our study is higher than that observed in literature by Faulkner and colleagues, i.e. 6.5% (2010). Moreover, the rate of drop out from our study, based on the number of patients recruited, is really low, i.e. 10.52%, and related to onset of instable clinic conditions, which are an exclusion criteria. Finally, the adherence to complete our trials shown by COPD patients (89.47%) is higher than that observed in literature by Pitta's study (2008), i.e. 29.26%, Steele's study (2008), i.e. 27.92%, Woo's study (2009), i.e. 25%, Ringbaek's study (2010), i.e. 46.87%. Considered the impossibility to modify inclusion/exclusion criteria into a trial of ExT, the rate of adherence and the number of drop out recorded suggest that our great effort practice of recruitment, managed by only one Exercise Specialist, and characterized by persistence and flexibility strategies towards patients, seems to be more effective to recruit and maintain adherence of COPD patients. We assume that the Exercise Specialist participation at the all recruitment phases could establish a positive relationship of confidence within the patients, according with the evidence that attitude and knowledge, about the health and PA promotion field, of specialists and people, involved at any level of the disease management, could influence the acquisition process of an healthy lifestyle (Geense et al. 2013; Schutzer & Graves 2010).

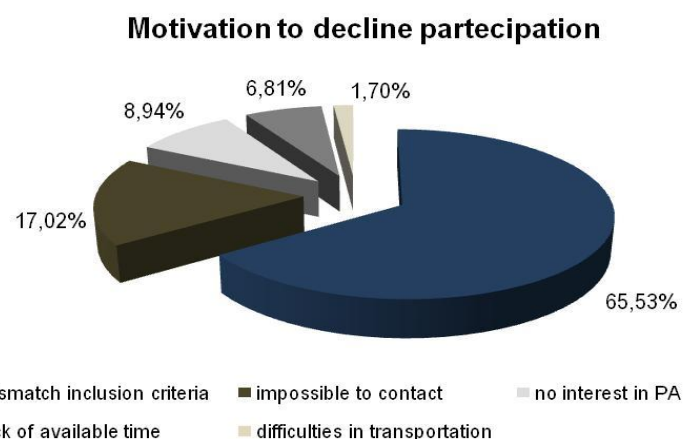


Figure S1.i – All motivation recorded in decline participation and drop out from the trial.

Results from the analyses of the motivations recorded to not attempt in our ExT trial confirm literature's findings that the most frequently barrier to engage older adults and COPD patients into a PA program is related to health, illness, pain and co-morbidities (Schutzer & Graves 2010; Keating et al. 2011). The second major recorded factor which obstructs our recruitment was related to mistakes and/or lack of patients' personal data reported in medical records. However, in line with previously reported studies, we found that lack of interest in PA exercise program and lack of available time to engage into an ExT reduce COPD patients interest and motivation to take part in a PR program, probably due to a lack of perceived benefits and a disruption to usual routine (Keating et al. 2011; Fischer et al. 2007). These data acquire higher value considering that it was established that a low ratio of COPD patients have true knowledge about characteristics and benefits of PA in PR program (Karapolat et al. 2012). Finally, travel to the pulmonary rehabilitation centre, difficulties with transportation, mobility, distance and location of programs seems to influence recruitment, according to literature (Keating et al. 2011). In regard to the EMI-2 analysis, our study shows a low baseline total scores of motivation to practice physical activity in recruited COPD patients, confirming that the factors to attend initial appointment may be different to the factors that influence program completion (Young et al. 1999; Fischer et al. 2007; Keating et al. 2011). As expected, no significant differences in baseline total scores of motivation between the groups were found, considered that EMI-2 total score was one of the three randomization parameters. However, the significant improvements among motivation items, observed only in FC group, after 3 and 6 months of ExT suggest that an high, structured and constantly supervised PA program could positive influence COPD patients' intrinsic and self-determined extrinsic motives (Figure S1.j). According with Dacey (2008) about the positive link between high level of PA and increases of intrinsic and self-determined extrinsic motives in older adults, also COPD patients seems to modify their motivation through the regular practice of ExT. Significant modifications in motivation at short-term PA, i.e. after 3 months of ExT, were observed in Socio/Emotional benefits, Weight management and Enjoyment items, instead after a long-term PA it were observed significant improvement only in Socio/Emotional benefits and in Enjoyment items. In literature, Socio/Emotional benefits items are considered as self-determined extrinsic motives because they reflect personal values not typically dependent on external approval. Moreover, Socio/Emotional benefits seems to discriminate actives from sustained maintainers in older adults (Dacey et al. 2008). Therefore, at the light that was recorded only one drop out from the FC group, caused by illness, and that the FC group shows significant improvement in Socio/Emotional benefits items in both short- and long-term period, we assume that enhancing

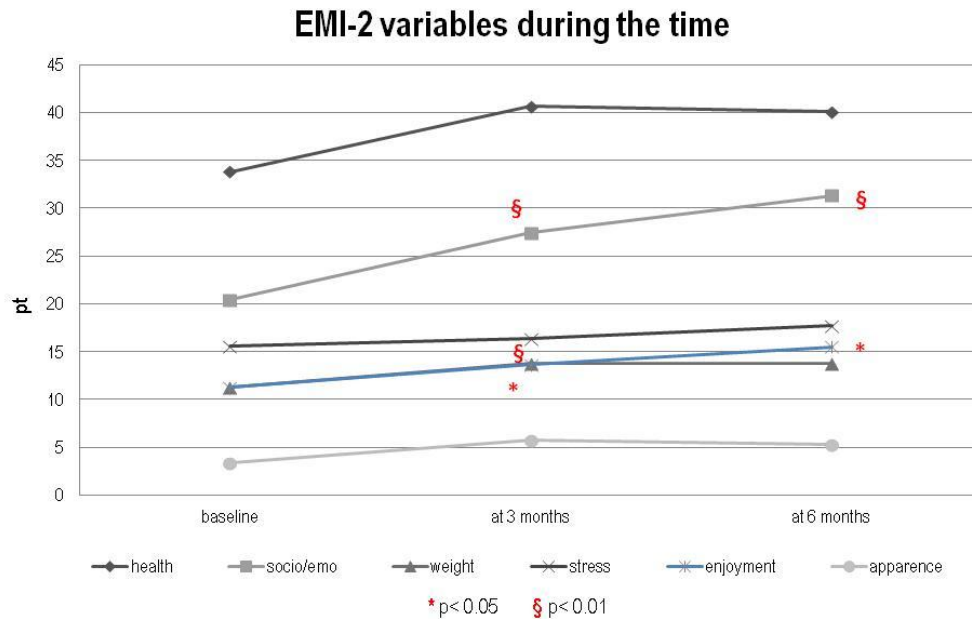


Figure S1.j – Changes in Intrinsic and self-determined extrinsic motives in FC group.

level of self-determined extrinsic motivation are associated with increased engagement and commitment into an ExT. Dacey and colleagues (2008) observed that high Enjoyment score is related to high levels of PA, confirming previous study in which Enjoyment was considered a key factor in older adults PA adherence (Salmon et al. 2003; Bocksnick et al. 2001; Stead et al. 1997). Considered that EMI-2 examines Enjoyment as an emotion and, thus, represents an intrinsic motivation (Ryan et al. 2002), the significant improvements in Enjoyment items at both short- and long-term period suggest that also COPD patients improve their intrinsic motivation when engaging in a structured and constantly supervised PA program. Moreover, these findings suggest that ExT and PA programs for COPD patients should be not only disease-specific tailored (Young et al. 1999) but also focused on patients' need and interest in order to design a PA regiment that reflects their personal preferences and capabilities (Cress et al. 2006) and to improve satisfaction (Katula et al. 2004). Although Weight management item is related to nonself-determined extrinsic motivation and it was the only motive measure that yielded no differences between activity levels in older adults (Dacey et al. 2008), we found a significant short-term improvement of this items. Considered the importance of weight management is PR (B.R. Celli, MacNee, et al. 2004; Rabe et al. 2007; GOLD 2013) we hypothesize that this improvement may be affected by an increase of knowledge regarding the disease, the management and the HRQL factors. Although several studies reported high rate of anxiety and depression among COPD patients and positive effects of PA to decrease these symptoms (Brenes 2003; G.-C. Funk et al. 2009), in our study we did not record any significant improvement in Stress Management items.

We assume that a more-specific instrument of investigation about depression and anxiety symptoms in COPD patients could be more effective to detect modification. Finally, COPD patients did not improve or change the Appearance subscale after participation into an ExT, according with previous studies that recognized Appearance as a nonself-determined extrinsic motivation, reflecting a desire to attain ego enhancement, social approval or feelings of self-worth, which decreased as importance with age.

Conclusion

Recruitment of COPD patients is very challenging and the major cause of not-participation are related to mismatched inclusion criteria. Rate of adherence and number of drop out recorded in this study suggest that a great effort practice of recruitment, managed by only one Exercise Specialist, characterized by persistence and flexibility strategies towards patients, seems to be more effective. Results from the analyses of the motivations recorded to not engage in ExT program confirm literature's findings that the most frequently barrier reported in literature for older adults, i.e. instable clinic conditions, lack of available time, lack of perceived benefits and difficulties in transportation. Improving in level of liaison between specialist physicians and other healthcare professionals engaged in pulmonary management should be empathize. Significant improvements among motivation items, both at short and long-term, suggest that an high, structured and constantly supervised PA program could positive influence COPD patients' intrinsic and self-determined extrinsic motives. The analysis of subscales highlighted the importance to design ExT programs for COPD considering patients' need and interest in order to reflect personal preferences and capabilities. To our knowledge, there are no other studies that analyze intrinsic and self-determined extrinsic motivation in COPD patients based on EMI-2 assessment. In order to increase COPD patients recruitment, to enhance the chances of treatment disease modalities and to promote maintenance of an active lifestyle, further investigations should be conducted to access both knowledge and intrinsic/extrinsic motivation to PA and ExT in PR at different disease stages.

Study 2

University of Verona



Master School of Translational and Biomedical Sciences

**Doctorate Course in Science of Physical Exercise
and Human Movement**

MODELS OF PHYSICAL ACTIVITY: ACTIVE LIFESTYLE PROMOTION FOR COPD PATIENTS

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Background

PR is considered a recommended multi-component intervention (Ries et al. 2007), in which ExT is the most effective part to improve exercise capacity, muscle strength, symptoms and QOL (GOLD 2013; Egan et al. 2012; D. E. O'Donnell et al. 2008). Sedentary lifestyle is recognized as one of the most important factor in physical deconditioning, worsening QoL, increasing disability and risk of death (Pitta et al. 2005; Vorrink et al. 2011). Therefore Long-term strategies to promote health, increase active behaviors and stress adherence to therapy are advocated in COPD patients, as well as the general population (Kahn et al. 2002; Wilson et al. 2005; Roche 2009; Caress et al. 2010). Unfortunately, there are few health-care structured programs of PA and ExT available (Valero et al. 2009; Dourado et al. 2009).

Purpose

The aim of the study is to evaluate modifications in body composition, health-related physical parameters, life style and QoL provided by two different and easily applied-field models of APA for COPD patients.

Design

A longitudinal, randomized controlled trial was designed

Subjects

Thirty-eight COPD males patients (mean post-bronch. FEV₁=69.28±21.5% of predicted; post-bronch. FEV₁/FVC= 57.68±13.9% of predicted; age 66.63±4.6 years) were involved. Participants were randomized and assigned to one of the three evaluation groups: Fitness Center based group (FC), Educational PA group (EDU) and Control group (CG). Ethical approval by Department of Neurological, Neuropsychological, Morphological and Movement Sciences, University of Verona, and informed consent by patients were obtained.

Measures

The differences between groups were assessed using two-way ANOVA was used. Post hoc analysis using Bonferroni correction was provide.

Results

No significant difference were found between groups at baseline in %FEV1, %FEV1/FVC, EMI-2 total score (mean 115.62 ± 37.95) and met/min/set at IPAQ (2324.8 ± 3805.42). Four patients dropped out during the 6 months trial and three in the follow up period. During the study no accident occurred. Mean overall FC attendance was $87\% \pm 3.24$, while EDU attendance at PA session was 100%. Between T1-T2, FC group shows significant improvement in %BMC (0.112 ± 0.029 , $p < 0.01$), Biceps curl 1RM (1.9 ± 0.6 , $p < 0.05$), Chest press 1RM (8.1 ± 1.7 , $p < 0.001$), Balance test (48.5 ± 14.2 , $p < 0.05$). EDU group shows significant modification in FAT (-736.4 ± 240.0 , $p < 0.05$), BMI (-0.332 ± 0.106 , $p < 0.05$), Leg Extension 1RM (7.2 ± 2.4 , $p < 0.05$), Chest Press 1RM (6.1 ± 1.7 , $p < 0.05$) and Back Scratch (2.7 ± 0.7 , $p < 0.01$). The CG group shows significant differences in BMI (-0.588 ± 0.157 , $p < 0.01$), FAT ($-1086.4.4 \pm 365$, $p < 0.05$), and BTM (-1849.8 ± 494.1 $p < 0.01$). Between T1-T3, the FC shows significant improvement in %BMC (0.071 ± 0.024 $p < 0.05$), Chest Press 1RM (9.8 ± 2.4 , $p < 0.01$), Balance ($+108.92\%$ $p < 0.001$), IPAQ moderate activity (1024 ± 272 , $p < 0.01$), IPAQ sedentary hours (-3.3 ± 0.7 , $p < 0.01$) and MRF-26 (-2.3 ± 0.7 , $p < 0.05$). EDU group shows significant modification in 6MWT Borg score (-1.37 ± 0.41 $p < 0.05$), IPAQ walking activity (618 ± 208 , $p < 0.05$), IPAQ sedentary hours (-3.6 ± 0.7 , $p = 0.000$) and MRF-26 (-2.1 ± 0.7 , $p < 0.05$). CG group did not shows significant differences. At follow up, FC shows significant changes in %BMC (-0.069 ± 0.020 $p < 0.05$), 6MWD (-48.2 ± 14.8 , $p < 0.05$), Leg Extension 1RM (-9.3 ± 2.8 , $p < 0.05$), Chest Press 1RM (-11.6 ± 2.1 , $p = 0.000$), Sit & Reach (-3.8 ± 0.9 , $p < 0.01$), Balance (-21.0 ± 7 $p < 0.05$). EDU group shows significant modification in 6MWT Borg score (-1.36 ± 0.41 $p < 0.05$), Leg Press 1RM (-32.6 ± 9.1 , $p < 0.05$), Leg Extension 1RM ($-10 \pm 5 \pm 1.9$, $p < 0.001$), Chest Press 1RM (-14.3 ± 1.3 , $p = 0.000$), Back Scratch (-4.3 ± 1.3 , $p < 0.05$), IPAQ sedentary hours (-3.5 ± 0.9 , $p < 0.01$) and MRF-26 (-2.9 ± 0.8 , $p < 0.05$). CG group shows significant difference in Chest Press 1RM (-10.9 ± 2.6 , $p < 0.01$). No significant modification were observed in SenseWear PRO-2 administration.

Conclusion

According to expert panel position stand (Glaab et al. 2010), our study's results confirms the need of a multifaceted approach in PR programs. Our study demonstrates that also an easily applied-field models of COPD specific APA training could be efficient in order to improve some of these HRQL. The improvements in bone mass content, strength of trunk muscles and patients' self-perceived disability seem to be better provide by the "well rounded" APA program. Moreover, our study shows that APA exercise specialist support is necessary to provide and maintain long-term significant health's gains. Finally, our trial highlights that improvement in functional exercise capacity does not automatically turn into a more active lifestyle. According to Conn (2008), furthers studies are aimed to identify feasible, acceptable and effective APA intervention, which transfer achievements provide reachable changes in lifestyle, both at short- and long-term.

Key words: COPD; exercise training; physical activity; short term; long term; lifestyle; active behavior; educational; well rounded program, quality of life; health-related quality of life

Background

PR is considered a recommended standard of care and management for COPD patients (GOLD 2013), and a multi-component intervention (Ries et al. 2007), in which ExT is the most effective part to improve exercise capacity, muscle strength, symptoms and QOL (GOLD 2013; Egan et al. 2012; D. E. O'Donnell et al. 2008; Ries 2008; Nici et al. 2006). Any patient with mild to severe COPD and activity limitation should undergo ExT (Ries et al. 2007; Chavannes N.H. et al., 2001), despite impaired lung function continues to persist after PR (Dressendorfer et al. 2002). At current, the model of COPD-specific downward spiral of symptom-induced inactivity is widely accepted (B.R. Celli, MacNee, et al. 2004). In fact, sedentary lifestyle is recognized as one of the most important factor in physical deconditioning, worsening QoL, increasing disability and risk of death (M.A. Spruit et al. 2004; Pitta et al. 2005; Pitta et al. 2006; Vorrink et al. 2011). Therefore long-term strategies to promote health, increase active behaviors and stress adherence to therapy are advocated in these patients, as well as the general population (Kahn et al. 2002; Wilson et al. 2005; Roche 2009; Caress et al. 2010). It was established that the “well-rounded PA programs” is the best ExT modality to achieve health benefits and promote active lifestyle in adults and elderly people (Jones C.J. & Rose, 2005). According to ACSM position stand, it is focused on endurance, strength, balance, flexibility training, posture and maintenance of a body composition (M. E. Nelson et al. 2007). Usually in clinical PR practice, ExT includes both aerobic and resistance training prescriptions (C. L. Rochester 2003; van Helvoort et al. 2010), despite COPD-specific ExT guidelines are not provided and yet under debate (Butcher & R. L. Jones 2006; C. B. Cooper 2001; O'Shea et al. 2009). Panel discussion issues are concerned to intensity, i.e. high vs. low intensity (Butcher & R. L. Jones 2006; C. L. Rochester 2003; C. B. Cooper 2001), type, i.e. resistance vs. endurance and/or vs. resistance coupled with endurance (M.A. Spruit et al. 2002; O'Shea et al. 2009) and frequency of training (Ringbaek et al. 2010). Moreover, evidences about benefits maintenance (C. L. Rochester 2003), compliance to long-term ExT, i.e. home-based program vs. high-intensity maintenance (Troosters et al. 2005), effectiveness of short- and long-term adherence strategy, i.e. educational program vs. PA counseling vs. health mentoring (C. L. Rochester 2003; Walters et al. 2012) and COPD-specific recommendations for adequate DPA level to achieve health benefits (Hartman et al. 2010) are still conflicting. Finally, the inclusion of ExT in the health care assistance is considered difficult due to a limited number of local health-care structured programs (Valero et al. 2009; Dourado et al. 2009).

Purpose

Considered ExT effectiveness to improve several HRQL, current debates and limited number of local health-care structured program for COPD patients, further studies are necessary to assess if easily applied-field models of adapted fitness activity are effective to achieve the major PR outcomes and to provide reachable changes in lifestyle, both at short- and long-term. Therefore, aim of the study is to evaluate modifications in body composition, health-related physical parameters, life style and QoL provided by two different and easily applied-field models of adapted fitness activity for COPD patients.

Methods

Design

This study is a longitudinal, randomized controlled trial, designed to assess modifications leaded by two different easily applied-field models of adapted fitness activity for COPD patients. Outcomes assessed are anthropometric parameters, i.e. BMI, body and bone composition, health related physical performances, i.e. exercise tolerance, upper and lower limb strength, flexibility and balance, life style behavior, i.e. DPA level, and QoL as measure of perceived disability. Ethical approval by Department of Neurological, Neuropsychological, Morphological and Movement Sciences (University of Verona), Medical Hospital Management approval of ULSS20, and informed consent by patients were obtained (Figure S2.a).

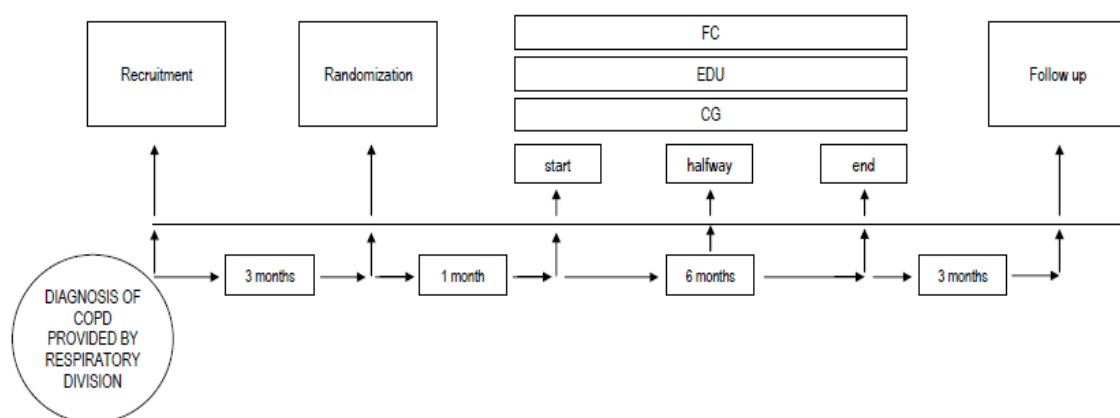


Figure S2.a – Study 1 procedures

Procedures

The data were obtained during the periods between January and December 2012, in which were recruited and randomized participants in the longitudinal trial. Administration was performed at baseline (T1), after 14 weeks (T2) and after 28 weeks (T3) of ExT. A 3-months follow up (T4) re-administration was also provide.

Sample

The convenience sample of eligible patients enrolled in the clinical trial had the following criteria (Table S2.b).

Table S2.b – Study 2 participant inclusion and exclusion criteria	
Inclusion	Exclusion
65 years \pm 5	4 stage of COPD
males	Instable cardiac disease
Stage 1 to 3 GOLD classification	Pneumonia, pulmonary embolism, pulmonary vascular disease, respiratory infections
Clinical stability for at least 1 months	Lung cancer, thoracic malignancy, malignancies
	Bone fractures, fractures

Participants were recruited from the Cardiovascular and Thoracic Department, Respiratory Division, of ULSS 20, Verona, Italy. Between the period of September and October 2011, eligible patients were singled out and advised about trial with an introduction mail. Contacted patients were invited at a first introducing meeting at the Faculty of Science Sports of the University of Verona. During the meeting, research's purpose and details were provided. Also information about disease and ExT benefits on health, QoL and exercise capacity were given. Subscribed patients provided informed consent. Therefore, 38 patients (post-bronch %FEV1 = 69.28% \pm 21.5 of predicted; post-bronch %FEV1/FVC =57.68% \pm 13.9 of predicted) were randomized in three different groups: Fitness Center based group (FC=13), Educational PA group (EDU=12) and Control group (CG=13). Randomization parameters were disease stage, according to GOLD classification (GOLD 2013), total recorded score motivation, assessed by EMI-2 (Markland & Hardy 1997) and the share of practiced PA calculated by administration of the International Physical Activity Questionnaire-short form (IPAQ 2005). COPD patients randomized into the FC group attended 3 time/wk, 90-minute of supervised COPD-specific (B.R. Celli, MacNee, et al. 2004; C. B. Cooper 2001; C. L. Rochester 2003; O'Shea et al. 2009) APA program, delivered by

a qualified APA exercise practitioner, for 6 months, i.e. period between March and October 2012, according to ACSM position stand (Table S2.c) (M. E. Nelson et al. 2007; Jones C.J. & Rose, 2005).

Table S2.c – Characteristics of ExT in FC group

Characteristics	Description
Rationale	Based on ACSM guidelines
Adaptation	ATS/ERS guidelines and panel recommendations
Training support	High support of APA Exercise Specialist
Duration	28 weeks (6 months), 3 times weekly, 90 min per session
Intervention	Well rounded program: endurance, strength, flexibility, balance
ExT prescription	Written and individually tailored PA regimens

Subjects of the EDU group were involved in 28 weeks low progressive supervised ExT, characterized by 14 weeks educational PA period and subsequently 14 weeks of self-selected PA. During the first educational period (Monninkhof et al. 2003), COPD patients were involved in practice PA session, i.e. 60 min/session, of traditional fitness center activity, aerobic group class, walking paths and nordic walking training in order to improve their knowledge about different training modalities (Karapolat et al. 2012) and management of exercise-induced symptoms (Langer et al. 2009). In order to improve patients active-choice in selection of preferred ExT (Cress et al. 2006), exercise specialist support was gradually reduced during the 14 weeks, i.e. from 1° to 5° week, 3 time/wk, from 6° to 10° week, 2 time/wk, from 11° to 14° weeks 1 time/wk. Stage-matched written material and information about different type of local PA facilities were provide to patients in order to stress and increase ExT adherence (Table S2.d).

Table S2.d – Characteristics of ExT in EDU group

Characteristics	Description
Rationale	Based on ACSM guidelines and Trans Theoretical Model
Adaptation	ATS/ERS guidelines and panel recommendations
Training support	Monthly decreasing APA Exercise Specialist support – autonomous PA
Duration	28 weeks; 14 weeks of APA Exercise Specialist support and 14 weeks of autonomous PA
Intervention	Traditional fitness center program, Aerobic group class, Walking paths and Nordic Walking
ExT prescription	Stage-matched written material; Information about local PA facilities.

Patients recruited in CG were not involved in any type of treatment but only in evaluation sessions. During the 6 months trial, 4 patients dropped out caused by instable onset clinically conditions, i.e. N=3 before halfway evaluation, from FC (N=1) and CG (N=2), N=1 between 3 and 6 months of training from CG. At follow up administration 3 patients from CG dropped out caused by lack of available time (N=2) and onset of instable clinic condition (N=1) (Figure S2.e).

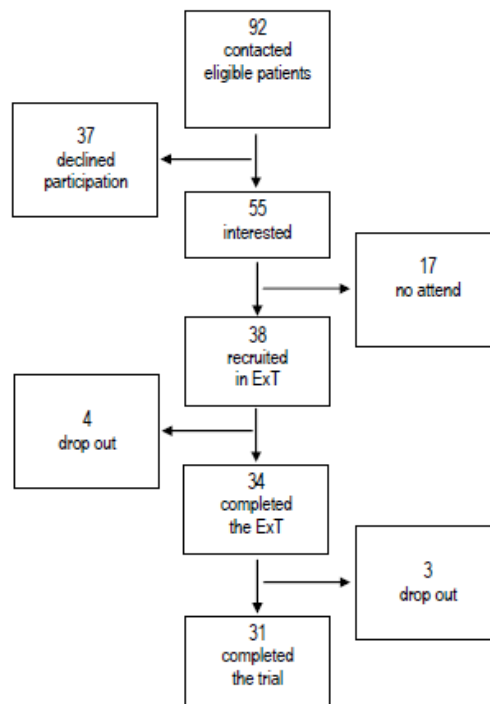


Figure S2.e – Patients recruitment to the Study 2

Measurements

Anthropometric characteristics

Dual energy-X ray absorptiometry scanner, i.e. DXA (QDR explorer W®, Hologic, MA, USA) was used to detect body composition (A. G. N. Agusti et al. 2003), i.e. FFM and LBM, and bone mass content, i.e. BMC. Also, BMI was calculated with formula:

$$\text{BMI} = \text{kg} / (\text{mt})^2 .$$

Health related Physical Parameters

6-min walking test

The 6-min walk test was conducted according to a standardized protocol (P. L. Enright & Sherrill 1998). Subjects were instructed to walk from one end to the other of a 30 meters, i.e. 100-ft., hallway at their own pace, while attempting to cover as much ground as possible in the allotted 6 minutes. Technicians encouraged subjects with the standardized statements “You’re doing well” or “Keep up the good work,” but were asked not to use other phrases. Subjects were allowed to stop and rest during the test, but were instructed to resume walking as soon as they felt able to do so. Rate of perceived exertion was measured with the Borg scale, i.e. 6-20 (C. B. Cooper 2001), and pulse rate were assessed at the start and end of the 6-min walk test. Subjects were also asked at the end of the walk whether they had experienced any of the following symptoms: dyspnea, chest pain, lightheadedness, or leg pain (C. G. Cote et al. 2008).

Muscular strength

In the study patients performed three different submaximal test, i.e. biceps strength by Biceps Curl test, pectoralis major, deltoids and triceps muscles by test at Chest Press isotonic device (Tecnogym®, Gambettola, ITA), quadriceps, gluteus maximus and gastrocnemius by test at Leg Press isotonic device (Tecnogym®, Gambettola, ITA), and quadriceps by test at Leg Extension isotonic device (Tecnogym®, Gambettola, ITA), calculating the 1RM value by Brzycki’s formula (Dohoney et al. 2002):

$$1RM = kg / (1,0278 - (0,0278 \times \text{repetitions' number})).$$

Flexibility and Balance tests

In order to assess flexibility related activity of subjects, the study provided two different flexibility test, i.e. Back Scratch Test to record shoulder range of motion, and Sit & Reach Test to analyze lower back’s flexibility capacity (C. J. Jones & Rikli 2002). To investigate postural steadiness during a static position, subject were involved in 1-Min of One Leg Stance test assessment of both lower arms (Figure S2.f) (Jonsson et al. 2004). Data obtained by each leg test were summed to calculated a total score.



Figure S2.f – Flexibility tests provided; a) Back Scratch test; b) Sit & Reach test; c) One Leg Stance Test.

Lifestyle Behavior

Daily Physical Activity Level

SenseWear PRO2 Armband (Bodymedia®, Pittsburgh, USA) was used in order to assess DPA parameters performed by subjects, such as total steps number, total energy expenditure and active energy expenditure above 3.0 METs. DPA was monitored for 3 days and daily mean (SD) were obtained. In patients with COPD, the SenseWear PRO2 Armband provides a valid and reproducible estimate of energy expenditure during walking at a slow to moderate pace in a laboratory setting (H. Watz et al. 2009).

International Physical Activity Questionnaire -short form

IPAQ short form is an instrument designed for population surveillance of PA and it has been developed and tested for use in adults, i.e. age range of 15-69 years. The IPAQ short form asks about three specific types of activity such as walking, moderate-intensity activities and vigorous-intensity activities. The items in the short IPAQ form were structured to provide separate scores on walking, moderate-intensity and vigorous-intensity activity. Computation of the total score for the short form requires summation of the duration, i.e. in minutes, and frequency, i.e. days, of the three assessed activity (Table S2.g) (Delbaere et al. 2009).(Delbaere et al. 2009; IPAQ 2005) Data cleaning and processing were carried out according to IPAQ guidelines (2005) in order to estimate the levels of PA (Table S2.h)

Table S2.g – MET Values and Formula for Computation of MET-minutes/week

Activity	Formula to estimate MET-minutes/week
Walking	3.3 * walking minutes * walking days
Moderate activity	4.0 * moderate-intensity activity minutes * moderate days
Vigorous activity	8.0 * vigorous-intensity activity minutes * vigorous-intensity days
Total physical activity MET-minutes/week	sum of Walking + Moderate + Vigorous MET-minutes/week scores.

Table S2.h – Levels of physical activity estimated by IPAQ

Level	Formula to estimate MET-minutes/week
Low	who not meet criteria for Categories 2 or 3 are considered to have a 'low' physical activity level:
Moderate	3 or more days of vigorous-intensity activity of at least 20 minutes per day; 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day; 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum Total physical activity of at least 600.
High	vigorous-intensity activity on at least 3 days achieving a minimum Total physical activity of at least 1500 MET-minutes/week; 7 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum Total physical activity of at least 3000 MET-minutes/week.

Quality of Life

Maugeri Respiratore Failure questionnaire, i.e. MRF-26 (Carone et al. 1999), was used in order to measure and quantify impairment in QoL due to the disease. It is characterized by assessment of impairment in ADL, i.e. 13 items, and self-perceived disability, i.e. 13 items. A total score were obtained for each patients at each evaluation session to record changes in self-patients viewpoint about their QOL. Choice of MRF-26 administration was based on its relation to patients ADL and easily application.

Adherence, drop out and EMI-2 administration during the longitudinal randomized trial

Adherence and/or drop out motivations were collected and recorded in a database. Moreover, EMI-2 (Markland & Hardy 1997) administration was performed in order to assess PA motivation scores and provide patients randomization.

Statistical methods

To address the purpose of this trial, statistical analysis of the data began with calculations of the arithmetic means and standard deviations of COPD patients and different intervention groups. The differences between groups were assessed using two-way analysis of variance (ANOVA). Then, post hoc analysis using Bonferroni correction was used to compare difference among testing session and groups. *P* values less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed with Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, IL).

Results

Baseline

All the assessed characteristics of the COPD patients recruited in the trial are depicted in Table S2.i. The 38 male patients with COPD (mean age 66.63y \pm 4.6) are affected by mild to severe airflow obstruction, i.e. post-bronch %FEV₁ = 69.28% \pm 21.5 of predicted, post-bronch %FEV₁/FVC =57.68% \pm 13.9 of predicted. No significant differences were found between groups.

Table S2.i – Characteristics of COPD patients at baseline (t1)

Variables	mean (SD)			
	Tot COPD (N=38)	FC (N=13)	EDU (N=12)	CG (N=13)
Age (years)	66.63 (4.6)	66.16 (4.26)	66.16 (4.34)	67.9 (5.76)
FEV ₁ (%)	69.28 (21.5)	60.12 (24.32)	71.17 (18.80)	77.27 (18.99)
FEV ₁ /FVC (%)	57.68 (13.9)	53.73 (17.73)	58.33 (13.74)	61.30 (8.84)

Effects of PA models on Anthropometric Parameters

Results related to anthropometric parameters are shown in Table S2.j.

In BMC no time x group interaction resulted from ANOVA. No difference between groups were observed. Post-hoc analysis highlighted significant mean factor time differences in FC, i.e. T1<T2 (*p*<0.01) and T1<T3 (*p*<0.05). No difference appeared in EDU and CG. In %BMC no time x group

interaction resulted from ANOVA. No difference between groups were observed. Post-hoc analysis highlighted significant mean factor time differences in FC, i.e. T1<T2 ($p<0.01$), T1<T3 ($p<0.05$), T3>T4 ($p<0.05$). No difference appeared in EDU and CG. In FAT no time x group interaction resulted from ANOVA. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in FC. In EDU T1>T2 ($p<0.05$). In CG T1>T2 ($p<0.05$). In %FAT no time x group interaction resulted from ANOVA. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in FC, EDU and CG. In LBM and %LBM no time x group interaction resulted from ANOVA. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in FC, EDU and CG. In BTM no time x group interaction resulted from ANOVA. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in FC, EDU. In CG T1>T2 ($p<0.01$). In BMI no time x group interaction resulted from ANOVA. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in FC. In EDU T1>T2 ($p<0.05$). In CG T1>T2 ($p<0.01$).

Effects of PA models on Health related Physical Performances

Results related to health related physical parameters are shown in Table S2.k.

Exercise tolerance

In 6MWD and BORG no time x group interaction resulted from ANOVA. No difference between groups were observed. In 6MWD post-hoc analysis highlighted no significant mean factor time differences in EDU and CG. In FC T3>T4 ($p<0.05$). In BORG Post-hoc analysis highlighted no significant mean factor time in FC and CG. In EDU T1>T3 ($p<0.05$) and T1>T4 ($p<0.05$).

1RM Muscle strength

In Leg Press and Leg Extension no time x group interaction resulted from ANOVA. No difference between groups were observed. In Leg Press, post-hoc analysis highlighted no significant mean factor time differences in FC and CG. In EDU T2>T4 ($p<0.05$). In Leg Extension post-hoc analysis highlighted no significant mean factor time differences in CG. In FC T2>T4 ($p<0.05$), T3>T4 ($p<0.05$). In EDU T1<T2 ($p<0.05$) and T2>T4 (0.001). In Biceps Curl no time x group interaction resulted from ANOVA. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in EDU and CG. In FC T1<T2 ($p<0.05$). In Chest Press significant time x group interaction resulted ($p=0.010$). Post-hoc analysis

highlighted significant mean factor time differences in FC, i.e. T1<T2 ($p<0.001$), T1<T3 ($p<0.01$), T2>T4 ($P<0.001$), T3>T4 ($P<0.001$). In EDU T1<T2 ($p<0.05$), T1>T4 ($p<0.01$), T2>T3 (0.001) and T2>T4 ($p<0.001$). In CG T1>T4 ($p<0.01$).

Table S2.j – Changes in anthropometric parameters in FC, EDU and CG groups

	mean (SD)							
	BMC (g)	BMC (%)	FAT (g)	FAT (%)	LBM (g)	LBM (%)	TBM (Kg)	BMI
Baseline								
FC	2180 (413.4)	2.8 (0.41)	24338 (10548)	29.6 (5.1)	53052 (11160)	67.4 (4.9)	79.5 (21.3)	28.4 (6.2)
EDU	2596 (488.8)	3.09 (0.42)	25324 (8178)	29.3 (5.0)	56923 (9342)	67.5 (4.9)	84.8 (16.3)	29.7 (4.5)
CG	2091 (467.5)	2.79 (0.3)	19021 (8033)	24.7 (5.6)	53964 (9256)	72.4 (5.4)	75.0 (16.0)	25.3 (3.2)
3 months								
FC	2246 (424.3)	2.91 (0.44)	23686 (10374)	29.0 (4.8)	53255 (12131)	68.0 (4.6)	79.1 (22.3)	28.2 (6.4)
EDU	2615 (492.2)	3.14 (0.43)	24588 (8204)	28.7 (5.3)	56775 (8924)	68.1 (5.2)	83.9 (15.8)	29.3 (4.4)
CG	2060 (408.5)	2.83 (0.27)	17935 (7493)	23.9 (4.8)	53232 (9859)	73.2 (4.5)	73.2 (16.5)	24.7 (3.4)
6 months								
FC	2216 (420.5)	2.87 (0.4)	23852 (10376)	29.3 (5.6)	52756 (10900)	67.7 (4.8)	78.8 (21.0)	28.0 (6.0)
EDU	2614 (504.1)	3.15 (0.4)	24500 (7314)	28.9 (4.7)	56349 (9189)	67.9 (4.6)	83.4 (15.5)	29.2 (4.3)
CG	2110 (493.5)	2.84 (0.26)	18376 (7897)	24.1 (5.4)	53639 (8949)	72.9 (5.2)	74.1 (15.8)	24.9 (3.0)
Follow up								
FC	2191 (430.1)	2.80 (0.4)	24638 (10172)	30.0 (4.7)	52996 (11532)	67.1 (4.5)	79.8 (21.3)	28.3 (6.0)
EDU	2605 (493.3)	3.10 (0.39)	25425 (7306)	29.6 (4.3)	56560 (9534)	67.2 (4.3)	84.5 (16.0)	29.6 (4.4)
CG	2135 (503.4)	2.82 (0.26)	19051 (7008)	24.8 (4.4)	54240 (9926)	72.2 (4.2)	75.4 (15.9)	25.4 (3.2)

Back Scratch and Sit & Reach

In Back Scratch test significant time x group interaction resulted ($p=0.011$). Post-hoc analysis highlighted no significant mean factor time differences in FC. In EDU $T1 < T2$ ($p < 0.01$) and $T2 > T4$ ($p < 0.05$). In CG $T1 > T2$ ($p < 0.01$). In Sit & Reach test no time x group interaction resulted from ANOVA. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in CG and EDU. In FC $T3 > T4$ ($p < 0.01$).

One Leg Stance Test

In Balance no time x group interaction resulted from ANOVA. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in CG and EDU. In FC $T1 < T2$ ($p < 0.05$), $T1 < T3$ ($p < 0.01$) and $T3 > T4$ ($p = 0.052$).

Effects of PA models on Lifestyle Behavior and Quality of Life

Results related to Lifestyle Behavior and Quality of Life are shown in Table S2.l and Table S2.m.

Lifestyle Behavior

In SenseWear PRO2 administration, Total Energy Expenditure, Active Energy Expenditure and Steps Number no time x group interaction resulted from ANOVA. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in FC, EDU and CG. In IPAQ short form, no time x group interaction resulted from ANOVA in vigorous activities. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in FC, EDU and CG. Moreover, no time x group interaction resulted from ANOVA in moderate activities. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in EDU and CG. In FC $T1 < T2$ ($p < 0.01$), $T1 < T3$ ($p < 0.01$). Also, no time x group interaction resulted from ANOVA in walking activity. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in FC and CG. In EDU $T1 < T3$ ($p < 0.05$). Furthermore, no time x group interaction resulted from ANOVA in total MET-min/week. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences in FC, EDU and CG. Finally, no time x group interaction resulted from ANOVA in total sitting hours per day. No difference between groups were observed. Post-hoc analysis highlighted significant mean factor time differences in FC, i.e. $T1 > T2$ ($P < 0.001$) and $T1 > T3$ ($p < 0.01$). In EDU $T1 > T2$ ($p < 0.001$) and $T1 > T4$ ($p > 0.01$). In CG $T1 > T2$ ($p < 0.05$).

Table S2.k – Changes in Health related Physical Parameters in FC, EDU and CG groups

	mean (SD)								
	6MWD (mt)	Borg (6-20)	Leg Press (Kg)	Leg Ext (Kg)	Biceps Curl (Kg)	Chest Press (Kg)	Back Scratch (cm)	Sit & Reach (cm)	Balance (sec)
Baseline									
FC	463 (117)	12.0 (2.0)	168 (48)	55 (17)	9.8 (3.1)	40 (9)	-7.4 (19.0)	-11.1 (12.4)	52 (47)
EDU	591 (72)	12.7 (0.9)	206 (76)	64 (21)	11.3 (1.9)	67 (15)	-8.6 (15.3)	-13.5 (13.8)	72 (47)
CG	549 (91)	12.0 (1.2)	199 (60)	71 (21)	12.6 (1.2)	49 (8)	2.2 (4.5)	-7.7 (10.5)	69 (20)
3 months									
FC	455 (145)	12.0 (2.3)	179 (69)	60 (21)	11.8 (3.3)	48 (8)	-5.9 (17.6)	-7.9 (13.5)	101 (38)
EDU	571 (53)	11.9 (1.0)	216 (56)	71 (19)	13.1 (3.0)	63 (11)	-5.9 (14.9)	-7.4 (14.4)	94 (30)
CG	571 (95)	13.0 (1.0)	176 (40)	70 (25)	11.8 (2.4)	50 (10)	-2.0 (4.9)	-8.2 (10.8)	76 (53)
6 months									
FC	495 (127)	12.2 (1.8)	203 (77)	62 (18)	11.9 (2.7)	50 (9)	-3.8 (16.0)	-4.5 (10.7)	109 (22)
EDU	540 (48)	11.3 (2.1)	198 (64)	65 (20)	12.8 (2.9)	54 (13)	-8.0 (15.7)	-10.7 (14.6)	104 (33)
CG	547 (101)	11.2 (1.0)	161 (46)	63 (25)	11.8 (3.0)	41 (13)	-2.0 (4.0)	-11.7 (13.2)	89 (48)
Follow up									
FC	447 (125)	12.3 (1.9)	165 (55)	53 (18)	9.8 (4.3)	38 (7)	-5.9 (18.6)	-8.3 (11.8)	88 (36)
EDU	506 (65)	11.3 (1.9)	184 (55)	60 (17)	12.2 (2.4)	49 (9)	-10.2 (16.0)	-11.6 (12.7)	89 (36)
CG	543 (101)	12.8 (0.8)	160 (29)	64 (28)	11.9 (2.8)	38 (9)	-3.4 (6.0)	-10.2 (10.4)	86 (53)

Quality of Life

In MRF-26 no time x group interaction resulted from ANOVA. No difference between groups were observed. Post-hoc analysis highlighted no significant mean factor time differences CG. In FC T1>T3 ($p<0.05$) and T2>T3 ($p<0.05$). In EDU T1>T3 ($p<0.05$) and T1>T4 ($p<0.05$).

Table S2.I – Changes in Lifestyle Behavior in FC, EDU and CG groups (SenseWear PRO2)

	mean (SD)		
	N° steps	Tot Energy Expenditure (j)	Active Energy Expenditure (j)
<i>Baseline</i>			
FC	5548 (3293.7)	8970 (1221.8)	1281 (892.7)
EDU	5524 (3156.3)	11226 (1570.3)	1832 (1522.1)
CG	6972 (86.97)	13150 (2189.2)	3580 (3771.7)
<i>3 months</i>			
FC	5501 (2840.6)	9223 (1961.8)	1388 (945.9)
EDU	6536 (3095.6)	10824 (2232.7)	2306 (2023.8)
CG	11118 (881.8)	13815 (1711.2)	3411 (587.6)
<i>6 months</i>			
FC	6046 (2775.4)	92.87 (1589.25)	1404 (644.35)
EDU	8110 (2724.3)	12082 (2059.9)	2421 (2070.8)
CG	10476 (1867.5)	13990 (15552.8)	4268 (2875.1)
<i>Follow up</i>			
FC	6184 (3612)	9029 (1468.82)	1371 (840.8)
EDU	5032 (2694)	10597 (1294.1)	1280 (1001.4)
CG	8914 (3544)	11361 (647.7)	1399 (7.1)

Table S2.m –Changes in Lifestyle Behavior (IPAQ-short form) and Quality of Life (MRF-26) in FC, EDU and CG groups

	mean (SD)					
	IPAQ – short form				MRF-26	
	Vigorous (MET- min/week)	Moderate (MET- min/week)	Walking (MET- min/week)	Tot (MET- min/week)	Sedentary (hours)	Disability (pt)
<i>Baseline</i>						
FC	720 (2113)	236 (497)	580 (512)	1409 (2314)	10.6 (2.4)	7.2 (3.8)
EDU	523 (1061)	720 (1544)	330 (357)	2929 (5229)	8.4 (2.4)	5.3 (2.1)
CG	2040 (3192)	750 (1020)	932 (1231)	334 (2619)	7.2 (1.2)	5.8 (6.1)
<i>3 months</i>						
FC	720 (2276)	1608 (1055)	897 (1452)	3039 (2815)	7.3 (2.7)	6.6 (4.4)
EDU	1440 (3133)	1338 (1722)	943 (780)	3959 (4813)	5.2 (2.1)	4.6 (3.5)
CG	2200 (3136)	40 (80)	643 (678)	2832 (2928)	3.8 (0.6)	3.9 (4.6)
<i>6 months</i>						
FC	640 (1197)	1260 (543)	892 (782)	2649 (1506)	7.3 (2.2)	4.5 (4.5)
EDU	290 (707)	763 (1497)	948 (906)	1835 (1687)	5.2 (2.0)	3.1 (2.7)
CG	0 (0)	1150 (1544)	317 (238)	1178 (1621)	3.8 (0.6)	5.7 (7.4)
<i>Follow up</i>						
FC	0 (0)	534 (1322)	932 (1224)	1333 (2418)	8.3 (4.7)	6.2 (4.3)
EDU	130 (310)	894 (1436)	1161 (1205)	3032 (3563)	5.2 (2.7)	2.2 (2.1)
CG	0 (0)	720 (1440)	2343 (1779)	2807 (2452)	6.0 (3.1)	2.9 (3.2)

Adherence and drop out

During the trial, 4 patients dropped out caused by instable onset clinically conditions, i.e. N=3 before halfway evaluation, from FC (N=1) and CG (N=2), N=1 between 3 and 6 months of training from CG. At follow up administration 3 patients from CG dropped out caused by lack of available time (N=2) and onset of instable clinic condition (N=1). FC adherence at ExT was ~87%, whereas in EDU group was 100% at first 3 months. At the end of the 6 months only 2 patients fill out the PA diary, 3 patients deliver the diary partially completed and 6 COPD patients didn't deliver, preventing to obtain any significant information.

Discussion

In order to determine the effectiveness of our-designed field models of COPD-specific APA training, a differential analysis of each parameter assessed in each exercise groups seems appropriate.

It was observed several nutritional and body composition abnormalities in patients with COPD (Bolton et al. 2004; A. G. N. Agusti et al. 2003; Steuten et al. 2006). Weight loss and reduction in BMI and a loss of FFM are considered independent poor prognostic indicators for survival (A. G. N. Agusti et al. 2003; Steuten et al. 2006; GOLD 2013), leading to increased morbidity, worsen QoL, reduced exercise performance and an higher mortality (Bolton et al. 2004). However, loss of FFM is considered the most important prognostic parameters (A. G. N. Agusti et al. 2003; Bolton et al. 2004). In our study we did not find overall significant changes in COPD patients body composition both at short and long-term ExT, probably related to several confounding mechanisms, i.e. drugs intake, systemic inflammation, and/or tissue hypoxia (A. G. N. Agusti et al. 2003). Moreover, body composition abnormalities were particularly prevalent in patients with severe to very severe COPD and chronic respiratory failure, i.e. ~50% of COPD patients in Stage III and IV (A. G. N. Agusti et al. 2003; Bolton et al. 2004; Steuten et al. 2006; Lainscak et al. 2011). In our study, very severe COPD patients were excluded and recruited only few (N=5) patients whit severe airflow obstruction. However, the significant modification about loss of FAT (g) and BMI reduction in EDU and CG groups were recorded only between the trial's first 3 months, i.e. between March and July 2012. We prompt a seasonal influence which affect these parameters and may lead into worsen QoL and survival rates in under- and normal weight patients (Franssen et al. 2008; Blum et al. 2011). Osteoskeletal dysfunctions were observed in patients with COPD (Bolton et al. 2004; A. G. N. Agusti et al. 2003). Osteoporosis is associated with poor health status and prognosis (GOLD 2013) and related to multiple causes, i.e.

malnutrition, sedentary behavior, smoking, steroid treatment, systemic inflammation and ageing (A. G. N. Agusti et al. 2003; GOLD 2013). In our study we found significant modifications in bone mass content only in FC group, recorded between T1-T2, i.e. $\Delta\text{BMC(g)} = 65.6 \pm 17$ $p < 0.01$, $\Delta\text{BMC(\%)} = 0.112 \pm 0.029$ $p = 0.001$, between T1-T3, i.e. $\Delta\text{BMC(g)} = 35.8 \pm 10.6$ $p < 0.05$, $\Delta\text{BMC(\%)} = 0.071 \pm 0.024$ $p < 0.05$, and between T3-T4, i.e. $\Delta\text{BMC(\%)} = -0.069 \pm 0.020$ $p < 0.01$. At the time of administration, none of FC patients were subjected to osteoporosis pharmacologic therapy, suggesting that a supervised COPD-specific APA program could influence favorably the bone health (Kohrt et al. 2004). Although endurance training is considered the fundamentally important component of any PR program (C. B. Cooper 2001; Ries 2008; Ries et al. 2007), at the end of our 6 months trial we did not observed an overall improvement in exercise tolerance assessed by 6MWT. A differential analysis of motivations for both exercise groups seems appropriate. Aerobic prescription in FC group was based on expert panel recommendations (C. B. Cooper 2001; C. L. Rochester 2003; Butcher & R. L. Jones 2006), i.e. aerobic interval training using large muscle groups of the legs, as treadmill and cycle ergometry, accumulation of 30 min of aerobic exercise on at least 3 d/wk, no use of maximum heart rate but regular use of RPE scale (range 6–20) to monitor exercise intensity. Progression of activities and intensity adjustment tailored to tolerance and preference were regularly provided (W. J. Chodzko-Zajko et al. 2009; Cress et al. 2006; Langer et al. 2009). No changes in FC exercise tolerance may be related to low level of DPA, suggesting that specific-COPD supervised APA training should be coupled with increased practice of autonomous PA (Pitta, Troosters, et al. 2008; Nici et al. 2006; Ferreira et al. 2009; Lacasse et al. 2006; Ries et al. 2007). Similar observation could be carried out regarding EDU group, in which patients were involved in a educational program (Monninkhof et al. 2003; Cress et al. 2006), designed to improve knowledge about training modalities (Karapolat et al. 2012) and exercise management (Langer et al. 2009), and to acquire an active behavior (Langer et al. 2009). In our study any modification in EDU group 6MWT performance was observed. Unsupervised training seems to lack transfer achievements in aerobic exercise capacity, improving only long-term RPE, i.e. between T1-T3 ($\Delta\text{RPE (pt)} = 1.36 \pm 0.41$ $p < 0.05$) and between T1-T4 ($\Delta\text{RPE (pt)} = 1.36 \pm 0.41$ $p < 0.05$). Therefore, as suggesting before, the best presumable intervention in COPD patients' exercise tolerance seems to be the coalescence of both supervised and unsupervised training in order to accumulate at least 30 min of aerobic exercise, most of days in a week (W. J. Chodzko-Zajko et al. 2009; C. B. Cooper 2001). Significant reduction between T1-T4, i.e. $\Delta\text{6MWD(mt)} = -48.2 \pm 14.8$ $p < 0.05$) observed in 6MWD of FC patients support our assumes. Most of recent researches suggested that sedentary lifestyle is unlikely to be the only explanation for COPD myopathy, which results in reduced muscle

strength performances of COPD patients (M. P. Engelen et al. 2000; Couillard & Prefaut 2005; Kim et al. 2008). COPD muscle wasting is usually characterized by several metabolic, morphological and/or structural muscle abnormalities that lead to dysfunction (Couillard & Prefaut 2005). Moreover, COPD muscle strength alterations are not homogenous between various muscle groups, with prevalence in lower limbs (Mador & Bozkanat 2001; Kim et al. 2008). In fact, in our study we observed differences in ExT trends' response between muscular groups assessed. The most responsiveness muscular group to strength-specific ExT is those of trunk, which was tested by 1RM Chest Press Test. Significant improvements in Chest Press performance were observed both ExT groups when involved in supervised training, i.e. FC between T1-T2, $\Delta 1RM(kg) = 8.1 \pm 1.7$ $p=0.001$, between T1-T3, $\Delta 1RM(kg) = 9.8 \pm 2.4$ $p<0.01$, and EDU between T1-T2, $\Delta 1RM(kg) = 6.1 \pm 1.7$ $p<0.05$. In case of interruption or reduction in supervision, Chest Press test performances decreased in both ExT groups, i.e. FC between T3-T4, $\Delta 1RM(kg) = -11.6 \pm 2.1$ $p=0.000$, between T2-T4, $\Delta 1RM(kg) = -9.9 \pm 1.2$ $p=0.000$, and EDU between T2-T3, $\Delta 1RM(kg) = -9.6 \pm 2.0$ $p=0.001$ and between T2-T4, $\Delta 1RM(kg) = -14.3 \pm 1.3$ $p=0.000$. These observations are confirmed by CG and EDU groups recorded trend, i.e. CG between T1-T4, $\Delta 1RM(kg) = -10.9 \pm 2.6$ $p<0.01$, and EDU between T1-T4, $\Delta 1RM(kg) = -8.2 \pm 1.9$ $p<0.01$. Different response was observed in lower limb strength performances. Significant improvements were recorded only in EDU patients at Leg Extension test, i.e. T1-T2, $\Delta 1RM(kg) = 7.2 \pm 2.4$ $p<0.05$. However, in case of interruption or reduction in strength-specific ExT, 1RM of lower limb decreased in both ExT groups, i.e. FC between T2-T4, Δ Leg Extension (kg) = -6.8 ± 2.1 $p<0.05$, between T3-T4, Δ Leg Extension (kg) = -9.3 ± 2.8 $p<0.05$, and EDU between T2-T4, Δ Leg Extension (kg) = 10.5 ± 1.9 $p=0.000$ and Δ Leg Press (kg) = -32.6 ± 9.1 $p<0.05$. We assume that no long-term modification provided by the lower limb strength training in ExT groups confirmed the unfavorable impact of muscle wasting on muscle performances (Kim et al. 2008) suggesting that traditional strength ExT is not enough effective to attack COPD lower limb strength impairment. Both interruption, reduction and lack of APA expert's supervision affect negatively flexibility performances of COPD patients, i.e. FC between T3-T4, Δ Sit & Reach (cm) = -3.8 ± 0.9 $p<0.01$, EDU between T2-T4, Δ Back Scratch (cm) = -4.3 ± 1.3 $p<0.05$, and GC between T1-T2, Δ Back Scratch (cm) = -4.2 ± 1.1 $p<0.01$. Despite decrements observed in joint ROM with age and established links among poor flexibility, mobility, and physical independence (W. J. Chodzko-Zajko et al. 2009), surprisingly, to our knowledge there are no studies about the effects of specific ROM exercises on flexibility outcomes and its impact in QoL of COPD population. Modification into static position's postural steadiness observed in FC group over the time, i.e. T1-T2, $\Delta 1LST(sec) = 48.5 \pm 14.2$ $p<0.05$ and T1-T3, $\Delta 1LST(sec) = 57.0 \pm 13.3$ $p<0.01$,

confirmed the effectiveness of “well rounded program” in improving balance in adults and elderly people (M. E. Nelson et al. 2007). Moreover, this result acquire more importance in PR considering that balance is a complex skill, i.e. integration and coordination of musculoskeletal and neural systems, and its deficit prevalence is increasingly recognized in COPD (Beauchamp et al. 2011). Both short- and long term impact in lifestyle of each ExT models were investigated by questionnaire administration, i.e. IPAQ, and by multisensor armband setting, i.e. SenseWear PRO-2. In IPAQ assessment, FC significantly improves MET-min/week in moderate activity, i.e. between T1-T2, Δ moderate (MET-min/week) = 1372 ± 375 $p < 0.01$ and between T1-T3, Δ moderate (MET-min/week) = 1024 ± 272 $p < 0.01$. Also EDU group shows significant changes only in walking activity between T1-T3, Δ walking (MET-min/week) = 618 ± 208 $p < 0.05$. These observation was confirmed by reported changes in sedentary time spent, i.e. FC between T1-T2 and T1-T3, Δ sedentary (hr) = -3.3 ± 0.7 $p < 0.01$, and EDU between T1-T2, Δ sedentary (hr) = -3.6 ± 0.6 $p = 0.000$, between T1-T3, Δ sedentary (hr) = -3.6 ± 0.7 $p = 0.000$ and between T1-T4, Δ sedentary (hr) = -3.5 ± 0.9 $p < 0.01$. Despite this positive results, modifications in daily energy expenditure and steps number (SenseWear PRO-2) were not recorded. Moreover total MET-min/week by IPAQ didn't show any modification. Therefore, we did not find objective data that support notion of an acquired COPD patients active behavior after participation at the ExT trial. Significant changes in IPAQ evaluation are probably due to an overestimation provided by patients about their self-perceived DPA. In fact, despite these questionnaire has been developed and tested for use in adults, i.e. age range of 15-69 years (Delbaere et al. 2009; IPAQ 2005), further investigations with large number of patients are aimed to verify effectiveness characterization of vigorous and moderate IPAQ items related to COPD breathe effort. Finally our study observed a significant short- and long term reduction of patients' self-perceived disability after ExT, i.e. FC between T1-T3 Δ MRF-26 (pt) = -2.3 ± 0.7 $p < 0.05$, and between T2-T3, Δ MRF-26 (pt) = -2.5 ± 0.7 $p < 0.05$, and EDU between T1-T3, Δ MRF-26 (pt) = -2.1 ± 0.7 $p < 0.05$. This results confirmed previous reported importance of ExT (GOLD 2013; Egan et al. 2012; D. E. O'Donnell et al. 2008) and the effectiveness of our easily applied-field models of APA in increasing QoL of COPD patients.

Conclusion

The aim of the study was to evaluate modifications in several HRQL of patients affected by mild to severe airflow obstruction, in order to verify the effectiveness of two different and easily applied-field models of COPD-specific APA training. It is well known that COPD is a complex and

multi-component disease, in which its impact on patients' daily life, health, and wellbeing is not heterogeneous (P. W. Jones 2001). According to expert panel position stand (Glaab et al. 2010), our study's results confirms the need of a multifaceted approach in PR programs, suggesting that standardized designs of ExT programs do not appeared to be adequately effective in enhancing the overall of specific-HRQL outcomes. However, considered that COPD affects lungs, extra-pulmonary organs, such as peripheral muscles and bone composition, and the interaction between patients and environment, our study demonstrates that also an easily applied-field models of COPD specific APA training could be efficient in order to improve some of these HRQL. The improvements in bone mass content, strength of trunk muscles and patients' self-perceived disability seem to be better provide by the "well rounded" APA program, i.e. FC, and may be resulting in enhanced bone health, increased in accessory respiratory function (Dourado et al. 2009) and better QoL. Improvements in patients' QoL after a PR are necessary to evaluate the treatment in terms of effectiveness (P. W. Jones & R. M. Kaplan 2003; Domingo-Salvany et al. 2002). Moreover, our study shows that APA exercise specialist support is necessary to provide and maintain long-term significant health's gains. Our results confirm previous studies finding about less effectiveness of education, verbal advice and guidance about exercise as compared to supervised ExT program (C. L. Rochester 2003), suggesting that APA exercise specialist should be considered as a resource, especially in aftercare programs. Finally, as observed by Breyer (2010), Pitta (2008) and Lacasse (2006) our trial highlights that improvement in functional exercise capacity does not automatically turn into a more active lifestyle. According to Conn (2008), furthers studies are aimed to identify feasible, acceptable and effective APA intervention, which transfer achievements provide reachable changes in lifestyle, both at short- and long-term.

Study 3

University of Verona



Master School of Translational and Biomedical Sciences

**Doctorate Course in Science of Physical Exercise
and Human Movement**

CONCENTRIC AND ECCENTRIC TORQUE IN COPD PATIENTS vs. HEALTHY CONTROLS

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Background

Presence of muscle wasting is common in Chronic Obstructive Pulmonary Disease (COPD) patients across all disease stages (Seymour et al. 2010) which leads to a reduction in skeletal muscle strength of lower limb (Kim et al. 2008; Donaldson et al. 2012). Surprisingly it has been observed that eccentric contraction results greater compared to healthy control subjects when normalized for lean body mass (Mathur et al. 2007).

Purpose

The aim of this study is to outline a description of COPD strength performances as a function of contraction modalities and velocities.

Design

A case/control, crossover, observational trial was designed.

Subjects

Thirty-five COPD males (mean FEV1=64.76±20.08% of predicted; FEV1/FVC= 57.35±13.56% of predicted; age 67.21±4.7 years) and 25 HC males (FEV1= 115.06±17.43% of predicted; FEV1/FVC=101.87±6.62% of predicted; age 65.15±5.69 years) were involved. Ethical approval by Department of Neurological, Neuropsychological, Morphological and Movement Sciences, University of Verona, and informed consent by patients were obtained.

Measures

Subjects performed an isokinetic knee extensors concentric and eccentric peak torque at 30 and 210 deg/s. Moreover, vastus lateralis muscle architecture, 6MWT and 1RM Leg Press were performed. One way ANOVA and Pearson coefficient were used to detect significant differences between groups and correlation between dependent and independent variables.

Results

As expected HC subjects was significantly better in lung function parameters, i.e. FEV₁ ($p<0.001$) and FEV₁/FVC ($p<0.001$), and in exercise capacity, such as 6MWT performances ($p<0.001$) and 1RM Leg Press ($p<0.05$). Of all contractions performed, only concentric 30deg/s peak torque was significantly higher in healthy control subjects compared to COPD patients ($p<0.05$). In this study, differences in muscle architecture, fast concentric and/or eccentric peak torque were no observed between groups. However, significant differences were found between groups in eccentric/concentric peak torque ratio (30 deg/sec $p<0.001$; 210 deg/sec $p<0.01$). Finally, significant correlations were found between FEV₁ and 6MWT (0.719 $p<0.001$), 1RM Leg Press (0.449 $p<0.001$), peak torque contraction at 30 deg/sec (0.427 $p<0.01$; 0.280 $p<0.05$), at 210 deg/sec (0.285 $p<0.05$; 0.276 $p<0.05$) and eccentric/concentric peak torque ratio at both velocities (-0.562 $p<0.001$; -0.292 $p<0.05$). Same results were observed between FEV₁/FVC and parameters assessed.

Conclusion

In conclusion COPD patients showed lower health related parameters and performed lower concentric contraction compared to healthy controls. Interestingly, COPD preserved eccentric contractions and fast concentric torque. Considered that eccentric contraction seems to involve fast twitch motor units (Duchateau & Enoka 2008) and COPD hypoxia leads fiber shift towards IIx fibers (H.R. Gosker, Van Mameren, et al. 2002), COPD males seem to develop a favorable profile to minimize the strength loss likely due to neural-muscular modification.

Key words: COPD; Lung function; Muscle dysfunction; Strength performance; Concentric peak torque; Eccentric peak torque; Isokinetic device

Background

Patients affected by COPD suffer from irreversible and mostly progressive airflow limitation caused by inflammation of the airways, lung parenchyma and pulmonary vasculature as a reaction to noxious gases such as cigarette smoke (B.R. Celli, MacNee, et al. 2004). In advanced stages, COPD is characterized by dyspnea, cough and excessive mucus production. These characteristics reduce the level of DPA of people affected by COPD and consequently have a great impact on their exercise capacity and QoL (P. W. Jones 1995; Nici et al. 2006; Van der Vlist & Janssen 2010). Despite an initial skepticism, several randomized-controlled trials and meta-analyses (Nici et al. 2006; Ries et al. 2007; Ries 2008) have supported notion that exercise training is a main component of a comprehensive pulmonary rehabilitation, becoming the cornerstone in the management of COPD (I. M. Weisman et al. 2003; Nici et al. 2006; W.D-C Man et al. 2009a). In addition to pulmonary manifestations, patients affected by COPD develop a great number of extrapulmonary manifestations, such as organ-specific dysfunction, nutritional abnormalities, weight loss and skeletal muscle wasting (A. G. N. Agusti et al. 2003; Barnes & B.R. Celli 2009; Huertas & Palange 2011). In fact several studies demonstrated that the main exercise limiting factor in COPD is related to leg fatigue and not, as expected, to dyspnea. Such outcome suggests that skeletal muscle function is also a fundamental factor in COPD patients exercise capacity (Van der Vlist & Janssen 2010). Moreover, these findings hinder more importance when related to notions that leg muscle mass and strength have been shown to better predict mortality, morbidity, health status and quality of life in COPD patients than lung function measures (Couillard & Prefaut 2005; W.D-C Man et al. 2009b; Butcher et al. 2012). Therefore, in the last decades, a considerable number of research focused their interests to better understand the characteristics and the mechanisms of COPD patients skeletal muscle wasting (Bernard et al. 1998; H.R. Gosker et al. 2000; H.R. Gosker, van Mameren, et al. 2002; Couillard & Prefaut 2005; Kim et al. 2008; W.D-C Man et al. 2009a; W.D-C Man et al. 2009b; Barreiro & Sieck 2013), and, furthermore, to describe their implications into strength performances, ExT and pulmonary PR (Mathur et al. 2007; W.D-C Man et al. 2009a; Butcher et al. 2012). Despite the evidence of clinical benefits due to ExT, the different mechanisms leading to changes in skeletal muscle are not yet fully understood (Barreiro & Sieck 2013). Moreover, a considerable debate continues with regards to the relative merits of additional strength training over traditional endurance training adopted during PR (M.A. Spruit et al. 2002; W.D-C Man et al. 2009a). Finally, the majority of research has focused on examining leg muscle function in patients with COPD has used either isometric or concentric quadriceps torque as correlates or outcome measures (Butcher et al.

2012). Recent trials suggest that peak eccentric torque of quadriceps is better correlate with functional tasks, than concentric one (Roig et al. 2008; Roig, Eng, D. L. Macintyre, D. Road, et al. 2010). To assess the eccentric contractions or fast-velocity contractions in healthy older adults and with disabilities an isokinetic device may be more useful as methods of assessing functional performance (Gur et al. 2002).

Purpose

Considered the lack of knowledge about the association between eccentric muscle strength and fast-velocity muscle contractions in COPD patients (Mathur et al. 2007; Butcher et al. 2012), this study would to investigate COPD patients strength performances as a function of contraction modalities and velocities

Methods

Design

This study is a case/control, crossover, observational trial. It was designed to assess differences between HC group and COPD patients in lifestyle, health related physical parameters, vastus lateralis muscle architecture and concentric/eccentric peak torque of quadriceps muscle. Assessment of parameters were obtained in two different testing sessions, i.e. one to recorded lung function parameters, architectural measurements and health related physical parameters, and a second evaluation to perform concentric/eccentric contraction at the isokinetic device, in randomized order. . The data were obtained during the periods between September and November 2012, in which were singled out, contacted and recruited the healthy control subjects and tested both the subjects' groups. One familiarization session was provided for both subjects' groups using the isokinetic dynamometer. Moreover, the DPA parameters were obtained by SenseWear PRO2 Armband (Bodymedia®, Pittsburgh, USA). Ethical approval by Department of Neurological, Neuropsychological, Morphological and Movement Sciences, University of Verona, Medical Hospital Management approval of ULSS20, and informed consent by participant were obtained (Figure S3.a).

Sample

In the study 60 male subjects were recruited, i.e. 35 COPD patients and 25 HC subjects. The convenience sample of COPD patients enrolled in the trial had the following criteria: age 65 years \pm 5, affected by mild to severe COPD and clinically stable for at least 1 months no diseases that would interfere with exercise, such as no evidences of instable cardiac diseases, no malignancies and bone fractures (Table S3.b). Participants were recruited from the Cardiovascular and Thoracic Department, Respiratory Division, of ULSS 20, Verona, Italy.

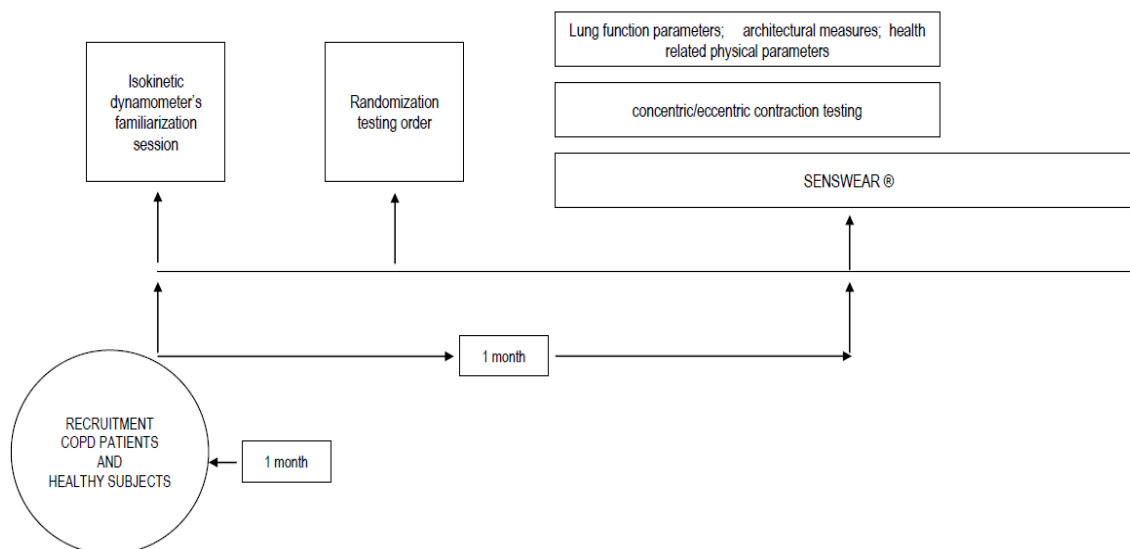


Figure S3.a – Study 3 procedures.

Table S3.b – Study 1 COPD patients inclusion and exclusion criteria

Inclusion	Exclusion
65 years \pm 5	4 stage of COPD
males	Instable cardiac disease
Stage 1 to 3 GOLD classification	Pneumonia, pulmonary embolism, pulmonary vascular disease, respiratory infections
Clinical stability for at least 1 months	Lung cancer, thoracic malignancy, malignancies
	Bone fractures, fractures

The sample of HC subjects enrolled in the trial had the following criteria: age 65 years \pm 5, without cardiovascular, metabolic and pulmonary disease, clinically stable for at least 1 months, no diseases that would interfere with exercise, such as no evidences of malignancies and bone fractures (Table S3.c). Participants were recruited between the participants at the local initiative “La Salute nel Movimento”, supervised by the Faculty of Exercise and Sports of the University of Verona, which involve adults and elderly people in different specific PA programs.

Table S3.c – Study 3 HC subject inclusion and exclusion criteria

Inclusion	Exclusion
65 years \pm 5	Pulmonary diseases
males	Pneumonia, pulmonary embolism, pulmonary vascular disease, respiratory infections
clinical stability for at least 1 months	Instable cardiac disease
	Metabolic disease
	Lung cancer, thoracic malignancy, malignancies
	Bone fractures, fractures

As a result of this screening process, 60 subjects were recruited and involved in assessments, i.e. 35 COPD patients ($FEV_1=64.76\pm20.08\%$ of predicted; $FEV_1/FVC= 57.35\pm13.56\%$ of predicted; age 67.21 ± 4.7 years) and 25 HC subjects ($FEV_1= 115.06\pm17.43\%$ of predicted; $FEV_1/FVC=101.87\pm6.62\%$ of predicted; age 65.15 ± 5.69 years).

Measurements

Pulmonary Function Test

FEV_1 and FVC were measured according to the methods of the ATS/ERS Task Force (M.R. Miller, R. Crapo, et al. 2005; M.R. Miller, Hankinson, et al. 2005; Wanger et al. 2005; Pellegrino et al. 2005) using a pulmonary function instrument with computer processing (Quark, Cosmed, Italy). The predicted value of FEV_1 and FEV_1/FVC were calculated according to American Thoracic Society/European Respiratory Society (1999).

Daily Physical Activity Level

SenseWear PRO2 Armband (Bodymedia®, Pittsburgh, USA) was used in order to assess DPA parameters performed by subjects, such as total steps number, total energy expenditure and active energy expenditure above 3.0 METs. DPA was monitored for 3 days and daily mean (SD) were obtained. In patients with COPD, the SenseWear PRO2 Armband provides a valid and reproducible estimate of energy expenditure during walking at a slow to moderate pace in a

laboratory setting and a high correlation between steps per day and movement counts as measured by a different accelerometer (H. Watz et al. 2009)

Health related Physical Parameters

6-min walking distance test

The 6-min walk test was conducted according to a standardized protocol (P. L. Enright & Sherrill 1998). Subjects were instructed to walk from one end to the other of a 30 meters, i.e. 100-ft., hallway at their own pace, while attempting to cover as much ground as possible in the allotted 6 minutes. Technicians encouraged subjects with the standardized statements “You’re doing well” or “Keep up the good work,” but were asked not to use other phrases. Subjects were allowed to stop and rest during the test, but were instructed to resume walking as soon as they felt able to do so. Rate of perceived exertion was measured with the Borg scale, i.e. 6-20 (C. B. Cooper 2001), and pulse rate were assessed at the start and end of the 6-min walk test. Subjects were also asked at the end of the walk whether they had experienced any of the following symptoms: dyspnea, chest pain, lightheadedness, or leg pain (C. G. Cote et al. 2008).

Muscular strength

In the study patients performed three different submaximal test, i.e. biceps strength by Biceps Curl test, pectoralis major, deltoids and triceps muscles by test at Chest Press isotonic device (Tecnogym®, Gambettola, ITA), quadriceps, gluteus maximus and gastrocnemius by test at Leg Press isotonic device (Tecnogym®, Gambettola, ITA), and quadriceps by test at Leg Extension isotonic device (Tecnogym®, Gambettola, ITA), calculating the 1RM value by Brzycki’s formula (Dohoney et al. 2002):

$$1RM = kg / (1,0278 - (0,0278 \times \text{repetitions' number})).$$

Flexibility and Balance tests

In order to assess flexibility related activity of subjects, the study provided two different flexibility test, i.e. Back Scratch Test to record shoulder range of motion, and Sit & Reach Test to analyze lower body’s flexibility capacity (C. J. Jones & Rikli 2002). To investigate postural steadiness during a static position, subject were involved in 1-Min of One Leg Stance test assessment of both lower arms (Tinetti M.E. 1986; Jonsson et al. 2004)(Figure S3.d).



Figure S3.d – Flexibility tests provided; a) Back Scratch test; b) Sit & Reach test; c) One Leg Stance Test.

Architectural Muscle Measurements

Architectural muscle characteristics, i.e. Fascicle Length, Fascicle Thickness and Angle Pennation, were provided by the images' analysis recorded at ultrasound scanner (ACUSON P50 SIEMENS, Germany) at 39% distal of vastus lateralis muscle (Blazevich A.J. 2006). Two images were obtained for each subjects and by Image J. Ink software (...), fascicle thickness and pennation angle were directly measured. Fascicle length was assessed by Guilhem's formula (2011) (Figure S3.e):

$$Lf1 = d5-6 + \frac{d2-6}{\sin\theta_1} + \frac{d4-5}{\sin\theta_1}$$

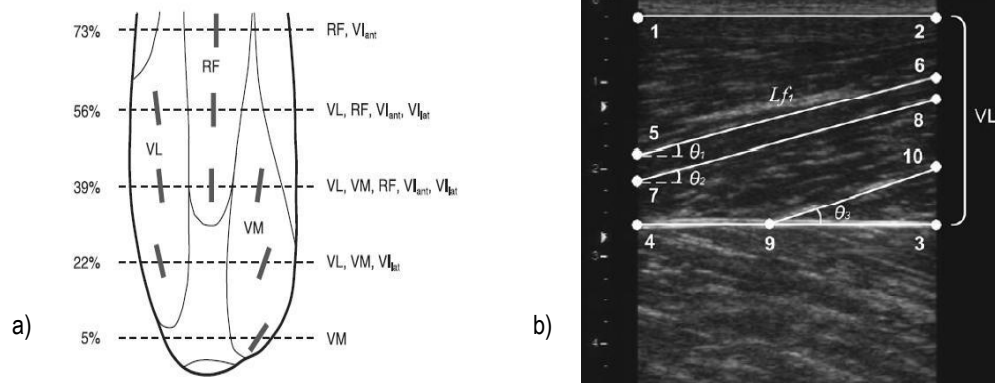


Figure S3.e –a) Muscle site to record with ultrasound scanner; b) References Guilhem's muscles analysis;

(from Blazevich A.J. 2006 and Guilhem & Cornu 2011)

Isokinetic Dynamometer Strength Evaluation

To assess subjects' strength performances of extensor muscles of lower limbs as a function of contraction modalities and velocities, we performed an isokinetic dynamometer (Cybex Norm, Ronkonkoma, USA) protocol in order to record concentric and eccentric contraction of the quadriceps dominant limb at both 30deg/s and 210 deg/s (Mathur et al. 2005). After a warm up session, subjects performed 3 maximal repetitions of each contractions at both angular velocities. For each subjects it was recorded the maximum score provided in each of the four contractions assessed.

Statistical methods

To address the purpose of this trial, statistical analysis of the data began with calculations of the arithmetic means and standard deviations of COPD and HC groups in each test. The differences between groups were assessed using one-way analysis of variance (ANOVA). Pearson coefficient was used to detect correlation between dependent and independent variables. *P* values less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed with Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, IL).

Results

Pulmonary Function Test

The characteristics of the COPD patients and HC group are depicted in Table S3.f. The 35 patients with COPD presented mild to severe airflow obstruction, i.e. FEV₁ 64,76% ±20,08 post-bronch. predicted, FEV₁/FVC 57,35% ±13,56 post-bronch. predicted. The 25 HC subjects shown absence of any pulmonary disease, i.e. FEV₁ 115.06% ±17.43 predicted, FEV₁/FVC 101.87% ±6.62 predicted. Significant differences (*p* < 0.001) were found between groups, both in %FEV₁ and %FEV₁/FVC.

Table S3.f – Pulmonary function parameters in COPD group and HC group			
	mean (SD)		
Variables	COPD group	HC group	p
Age	67.21 (4.7)	65.15 (5.68)	N.S.
%FEV ₁	64.76 (20.08)	57.35 (13.56)	0.000
%FEV ₁ /FVC	115.06 (17.43)	101.87 (6.62)	0.000

Daily Physical Activity Level

The characteristics of the COPD patients and HC group are depicted in Table S3.g. Lower significant value of DPA at each variables recorded, i.e. steps number ($p < 0.001$), total energy expenditure ($p < 0.01$) and active energy expenditure among 3.0 METs ($p < 0.01$) than HC group were found.

Table S3.g – Daily physical activity level in COPD group and HC group			
	mean (SD)		
Variables	COPD group	HC group	p
steps number	6023 (2950)	10592 (5686)	0.000
tot energy expenditure (j)	10103 (1827)	11367 (1429)	0.006
active energy expenditure (j)	1723 (1731)	3077 (1889)	0.006

Health related Physical Activity Parameters

The characteristics of the COPD patients and HC group are depicted in Table S3.h. COPD patients shown significant lower performances in each variables assessed, i.e. 6MWT distance ($p < 0.001$), 1RM Leg Press ($p < 0.05$), 1RM Biceps Curl ($p < 0.001$), 1RM Chest Press ($p = 0.001$), Back Scratch test ($p < 0.05$), Sit & Reach test ($p < 0.05$) and total score at One Leg Stance test ($p < 0.01$) than HC group.

Table S3.h – Health related physical activity parameters in COPD group and HC group			
mean (SD)			
Variables	COPD group	HC group	p
6MWD (mt)	474 (107)	668 (69)	0.000
1RM Leg press (kg)	183 (59)	215 (37)	0.019
1RM Biceps curl (kg)	10.3 (2.3)	12.6 (1.9)	0.000
1RM Chest press (kg)	44 (12)	55 (11)	0.001
Back Scratch test (cm)	- 6.7 (15)	0.7 (7.2)	0.024
Sit & Reach test (cm)	- 9.8 (12.9)	- 3.9 (7.9)	0.048
Tot One stance leg test (sec)	57 (46)	103 (30)	0.000

Architectural Muscle Measurements

The characteristics of the COPD patients and HC group are depicted in Table S3.i. No significant differences were found between groups in each variables assessed, i.e. Fascicle Length, Fascicle Thickness and Angle Pennation.

Table S3.i – Architectural muscle measurements in COPD group and HC group			
mean (SD)			
Variables	COPD group	HC group	p
Fascicle length (mm)	126 (16)	128 (17)	N.S.
Fascicle Thickness (mm)	20,1 (3,8)	20,3 (3,0)	N.S.
Penn. Angle (°)	8,5 (2,6)	8,6 (2,7)	N.S.

Isokinetic Dynamometer Strength Evaluation

The characteristics of the COPD patients and HC group are depicted in Table S3.j. Only concentric peak torque at 30 deg/s resulted greater in HC group ($p<0.05$) than COPD group, instead concentric contraction at 210 deg/s and eccentric contraction at both angular velocities, i.e. 30 and 210 deg/s, didn't show any differences. Nonetheless, eccentric/concentric peak torque ratio was significantly greater in COPD at 30 deg/s ($p<0.001$) and at 210 deg/s ($p<0.05$) than HC group.

Table S3.j – Isokinetics dynamometer strength evaluation in COPD group and HC group			
Variables	mean (SD)		p
	COPD group	HC group	
Conc 30°/s (N/m)	158 (47)	181 (27)	0.038
Conc 210 °/s (N/m)	90 (24)	99 (16)	N.S.
Ecc 30°/s (N/m)	209 (57)	219 (41)	N.S.
Ecc 210 °/s (N/m)	189 (46)	203 (36)	N.S.
Ecc /conc 30°/s	1.43 (0.15)	1.21 (0.16)	0.000
Ecc /conc 210°/s	2.27 (0.25)	2.06 (0.32)	0.008

Correlation between Pulmonary Function Parameters and Performances assessed

Pulmonary Function and Daily Physical Activity Level

Correlation between Pulmonary function parameters and DPA variable recorded are depicted in Table S3.k. Direct significant correlation were found between %FEV₁ and of DPA at each variables recorded, i.e. steps number (p < 0.001), total energy expenditure (p < 0.01) and active energy expenditure among 3.0 METs (p < 0.05). Same results were observed between %FEV₁/FVC and DPA variables, i.e. steps number (p < 0.001), total energy expenditure (p < 0.01) and active energy expenditure among 3.0 METs (p < 0.05).

Table S3.k – Correlation between %FEV ₁ , %FV ₁ /FVC and Daily physical activity level		
Variables	R; * p < 0.05; ** p < 0.01; *** p < 0.001	
	%FEV ₁	%FEV ₁ /FVC
steps number	0.472***	0,452***
tot energy expenditure	0.406**	0,411**
active energy expenditure	0.329*	0,289*

Pulmonary Function and Health related Physical Parameters

Correlation between Pulmonary function parameters and Health related physical parameters recorded are depicted in Table S3.l. Direct significant correlation were found at the analysis between %FEV₁ and variables assessed, i.e. 6MWT distance (p < 0.001), 1RM Leg Press (p<0.001), 1RM Biceps Curl (p < 0.001), 1RM Chest Press (p > 0.01). Same results were

observed between %FEV₁/FVC and variables, i.e. 6MWT distance (p < 0.001), 1RM Leg Press (p < 0.01), 1RM Biceps Curl (p < 0.001), 1RM Chest Press (p > 0.01).

Table S3.I – Correlation between %FEV₁, %FV₁/FVC and Health related physical parameters

R; * p < 0.05; ** p < 0.01; *** p < 0.001		
Variables	%FEV ₁	%FEV ₁ /FVC
6MWD (mt)	0.719 ***	0,735 ***
1RM Leg press (kg)	0.446***	0,423**
1RM Biceps curl (kg)	0.451***	0,512***
1RM Chest press (kg)	0.384**	0,411**

Pulmonary Function and Isokinetic Dynamometer Strength Performances

Correlation between Pulmonary function parameters and Isokinetic dynamometer strength performances are depicted in Table S3.m. Direct significant correlation were found at the analysis between %FEV₁ and variables assessed, i.e. concentric contraction at 30deg/s (p < 0.01), concentric contraction at 210 deg/s (p<0.05), eccentric contraction at 30 deg/s (p < 0.05), eccentric contraction at 210 deg/s (p < 0.05). Same results were observed between %FEV₁/FVC and variables, i.e. concentric contraction at 30deg/s (p < 0.001), concentric contraction at 210 deg/s (p<0.05), eccentric contraction at 30 deg/s (p < 0.05), eccentric contraction at 210 deg/s (p < 0.05). Moreover, results shown that eccentric/concentric peak torque ratio was inversely correlated with FEV₁ (p < 0.001) and FEV₁/FVC (p < 0.001). Same results were observed between eccentric/concentric peak torque ratio and pulmonary function parameters, i.e. FEV₁ (p < 0.05) and FEV₁/FVC (p < 0.01).

Discussion

As expected, HC subject showed a normal morphology of flow-volume curve and no-evidences of airflow limitation were observed. The analysis of DPA levels confirmed that COPD patients are markedly inactive, showing a more sedentary behavior than HC group (Schonhofer et al. 1997; Pitta et al. 2005; Hernandez et al. 2009; Walker et al. 2008; Troosters et al. 2010; Gouzi et al. 2011; Vorrink et al. 2011).

Table S3.m – Correlation between %FEV₁, %FV₁/FVC and Isokinetic Dynamometer Strength performances

R; * p < 0.05; ** p < 0.01; *** p < 0.001		
Variables	%FEV ₁	%FEV ₁ /FVC
Conc 30°/s (N/m)	0.427 **	0.443 ***
Conc 210 °/s (N/m)	0.285 *	0.332 *
Ecc 30°/s (N/m)	0.280 *	0.263 *
Ecc 210 °/s (N/m)	0.276 *	0.297 *
Ecc /conc 30°/s	- 0.562 ***	- 0.615 ***
Ecc /conc 210°/s	- 0.292 *	- 0.371 **

Moreover, the significant lower levels of health related parameters' performance of COPD patients are in line with results of several previous studies (Steiner & M. D. L. Morgan 2001; Butcher & R. L. Jones 2006; Kim et al. 2008; W.D-C Man et al. 2009a), confirming a COPD patients reduction in functional fitness. Surprisingly, the analysis of strength performances at the Isokinetic dynamometer confirmed not entirely Mathur's findings (2007). In fact, in our study we observe only a significant lower strength performance in COPD patients when they are involved in a slow-concentric contraction of lower limbs, whereas Mathur and colleagues (2007) observed significant lower performances of COPD patients in both absolute knee extensor concentric and eccentric torque at 30 deg/sec than the HC. These differences between our and Mathur's study could be due to the COPD number and stage disease of the sample recruited, i.e. 35 mild to severe vs. 20 moderate to severe COPD patients. Finally, in our study, the COPD patients' eccentric/concentric peak torque ratio at both slow and fast velocities resulted significantly higher than HC, suggesting that HC concentric and eccentric contraction of the knee extensors express similar torque value, whereas COPD patients maintain a normal range only in the eccentric contraction at both velocities. In terms of correlation, our study's results confirm airflow obstruction as a key factor leading in reduction of moderate PA and DPA (Steele et al. 2003), which values are the most outcome in terms of HRQL (Jehn et al. 2012) and better predictors of physical function (Pitta et al. 2005). Moreover, our findings are in line with previous studies' observations, which highlighted an early reduction of DPA before the disease and symptoms onset (Gouzi et al. 2011; Vorrink et al. 2011). Also, we confirm that health related physical parameters, such as exercise tolerance and strength performance, are negative influenced by pulmonary obstructive disease (Bernard et al. 1998; Serres et al. 1998; Mador & Bozkanat 2001; Kim et al. 2008; C. G. Cote et al. 2008; W.D-C Man et al. 2009b). Furthermore, the analysis of

correlation between concentric/eccentric contraction at both velocities and pulmonary function showed an influence of airflow obstruction into muscular peak torques, resulting in enhancement of eccentric/concentric peak torque ratio as a function of increased disease severity. These results are according to previous studies which considered eccentric strength as a strong contributor of functional performance in patients with COPD (Butcher et al. 2012). Finally, no evidences of different muscle architecture between groups lead us to assume that low strength performances recorded in COPD patients are not due to neural-muscular modifications. In literature it was observed COPD patients' chronic moderate-to-severe hypoxemia and/or repeated episodes of hypoxemia due to exercise-induced desaturation or sleep apnoea (Couillard & Prefaut 2005; Kim et al. 2008). These observations, couplet to evidence of a change in proportion of slow twitch fibers in favor of fast ones (Couillard & Prefaut 2005; Kim et al. 2008), led to hypothesize that COPD hypoxemic condition may be a determining factor in this mechanism shift (H.R. Gosker, Van Mameren, et al. 2002). Furthermore, Enoka (1996) and Duchateau (2008) observed that eccentric contraction seems to be characterized by a unique neural mechanisms involving fast twitch motor units. Therefore, considered these evidences, we assume that COPD patients develop a favorable contraction profile, performing an eccentric torque, in order to minimize strength loss related to low ratio of type I fibers.

Conclusion

In conclusion, COPD patients showed lower health related parameters and performed lower concentric contraction compared to healthy controls. Interestingly, COPD preserved eccentric contractions and fast concentric torque. Considered that eccentric contraction seems to involve fast twitch motor units (Duchateau & Enoka 2008) and COPD hypoxia leads fiber shift towards IIx fibers (H.R. Gosker, Van Mameren, et al. 2002), COPD males seem to develop a favorable profile to minimize the strength loss likely due to neural-muscular modification. Further investigations would be aimed to assess neural contribution in contraction performances of COPD patients (Komi et al. 1987). Whereas 6MWD less than 350mt (Cote 2008) was estimated to predict increased risk of mortality. Muscle strength was considered a poor predictor of functional impairment (Pitta et al. 2005). Current knowledge about muscle wasting (W.D-C Man et al. 2009b) and recent researches about COPD eccentric contraction (Butcher et al. 2012) lead us to consider to use eccentric/concentric peak torque ratio as a clinic threshold of impairment. Finally, considered the preservation of eccentric contraction in COPD patients provided by our study, the effectiveness of lengthening training in strength increments and the lower cardio-respiratory

response in eccentric exercise than concentric (Roig et al. 2008), further investigations are aimed to verify strength improvement, reduction of muscle wasting and increment on QoL provided by eccentric training in comparison with traditional exercise.



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