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TITLE OF THE DOCTORAL THESIS

CHARACTERIZATION OF FATIGUE AND EFFECT OF EXERCISE TRAINING IN SEVERE COPD

S.S.D. MEDF02

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SUMMARY

Fatigue can be described as perceptive fatigue (PF), the subjective feeling of tiredness, exhaustion, or lack of energy, which occurs in daily life, and neuromuscular fatigue (NMF), the reduction of muscle strength and neuromuscular activation during a given task. Both aspects have been described as having a strong impact on the activity of daily life and the quality of life of COPD patients. Very few studies have so far described the presence of both types of fatigue and the impact of exercise training on it in the severest COPD patients, who have already developed chronic respiratory failure (CRF) and are undergoing long-term oxygen therapy. This PhD work aimed to describe the relationship between PF and NMF, comparing patients with and without CRF,to evaluate the scientific literature regarding the effect of exercise training on both PF and NMF in COPD patients, and to study the effect of a pulmonary rehabilitation intervention, including exercise training, in CRF patients. These objectives were evaluated through three dedicated projects described in this thesis. The results can be summarized in the following key points: a) Patients with severe COPD with CRF in LTOT develop higher levels of perceived fatigue and dyspnoea than COPD patients without CRF, while the extent of neuromuscular fatigue is similar in both groups; b) The literature describes the overall beneficial effect of physical training on PF in the COPD population, but no randomized controlled trials have been evaluated the impact on NMF; c) Pulmonary rehabilitation, including exercise training, can reduce PF and improve exercise tolerance and quality of life in COPD with CRF; d) Patients with severe baseline PF and peripheral NMF improve after rehabilitation more than patients without fatigue. Patients with peripheral NMF at baseline had a twofold improvement in exercise tolerance; e) There is a clear mismatch between the perception of fatigue and objective neuromuscular fatigue at baseline and in the change achieved after rehabilitation. A better understanding of the determinants of fatigue may allow the design of new individualized strategies to increase the acute muscle load during the training session and counteract the negative influences of fatigue on daily life. For this

reason, a specific assessment for both aspects of fatigue should be mandatory in the clinical and rehabilitation settings. Further evaluations are needed about tailored interventions.

RIASSUNTO

La fatica può essere descritta come fatica percettiva (PF), la sensazione soggettiva di stanchezza, esaurimento o mancanza di energia, che si verifica nella vita quotidiana, e fatica neuromuscolare (NMF), ovvero la riduzione della forza muscolare e dell'attivazione neuromuscolare durante un determinato compito. Entrambi gli aspetti sono stati descritti come aventi un forte impatto sull'attività di vita quotidiana e sulla qualità della vita dei pazienti con BPCO.
Pochissimi studi hanno finora descritto la presenza di entrambi i tipi di affaticamento e l'impatto su di esso dell'esercizio fisico nei pazienti affetti da BPCO più grave, che hanno già sviluppato insufficienza respiratoria cronica (IRC) e sono sottoposti a ossigenoterapia a lungo termine.
Questo lavoro di dottorato mira a valutare la letteratura scientifica sull'effetto dell'allenamento fisico sia sulla PF che sulla NMF nei pazienti con BPCO, descrivere la relazione tra PF e NMF, confrontando pazienti con e senza IRC, nonchè studiare l'effetto dell'esercizio nei pazienti con IRC.
Questi tre obiettivi sono stati valutati attraverso tre progetti dedicati descritti in questa tesi.
I risultati possono essere sintetizzati nei seguenti punti chiave:
a) I pazienti con BPCO grave con IRC in LTOT sviluppano livelli più elevati di affaticamento percepito e dispnea rispetto ai pazienti con BPCO senza IRC, mentre l'entità dell'affaticamento neuromuscolare è simile in entrambi i gruppi.
b) La letteratura descrive l'effetto benefico complessivo dell'esercizio fisico sulla PF nella BPCO, mentre non sono stati condotti studi randomizzati e controllati per valutare l'impatto sulla NMF.
c) La riabilitazione polmonare, comprensiva di un programma strutturato di esercisio fisico, può ridurre la PF migliorando inoltre la tolleranza all'esercizio e la qualità della vita nella BPCO con IRC.
d) I pazienti con PF basale grave e NMF periferica migliorano dopo la riabilitazione di più rispetto ai pazienti non affativati all'inizio del percorso riabilitativo. I pazienti con NMF periferico al basale presentavano inoltre un

duplice miglioramento nella tolleranza all'esercizio rispetto al gruppo non affaticato.

e) Vi è una chiara discrepanza tra la percezione della fatica e la fatica neuromuscolare oggettiva, sia al basale che riguardo al cambiamento ottenuto dopo la riabilitazione. Una migliore comprensione dei determinanti della fatica può consentire la progettazione di nuove strategie individualizzate con l'obiettivo di aumentare il carico muscolare acuto durante la sessione di allenamento e contrastare le influenze negative della fatica sulla vita quotidiana.

Per questo motivo, una valutazione specifica per entrambi gli aspetti della fatica dovrebbe essere obbligatoria in ambito clinico e riabilitativo. Ulteriori studi sono necessari dopo questo lavoro di dottorato per quanto riguarda lo studio di interventi personalizzati.

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Last but not least, I want to thank family and friends for showing interest in my work and for your encouragement. I am particularly grateful to my husband Angelo and our two daughters Alice and Sofia. *Thanks for your patience and encouragement. In the end, you are what really matters.*

Mara

1. INDEX

2. ABBREVIATIONS LIST

COPD : Chronic Obstructive Pulmonary Disease

PF: Perceptive Fatigue

NMF: NeuroMuscular Fatigue

GOLD: Global Initiative for Chronic Obstructive Lung Disease

PR: Pulmonary Rehabilitation

CRF: Chronic Respiratory Failure

LTOT: Long Term Oxygen Therapy

MVC: Maximal Voluntary Contraction

PPO: Peak Power Output

MVA%:]Percentage of maximal Volontary Activation

PR : Pulmonary Rehabilitation

RPE: Rating of Perception

PPO: Peak Power Outcome

GOLD: Global Initiative for Chronic Obstructive Lung Disease

SMR: root of the mean and

MF: median frequency

CP: critical power

Tlim: time to exhaustion

CWCT: Constant Workload Cycling Test

3. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently defined as "a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases" (Gold, 2018) Breathlessness, cough, and sputum production are cardinal symptoms of patients with chronic obstructive pulmonary disease (COPD). These respiratory symptoms are routinely assessed to monitor disease stability and also as outcomes of the efficacy of COPD-specific pharmacological therapies (Qaseem A, 2011).

Fatigue is another important symptom, however, is often ignored in clinical practice and research (Spruit MA, 2017).

Perceptive fatigue (PF) is a multidimensional perception defined as "the subjective feeling of tiredness, exhaustion or lack of energy, which occurs on a daily basis (Gruet M, 2018). It is present in about 50–70% of patients with COPD and can prevents them from doing regular activities of daily life (Spruit MA, 2017). Several factors can lead of perceived moderate to severe PF in the environment of a patient with COPD, some precipitating such as hypoxemia or hypercapnia, exacerbations or related treatments, other perpetuating such as systemic problems (i.e anemia, low-grade of systemic inflammation ect), physical and psychological issues (i.e lower-limb muscle weakness, anxiety, depression…) or behavioral problems (i.e dysfunctional cognitions , low social support etc) (Spruit MA, 2017).

Among the physical factors involved, patients with COPD suffer of an important reduction in muscle force and neuromuscular activation during a given task, commonly defined as **neuromuscular fatigue (NMF)** (Gandevia SC, 2011; Marillier, 2021).

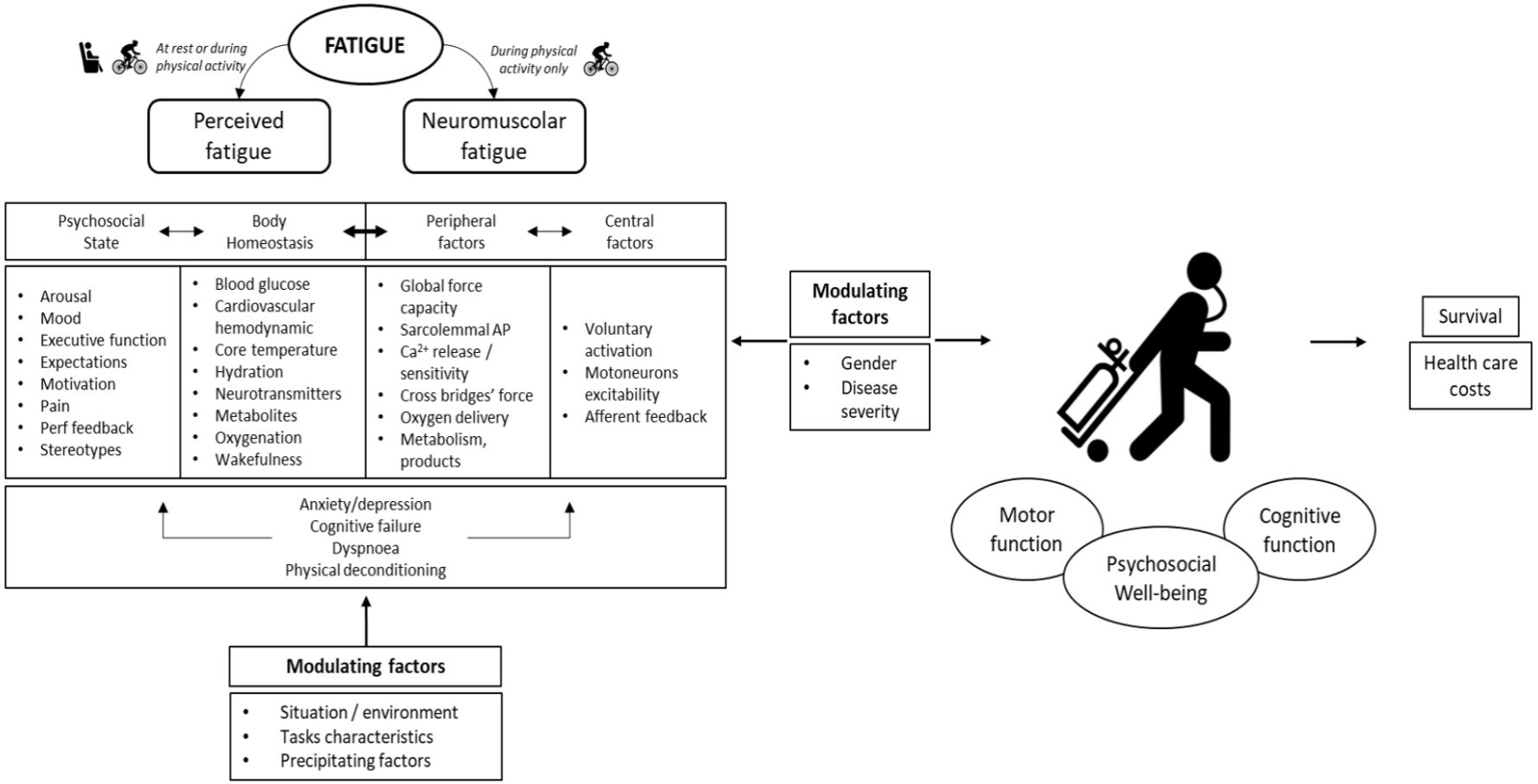
The development of NMF observed in the disease progression of COPD and related to a vicious circle of inactivity is, at least in part, attributable to changes in

locomotor muscles properties with an increased activity of glycolytic enzymes and shifting to non-oxidative fibers (Marillier, 2015, Maltais F, 2014). NMF also appears related to impaired oxygen delivery to locomotor muscles due to hemoglobin desaturation (Amann M, 2006) and to the increased sympathetic vasoconstrictor activity of the limbs caused by supraspinal reflex activated from the non-myelinated group III-IV afference (Dempsey JA, 2006) of respiratory fatigued muscles.

Contemporary models of fatigue suggest that fatigue is the result of a complex interaction between physiological activity and psychological state. For instance, in their Integrative Governor theory, St Clair Gibson et al (St Clair Gibson A, 2018) proposed that the competitive, dynamic interplay between physiological and psychological homeostatic drives regulates exercise performance and the fatigue process. In the same vein, Enoka and Duchateau (Enoka RM, 2016) proposed a definition of fatigue that includes (1) the "perceived" component, referring to the sensations about fatigue or PF, and (2) the "performance" component or NMF, referring to the capacity of the neuromuscular system to meet the requirements of a given task. Importantly, the definition also suggests the interdependence relationship of the two components. Based on this taxonomy, the same authors proposed a generic model of fatigue (adapted and modified from Kluger et al. (Kluger BM, 2013), initially developed for neurological diseases). In this model, PF depends on two domains: maintenance of homeostasis (e.g., blood glucose) and psychological state (e.g., mood). Also NMF depends on two domains: contractile function (e.g., calcium kinetics) and muscle activation (e.g., activation patterns). This model has the advantage of being universal and can be virtually adapted for every disease including very severe COPD, the relative weight of each factor and their reciprocal interaction depending on the disease course.

Several therapeutic options have been proposed for the treatment of COPD patients with the aim of reversing symptoms, including fatigue. The most widely applied treatments are summarized in the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (Gold, 2018) (**table 1**).

Figure 1: Major factors contributing of domains of fatigue in severe COPD patients.



Legend: The domains of perceived and neuromuscular fatigue are controlled by different factors acting at a micro- and macro-level. Modulating factors which can influence the respective weight of each factor contributing to fatigue (modified from Gruet M, 2018).

Table 1: GOLD guidelines for COPD treatment

	Grade of Severity			
	1 (mild)	**2 (moderate)**	**3 (severe)**	**4 (very severe)**
FVC **FEV1**	<0·70	<0·70	<0·70	<0·70
FEV1	≥80% of predicted	50–80% of predicted	30–50% of predicted	<30% of predicted or <50% of predicted plus chronic respiratory failure
Treatment	Influenza vaccination and short-acting bronchodilator* when needed	Influenza vaccination, short-acting and ≥1 long-acting bronchodilator* when needed; consider **Pulmonary Rehabilitation**	Influenza vaccination and short-acting and ≥1 long-acting bronchodilator* when needed, inhaled glucocorticosteroid if repeated exacerbations; consider **Pulmonary Rehabilitation**	Influenza vaccination and short-acting and ≥1 long-acting bronchodilator* when needed, inhaled glucocorticosteroid if repeated exacerbations, long-term oxygen if chronic respiratory failure occurs; consider **Pulmonary rehabilitation** and surgery

Legend: *β2 agonists or anticholinergics.

Among these, the pulmonary rehabilitation (PR) approach, including physical training, is one of the most effective treatments for patients with advanced diseases (Spruit MA, 2013). Lack of physical activity can be a mechanism by which fatigue occurs (particularly through peripheral muscle deconditioning and reduced strength capacity), but an elevated stretch of fatigue can also prevent some patients engaging in physical activities regular. Longitudinal observational and interventional studies, which control confounding factors, are clearly warranted to obtain further insights into the factors underlying the elevated fatigue trait and its development and evolution in the natural history of the disease (Gruet

M, 2018). Shedding light on the attributes of fatigue will allow for the creation of new individualized interventions, with the aim of (1) increasing acute muscle load during a given exercise session (a prerequisite for training efficiency) and, (2) reducing PF and both chronic and acute NMF under various conditions. Achieving both of these goals can in turn improve patients' health and thus reduce the costs of medical care (Gruet M, 2018).

The main topic of my PhD program was to investigate fatigue (both subjective and objective) focusing on the most severe subgroup of COPD patients, who have already developed **chronic respiratory failure (CRF),** having been very little studied and considered by the literature so far.

In particular, my main interest was related to the relationship between them and the impact of exercise training. So far, it is unclear whether PF and NMF are progressively deteriorating in patients with very severe COPD and the ability of physical training to modify this condition.

Objectives of the thesis:

Focusing on patients with severe COPD, the objectives of my PhD program have been:

a) to evaluate the scientific literature about the effect of exercise training on both PF and NMF in COPD;

b) to describe the relationship between PF and NMF, compare patients with and without CRF;

c) to study the effect of exercise training on PF and NMF in CRF patients, and the relationship with the principal PR outcome measures.

These objectives have been pursued in the three doctoral projects listed and describe below:

PROJECT 1: The impact of exercise training on fatigue in patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis.

PROJECT 2: Fatigue in Copd Patients Under Long Term Oxygen Therapy: A Cross-Sectional Study.

PROJECT 3: Pulmonary Rehabilitation effect on fatigue in COPD patients with Chronic Respiratory Failure.

4. INTERNAL CHAPTERS

4.1 SEVERE COPD: PATHOPHYSIOLOGY AND FUNCTIONAL CHARACTERISTICS

4.1.1 COPD: CLINICAL AND FUNCTIONAL FEATURES

According to the definition proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease, 2017 update, *"COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases* (Vogelmeier CF, 2017).
In addition to functional abnormalities, individuals with COPD present varying degrees of emphysema and chronic bronchitis.

Chronic bronchitis, which is defined in clinical terms, is the presence of a chronic productive cough for 3 months in each of 2 successive years, provided other causes of chronic cough have been ruled out (American Thoracic Society, 1995).
Airway obstruction is caused by inflammation and nonspecific bronchial hyperreactivity associated with chronic bronchitis. Unfortunately, many surveillance systems that attempt to estimate the burden of chronic bronchitis do not use that specific definition and only estimate "physician-diagnosed" chronic bronchitis or recurrent episodes of bronchitis (typically 3 episodes) in the previous year.

Emphysema, which is defined in anatomical terms, is the destruction of alveolar walls and permanent enlargement of the air spaces distal to the terminal bronchioles (American Thoracic Society, 1995). The ensuing loss of lung elastic recoil and intra luminal pressure in the terminal airways causes small airways to lose their patency, especially during forced expiratory maneuvers. The collapse of these airways causes airflow limitation independent of exertion. Clinically, the patient experiences progressive dyspnea and variable cough. It is not clear how most clinicians diagnose emphysema. Though the use of imaging,

such as a computed tomography, would be optimal, it is likely that the majority of cases are diagnosed using different methods.

Chronic pulmonary obstructive disease (COPD) is one of the leading causes of death globally. The prevalence of COPD was 12.16%, being higher in men (15.70%) than in in women (9.93%). Among all WHO regions, the highest prevalence was recorded in the Region of the Americas (14.53%), and the lowest was recorded in the South-East Asia Region/Western Pacific Region (8.80%) (Varmaghani M, 2019).

Risk factors for COPD include a deficiency of natural antiproteases (α1-antitrypsin or antiprotease); exposure to tobacco, biomass, or industrial smoke; previous pulmonary infections; asthma; and abnormal pulmonary development caused by prenatal or early life events (Celli BR, 2018). The majority of cases of COPD in the developed world are related to tobacco consumption; thus, its importance should be emphasized as a definite and preventable cause of the disease. However, about one-third of patients with COPD, or more correctly with irreversible airflow obstruction, are individuals who never smoked

COPD has been clinically defined by the presence of some cardinal symptoms that include dyspnea, cough, and sputum production (Woodruff PG,.2016; Rodriguez-Roisin R, 2017).

The demonstration of airflow obstruction is an indispensable criterion for diagnosing COPD, and the gold standard is the finding by spirometry of a reduced forced expiratory volume in 1 second and forced vital capacity (FEV_1/FVC) quotient (Vogelmeier CF, 2017).

The old GOLD criteria classify COPD into 4 stages, according to FEV1 %:

Stage 1: FEV180% of predicted

Stage 2: FEV150% to80% of predicted;

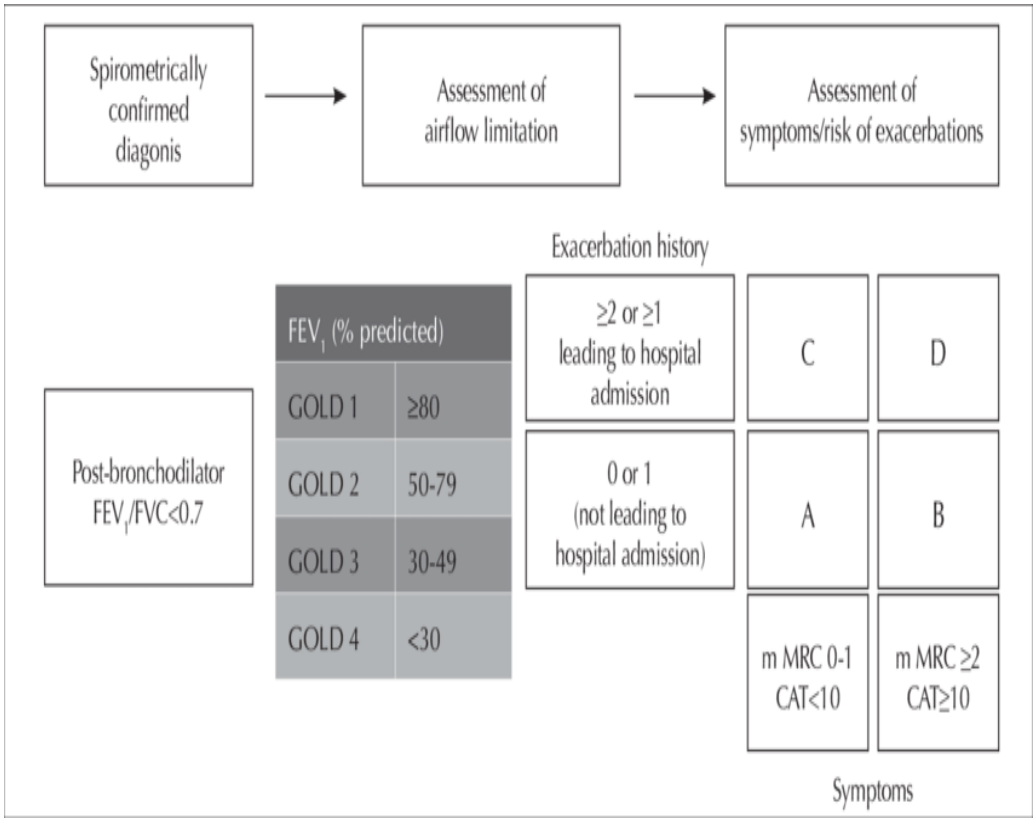
Stage 3: FEV130 to50% of predicted

Stage 4: FEV130% of predicted

Recently a new GOLD classification (GOLD, 2019) has been proposed a classification based on both lung function and exacerbation history, with the symptoms experienced by patients (quadrant classification) in addition to the staging system based on levels of airflow obstruction (airflow based classification)

previously used. In this new GOLD classification it was included the Modified British Medical Research Council (mMRC) (Bestall JC, 1999) and the Questionnaire and COPD Assessment Test (CAT) (Gupta N, 2014) to assess symptoms. The mMRC is used to assess breathlessness of patients with COPD. The CAT is an eight-item measure of impairment experienced from COPD, with scores ranging from 0 to 40. Higher scores on the CAT indicate a larger impact of COPD on the patient's life. Symptom burden and risk of exacerbation are also classified into GOLD groups A through D, which is used to guide therapy. Classification is patient-specific, and each patient's treatment regimen should be tailored specifically to their needs (GOLD, 2019).

Figure 2: New GOLD Classification algorithm.



Legend: GOLD: Global Initiative for Chronic Obstructive Lung Disease, FEV1: Forced Expiratory Flow at first second, FVC: Forced Vital capacity, MRC: Medical Research Council; CAT: COPD assessment Test.

This complex syndrome is characterized by inflammation not only of the lungs and airways but also systemic (Eagan TM, 2010), which leads to an increased risk of comorbidity, functional deterioration, as well as limitations in performing daily life activities and decrease in the health-related quality of life (Agustí A,2012).

Skeletal muscle dysfunction is an overreaching condition that is associated with the disease progression in COPD and affects the physical capacity and overall quality of life of the patients. It is caused by loss of muscle mass and oxidative capacity (Maltais, 2014).
During the disease course, these patients can experiment Acute Exacerbation defined as episodes of acute worsening of dyspnea, and/or cough and sputum production, and/or increased sputum purulence (GOLD, 2018).

COPD treatments

According to the GOLD 2022 strategy report, the main goals of COPD treatment are reduction in both symptoms and future risk of exacerbations. These are supported by additional factors that contribute to these goals, including improvements in exercise tolerance and health status, prevention and treatment of exacerbations, prevention of disease progression, and a reduction in mortality. However, goals such as reducing mortality and preventing disease progression may be difficult to achieve, and health status is also complex to measure and treat.

Management strategies discussed in the GOLD recommendations include both pharmacologic and non-pharmacologic interventions.

Pharmacologic therapy can be used to reduce symptoms, reduce the frequency and severity of exacerbations, improve health status and increase exercise tolerance in patients with COPD. Non-pharmacologic therapy is complementary and helps to supplement pharmacologic approaches (GOLD, 2022).

Among non-pharmacological treatments **Pulmonary Rehabilitation (PR)** is one of the main validated approach. It can be defined as a "comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of

people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors" (Spruit, 2013). It can address the vicious cycle of dyspnea, physical inactivity, deconditioning, and isolation tipical of this disease. (Corhay JL, 2014). From a physiological point of view, it may result in improvement of oxidative capacity and skeletal muscle adaptation depending on the intensity and frequency of exercise. Early initiation of PR can potentially minimize the effect of acute exacerbations on the skeletal muscle and prevent the deterioration of skeletal muscle to a significant extent (Gayan-Ramirez GJ, 2018) thus appearing to be an effective strategy to change the course of the disease (Girdhar A, 2018) improving quality of life, psychosocial wellbeing, reducing mortality, and rate of hospitalization (Ryrsø CK, 2018) following successful completion of PR. The benefits of PR can be further maximized also by introducing supplemental nutrition (Collins PF, 2013).

4.3.2 SEVERE COPD WITH CHRONIC RESPIRATORY FAILURE

The main subgroup of patients evaluated in this doctoral thesis is those with very severe COPD who have already developed CRI. This chapter aims to describe this population in terms of pathophysiology, related problems, and the effect of long-term oxygen therapy on them.

The prevalence of hypoxemia among COPD patients remains somewhat uncertain. In a large general cohort of COPD patients (about 6000 patients), severe hypoxemia is relatively uncommon, with about a rate of 2% of patients needing a chronic prescription of Long Term Oxygen Therapy (LTOT) (Tashkin DP, 2008). Conversely, over 80% of the patients with advanced disease enrolled in a specific American National Emphysema Treatment Trial were using some form of oxygen therapy (Martinez FJ, 2006).

Pathophysiology of hypoxemia in COPD

The principal contributor to hypoxemia in COPD patients is ventilation/perfusion (V/Q) mismatch resulting from progressive airflow limitation and emphysematous destruction of the pulmonary capillary bed**.** In studies utilizing the multiple inert gas elimination technique, COPD patients with a predominantly emphysematous phenotype have increased ventilation of poorly perfused lung units (ie. high V/Q ratio), and hence increased physiological dead space (Wagner 1977). Conversely, subjects with a significant degree of airway disease are more likely to have a low V/Q ratio, with heterogeneous alveolar hypoventilation, substantial perfusion of under-ventilated areas, and consequent physiological shunt. V/Q mismatch due to pulmonary emphysema and small airways disease is measurable even in subjects with mild COPD (Barbera JA, 1990). Exacerbations of COPD are frequently associated with deterioration in gas exchange and associated hypoxemia. Unsurprisingly, increased inequality in V/Q relationships appears to be the major determinant of these changes (Barbera JA,1997). Increased tissue consumption of oxygen, with resultant decreased mixed venous oxygen tension also appears to contribute to increased hypoxemia during exacerbations, but is at least partially offset by a concomitant increase in cardiac output.

Dysregulated ventilatory control is another factor contributing to the occurrence and persistence of hypoxemia in COPD patients. Subjects with chronic airflow obstruction have blunted ventilatory responses to hypoxia, and this is particularly the case in those with chronic hypoxemia (Bradley,1979). In the majority of cases, this is not driven by diminished central nervous system output, with COPD patients often exhibiting increased neural drive to the respiratory muscles as the disease progresses. Rather, peripheral mechanisms related to disordered inspiratory muscle function and associated hyperinflation appear to be the key (Kent BD, 2011). Nonetheless, reduction in central ventilatory drive may be of relevance in cases of nocturnal hypoxemia, in bronchial type ("blue bloater") patients, and with use of sedatives, hypnotics, and alcohol (Kent BD, 2011). In addition, the presence of Obesity and may contribute to abnormalities in gas exchange (Franssen FM, 2008).

Consequences of hypoxemia in COPD

Systemic Inflammation

Subjects with COPD have increased circulating markers of systemic inflammation when compared with healthy controls (Gan WQ, 2004), and promotes cardiovascular disease, and the development of skeletal muscle dysfunction, osteopenia, and depression (Agusti AG.2005).

Several factors likely play a role in the genesis of systemic inflammation of COPD such as hyperinflation, airway inflammation, airflow obstruction, and tobacco use (Agusti AG, 2005). However, an independent role for tissue hypoxia seems likely. Evidence of a role for hypoxia in the induction of a response of transcription factor nuclear factor κB (NFκB) NFκB comes from in vitro, in vivo, and clinical studies. It is the master regulator of cellular inflammatory responses, controlling expression of key inflammatory cytokines, such as tumor necrosis factor alpha (TNFα) and interleukin-8 (Garvey JF, 2009). Intermittent hypoxia induces upregulation of NFκB- dependent cytokines in endothelial cells in vitro and it is typical of COPD, particularly during sleep or exertion (Ryan S, 2009).

In sustained hypoxia, NFκB appears to interact with HIF-1α to promote the expression of inflammatory genes, such as cyclo-oygenase II. Similarly, in a rodent model, 24 hours of sustained hypoxia has been shown to upregulate NFκB activity in pulmonary and cardiac tissue (Fitzpatrick SF, 2011).
Meanwhile, clinical studies in COPD patients have found that circulating levels of TNFα and soluble TNF receptors increase as arterial oxygen tension decreases. (Takabatake N, 2000). A growing body of evidence supports a role for tissue hypoxia in the genesis of this inflammation (Trayhurn P, 2008, Pasarica M, 2009; Tkacova R, 2010).
This systemic inflammation is at least partially reversible. Treatment with inhaled or oral corticosteroids has been shown to reduce the degree of systemic inflammation in COPD patients (Sin DD, 2004).
However, trials of more targeted antiinflammatory therapies have been disappointing. No objective clinical benefits and inflammatory reduction are defined for Blockade of TNFα with the monoclonal antibody and infliximab, in patients with moderate-severe COPD and may be associated with an increased risk of pneumonia (Dentener MA, 2008,. Rennard SI,2007).
The effect of supplemental oxygen therapy in this regard is uncertain, with some authors reporting an increase, and others a decrease, of inflammatory markers following oxygen administration (Carpagnano GE, 2004, Van Helvoort HA, 2006).

Muscle dysfunction

Chronic hypoxemia may contribute to skeletal muscle dysfunction via both systemic factors, such as direct inhibition of cellular pathways and local induction of oxidative stress. The Skeletal muscle dysfunction particularly affecting leg muscles, in particular the quadriceps, decreasing his muscle strength with reduced endurance capacity. In patients with moderate-severe disease, reduced quadriceps strength predicts increased mortality, independent of age, nutritional status, or degree of airflow obstruction (Swallow EB, 2007). A number of factors appear to interact in the generation of skeletal muscle dysfunction in COPD. These include disuse atrophy, malnutrition, corticosteroid usage, and hormonal dysregulation (Kim HC, 2008) . However, there is increasing evidence that chronic hypoxemia

may significantly contribute to this process. Healthy subjects exposed to chronic hypoxia at altitude undergo a reduction in muscle strength and endurance, with a concomitant alteration in composition (Wust RC, 2007). Similarly, chronically hypoxemic COPD patients have accentuated muscle dysfunction, an effect that is partially reversed by supplemental oxygen (Wust RC, 2007). Hypoxia may contribute to skeletal muscle dysfunction in COPD patients by a number of mechanisms. As discussed above, hypoxia helps generate the low-grade chronic systemic inflammation that characterizes COPD. TNFα can provoke muscle cell apoptosis and protein degradation via the ubiquitin/proteasome system (Kim HC, 2008). These findings have suggested that systemic inflammation may be a contributory factor in skeletal muscle dysfunction. Another possible contributor to skeletal muscle dysfunction is the generation of oxidative stress. Reactive oxygen species are produced in normal aerobic metabolism, and at physiological levels act in a beneficial manner, participating in cell signaling and host-defense against infection. However, higher concentrations of reactive oxygen species can mediate damage to lipids, proteins, and DNA, and drive inflammatory cascades. Reactive oxygen species generation is usually balanced by enzymatic (eg, superoxide dismutase) and nonenzymatic (eg, glutathione) antioxidant defense mechanisms. Oxidative stress occurs when there is an imbalance between the generation of reactive oxygen species and antioxidant capacity. Oxidative stress impairs skeletal muscle contractility, and subjects with COPD have evidence of increased oxidative stress, particularly following exercise (Couillard A, 2003).This effect appears particularly marked in chronically hypoxemic subjects, in whom markers of oxidative stress significantly increased in peripheral muscle at rest and following exercise (Koechlin C,2005).Chronic hypoxemia may also directly affect smooth muscle function. The AKt/mTOR (mammalian target of apamycin) pathway regulates skeletal muscle mass and prevents muscle atrophy (Bodine SC, 2001). Hypoxia has been demonstrated to downregulate this pathway in a rodent model, possibly via overexpression of the hypoxia-induced gene, REDD1 (regulated in development and DNA damage response), thus leading to reduced muscle mass (Favier FB, 2010).

Comparative analysis of skeletal muscle from hypoxemic and non hypoxemic COPD patients demonstrates inhibition of mTOR signaling in the former. Furthermore, von Hippel-Lindau protein appears to be overexpressed in the skeletal muscle of patients with COPD, thereby potentially impairing HIF-1α-mediated adaptive pathways in hypoxia (Jatta K,2009).

Exercise and CRF patients

Exercise may actually improve gas exchange in subjects with mild COPD, largely due to an improvement in V/Q relationships resulting from more even distribution of ventilation (Barbera JA, 1991).

However, in more severe disease, V/Q mismatching and peripheral oxygen extraction are increased, (Dantzker DR, 1986) and dynamic hyperinflation contributes to alveolar hypoventilation, (O'Donnell DE, 2002) with resultant exertional hypoxemia.

Desaturation with exercise appears to predict increased risk of mortality, (Casanova C, 2008) but the role of supplemental oxygen in this area is uncertain. A number of studies have shown it to provide short-term symptom relief and exercise performance, but longer-term data are lacking (Stoller JK, 2010). Similarly, there is little evidence in the published literature to support a role for ambulatory oxygen therapy in prolonging survival (Kent, 2021).

Regarding the exercise performance, Crisafulli et al. suggested that a simple walking aid like a rollator may be helpful in COPD patients receiving long-term oxygen therapy, particularly in those with lower residual exercise capacity (Crisafully E, 2007).

Polycythemia

COPD has long been recognized as an important cause of secondary polycythemia. When present in COPD, polycythemia can contribute to the development of pulmonary hypertension, and leads to pulmonary endothelial dysfunction, reduced cerebral blood flow, hyperuricemia and gout, and increased risk of venous thromboembolic disease.

Nevertheless, a recent analysis of a prospective cohort of 683 stable COPD outpatients revealed a low prevalence of it (only 6%), (Cote C, 2007)

while only 8.4% of over 2500 French patients with severe COPD receiving LTOT had a hematocrit greater than 55% (Chambellan A, 2005). This low prevalence may be at least partially attributable to the widespread prescription of LTOT in severe COPD populations.

Indeed, Chambellan et al. found mortality decreased by 14% for every 5% increase in hematocrit (Chambellan A, 2005). A number of explanations have been advanced to account for these findings. COPD is associated with chronic, low-grade systemic inflammation, which may lead to anemia of chronic disease, (Similowski T, 2006). and emerging evidence suggests clinically occult chronic kidney disease may be common in elderly patients with COPD, potentially leading to anemia via impaired production of erythropoietin (Incalzi RA, 2010).

The development of polycythemia in response to hypoxemia is critically dependent on the transcription factor hypoxia-inducible factor (HIF)-1, which functions as the master regulator of cellular oxygen homeostasis. HIF-1 is a heterodimeric protein consisting of a constitutively expressed β subunit, and an oxygen-regulated α subunit. In normoxic conditions, the latter is hydroxylated by a family of proline hydroxylases, and subsequently ubiquinated and degraded. The presence of cellular hypoxia allows stable HIF-1 to induce adaptive genes, such as vascular endothelial growth factor and erythropoietin (Semenza GL, 2009).However, HIF-1 can lead to maladaptive responses. One example of this is the generation of polycythemia in patients with COPD, resulting from HIF-1 upregulation driven by hypoxemia.

A number of interventions have been assessed in polycythemia COPD patients. In the Nocturnal Oxygen Therapy Trial, continuous oxygen therapy had a greater beneficial impact on mortality in patients with a hematocrit of 47.4%, (Nocturnal Oxygen Therapy Trial Group, 1980) while the Medical Research Council study showed LTOT reduced risk of death in patients with hypoxic cor pulmonale, hypercapnia, and secondary polycythemia. (Medical Research Council Working Party, 1981).

Pharmacological interventions, such as administration of theophylline (Oren R, 1997) or antagonism of the renin-angiotensin pathway with losartan, may reduce secondary erythrocytosis in COPD patients (Vlahakos DV, 2001).

In selected subjects, venesection can ameliorate pulmonary hypertension. (Weisse AB, 1975). While relatively uncommon in modern COPD populations, historic evidence suggests that, when present, polycythemia can contribute to diminished quality of life, increased morbidity, and excess mortality. As with pulmonary hypertension, its presence in a COPD patient should prompt consideration of supplemental oxygen therapy.

Neurocognitive dysfunction

Neurocognitive dysfunction appears to be relatively common in COPD populations, and appears to increase in prevalence with impairment in gas exchange (Dodd JW, 2010). When present, impaired cognitive function is associated with reduced quality in life, and may be predictive of increased morbidity and mortality in COPD patients. A number of factors have been postulated to contribute to this, including concomitant vascular disease and smoking. However, resting hypoxemia appears to be a key risk factor, with markedly increased prevalence among subjects with severe hypoxemia (Dodd JW, 2010). Suggested mechanisms include systemic inflammation and oxidative stress leading to direct neuronal damage, as well as depletion of neurotransmitters due to dysfunction of oxygen-dependent enzymes. Once again, the potential benefits of oxygen therapy are debated, with some authors failing to demonstrate any effect, (Incalzi RA,1993) while others have found supplemental oxygen to be protective against, or capable of ameliorating, neurocognitive dysfunction (Thakur N, 2010).

Oxygen supplementation

Although supplemental oxygen had been used in the treatment of patients with emphysema and chronic bronchitis for decades in order to maintain normal level of blood oxygenation, its ability to prolong survival in selected COPD populations was only conclusively established in the early 1980s. The Nocturnal Oxygen Therapy Trial and Medical Research Council trial, both relatively small by modern standards, demonstrated increased survival in markedly hypoxemic patients receiving more than 18 hours of supplemental oxygen per day when compared either with those receiving oxygen for 12 hours per day, or those receiving no treatment (Nocturnal Oxygen Therapy Trial Group. 1980; Medical Research Council Working Party, 1981). Subsequent studies have shown

supplemental oxygen can reduce pulmonary hypertension, improve neurocognitive function, increase exercise tolerance, and reduce frequency of exacerbations (Kim V, 2008).

Its utility in populations with moderate daytime hypoxemia, nocturnal hypoxemia, or exertional oxyhemoglobin desaturation remains less clear. The available evidence suggests that supplemental oxygen does not prolong survival in these patients, but further carefully designed studies investigating its potential to improve survival, function, and well-being are warranted (Kent BD, 2011).

Additional improvements in functional capacity are only likely to occur when the adjunct interventions enable patients to train at higher intensities during their general exercise-training programme. There exists a sound physiological rationale for correcting hypoxaemia as a strategy to improve performance and reduce symptoms during exercise in patients with COPD (Dilektasli AG, 2019). However, not all of the previous randomised clinical trials were able to achieve relevant contrasts in training intensities and treatment outcomes between oxygen and air groups (Nonoyama ML, 2007).

The study by Alison et al. (Alison JA, 2016) constitutes the largest RCT conducted in this area so far applied to patients with exercise desaturation.

It confirms that supplemental oxygen was not required for patients to train safely and to derive some benefits from exercise training. However, some concers are about different volume and intensity of training between groups.

At now, no clear indications are available about to oxygen supplementation in this group of patients. The administration of oxygen by high-flow nasal cannula, in comparison to standard way of administration (nasal probs, Venturi Mask) can improve both transcutaneous partial pressure of carbon dioxide and 6-min walking distance, suggesting the high-flow nasal cannula has benefits in the management of chronic obstructive pulmonary disease. The literature suggests no impact on hospitalisation and mortality, and it could be a good alternative in patients who survive the chronic obstructive pulmonary disease events. Still, the global impact of high-flow nasal cannula on the quality of life of patients with chronic obstructive pulmonary disease should be examined (Li Duan, 2022).

When administered in supraphysiological doses, oxygen therapy can lead to diminished ventilatory drive, increased ventilation/perfusion mismatch, and consequent hypercapnia. However, controlled oxygen therapy, targeting an saturation in the 90%–92% range, is not likely to result in clinically significant hypercapnia (Moloney ED, 2001).

The use of supplemental oxygen is not free of risk. Oxygen administration has been shown to generate oxidative stress and airway inflammation, which could theoretically contribute to further tissue damage and progression of disease (Kim V, 2008).

Finally, the drawbacks of LTOT use are not all medical. Quite apart from significant financial cost, and the perceived societal stigma of LTOT, the combination of cigarette smoking and oxygen use is a potentially lethal one. Although this is generally considered to be an absolute contraindication to the prescription of supplemental oxygen, reports suggest up to 20% of COPD patients receiving LTOT may be active smokers (Lacasse Y, 2006).

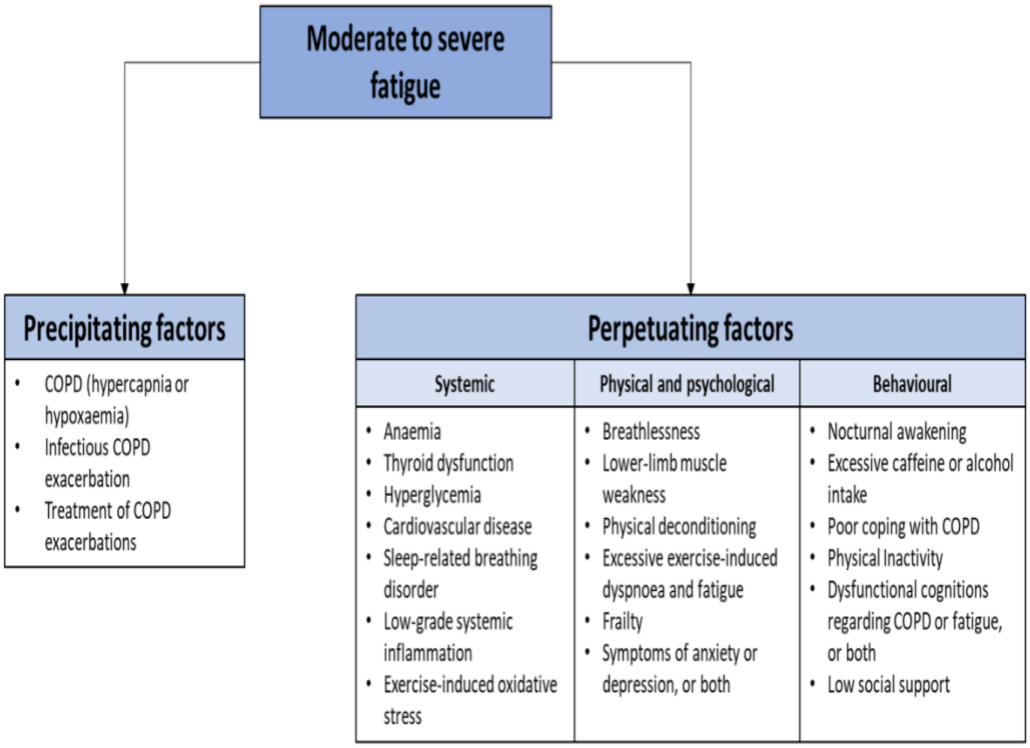
Whether supplemental oxygen therapy should be withdrawn from such patients remains an underexplored and a rather fraught question.

4.2 PERCEPTIVE FATIGUE IN COPD

After dyspnea, the Perceived Fatigue (PF), the feeling of fatigue is the second most important complaint in patients with COPD (Janson-Bjerklie S, 1986).
In general, many controversies have surrounded the definition of this symptom, and many years ago, some authors even argued that fatigue might be considered as a syndrome and not as a symptom. However, nowadays PF is recognized universally as a complex syndrome with both physical and psychological factors involved (Evengard B, 1998). In 1996, Ream and Richardson defined fatigue as being "a subjective and unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals' ability to function to their normal capacity" (Ream E, 1996). Patients with COPD describe their fatigue as a feeling of "general tiredness" or as a feeling of being "drained of energy" (Richardson A. 1997).
Fatigue can have major consequences on health status, as it may restrict patients' daily activities, lead to a worsened prognosis and is a predictor of mortality. Despite its high prevalence and negative impact on daily life, PF often remains unrecognized and untreated. If fatigue is not treated, it can worsen over time, even though the degree of airflow limitation remains stable (Edabi, 2021).
In order to develop effective interventions aimed at stabilising or reducing fatigue, it is important to know which factors precipitate and perpetuate fatigue in COPD. **(figure 3**). Spruit et al. (Spruit MA, 2017) recently offered a comprehensive model for framing the reported symptoms of moderate-to-severe fatigue in patients with COPD. Perceived fatigue may arise from a variety of factors, which can be divided into 3 main categories: systemic factors (e.g., cardiovascular disease or exercise-induced oxidative stress), physiological and psycholo¬gical factors (e.g., limb muscle dysfunction or symptoms of anxiety and/or depression), and behavioral factors (e.g., physical inactivity or low social support) factors. Perceived fatigue may also be precipitated by COPD exacerbations and their subsequent treatment. In this context, fatigue in COPD appears to be secondary to a multiplicity of factors which may act alone or in combination, both at rest and during physical activity (Gruet M. 2017). Although performance fatiguability and

neuromuscolar fatigue (e.g., limb muscle dysfunction) has been proposed to contribute to exaggerated perceived fatigue in these patients (Spruit MA, 2017), this model remains to be experimentally tested (**figure 3**).

Figure 3. Precipitating and perpetuating factors of PF.



Assessment of PF

To date, several studies have investigated factors associated with PF (Inal-Ince D, 2009; Theander K, 2008; Baghai-Ravary R, 2009; Kapella MC, 2000; Breukink SO, 1998; Breslin E, 1998; Kentson M, 2016). However, these studies differ greatly in their definitions and assessment methods of fatigue and in sample selection. In addition, many of these studies did not assess fatigue as their primary outcome, complicating the comparison of results. Fatigue is generally measured with three main types of instruments, namely, unidimensional symptom scales, multidimensional scales/questionnaires, and health-related quality of life questionnaires containing specific domains for fatigue. Most of these instruments can be labeled as "generic" because they have been used in various diseases including cancer but there are some newer questionnaires such as chronic respiratory disease questionnaire or such as the Manchester COPD fatigue scale, which circumvent the measurement of fatigue to the specific setting of chronic lung disease respectively to that of COPD.

Table 2 describes the principal assessment tools available in literature, with their characteristics.

Table 2: Assessment scales/subscales measuring PF in COPD.

Assessment scales	Items	Fatigue subscale	Type	Cut-off score	Internal consistency	Reliability
Chronic Respiratory (Disease) Questionnaire CRDQ/CRQ	5	1	7-point Likert	MCID 0.5 per item	0.51–0.83	0.90–0.93
Fatigue Severity Scale FSS	9	1	7-point Likert	4	0.88	0.84
Medical Outcomes Study 36-Item Short-Form Health Survey SF-36/MOS-36	4	1	1–6-point Likert	Participants have high fatigue if scores <2 SD from published mean age-adjusted normal vitality scores	0.71–0.92	0.62
Functional Assessment of Chronic Illness Therapy FACIT	13	1	5-point Likert	Mild: 24–36 Moderate: 12–23 Severe: 0–11	0.93	0.90
Visual Analogue Scale for Fatigue VAS-F/LFS	13	1	Visual analogue	Fatigued when score is above 50% of 100%	0.91–0.96	Not described
Multi-dimensional fatigue index;MFI-20	20	5	7-point Likert	≥13 (severe fatigue)	0.84	Not described
COPD and Asthma Fatigue Scale CAFS	12	1	5-point Likert	Not described	0.95	0.82
Memorial Symptom Assessment Scale MSAS	3	1	5-point Likert	Not described	0.76–0.87	0.40–0.94
Brief Fatigue Inventory BFI	9	1	11-point Likert	≥7	0.96	Not described
Edmonton Symptom Assessment System ESAS	1	1	11-point Likert	3–4 (moderate) 5–7 (severe)	0.79	0.45–0.86
Profile Of Mood States POMS	7	1	5-point Likert	Not described	0.80	Not described
M: Manchester COPD Fatigue Scale CFS	27	3	5-point Likert	Not described	0.97	0.97
Checklist Individual Strength CIS Subjective Fatigue subscale	8	1	7-point Likert	<27 (normal) ≥27 (moderate) ≥35 (severe)	0.90	Not described

Legend: MCID: minimal clinically important difference. Modified from Edabi, 2021

Prevalence and related factors

Lewko et al. (Lewko A, 2012) reported in 2012 that a combination of exercise capacity, muscle strength, airflow limitation, depression, dyspnoea and sleep quality is associated with fatigue in PF with COPD. In recent years, the number of studies on fatigue has increased drastically, providing evidence for the need of an updated review on the prevalence and predictors of fatigue. A recent literature review has summarised the existing knowledge about fatigue in patients with COPD by examining the prevalence of fatigue, physical, psychological, social and behavioural factors associated and the instruments that were most commonly used to assess fatigue (Ebadi Z, 2021).

On 196 studies evaluated the prevalence of fatigue ranged from 17–95% and it was related to age, sex, marital status, dyspnoea , forced expiatory volume in 1 s % predicted , number of exacerbations , number of comorbidities , number of medications , anxiety, depression, muscle strength, functional capacity, and quality of life. The **table 3** explains the main significant relationships among studies found between fatigue perception and other clinical and functional characteristics of the patients, divided in different clinical and social patients status (Ebadi Z, 2021).

Table 3. Correlations between fatigue perception and clinical factors.

Fatigue in COPD		R
Disease-severity factors	Comorbidities	0.10
	Dyspnoea	0.13 to 0.78
	AECOPD	0.27 to 0.38
	MED	0.35
	FEV_1 % pred	-0.55 to -0.076
Physical factors	Exercise capacity	-0.77 to -14
	Peripheral muscle strength	0.02 to 0.23
	BMI	0.02 to 0.23
Psychological fators	Depression	0.41 to 0.66
	Anxiety	0.36 to 0.61
	HRQoL	0.48 to 0.77
Sociodemographic factors	Age	-0.23 to 0.27
	Sex	0.11
	SES	0.10 to 0.11
	MS	-0.096

Legend: AECOPD: acute exarcerbations Chronic obstructive Pulmonary disease; FEV1: Forced Expiratory Flow at 1 second; BMI: Body Mass Index, MS: marital status; SES: socioeconomic status.

Interventions to Perceived fatigue

A series of interventions were evaluated in order to bring considerable improvements in fatigue and consequently in function and quality of life in COPD patients. A recent Cochrane review describes the presence of three systematic reviews (59 studies and 4048 participants) about it: the interventions proposed were self management, education programmes, nutritional support and pulmonary rehabilitation (Payne C, 2012).

Regarding the impact of exercise training our study (PROJECT 2, pg. 72) provided low-quality evidence of a positive impact of different exercise training programs on perceived fatigue in patients with COPD. Further studies are needed to assess the effects of exercise training on fatigue and to test tailored programs.

4.3. NEUROMUSCOLAR FATIGUE IN COPD

Exercise intolerance constitutes a central aspect in COPD, being associated with progressive disability and a lower survival (Spruit, 2013). The fundamental pathophysiological determinants are classically related to a chronic imbalance between the increased ventilatory demand and the reduced capacity to meet this demand (GOLD, 2007).

Studies have shown that, in addition to the pulmonary involvement, peripheral muscle dysfunction contributes to the reduced exercise capacity (ATS/ ERS 1999) and lower survival in these patients (Swallow EB, 2007). Although the mechanisms related to muscle dysfunction in COPD have yet to be clarified, it has been characterized by the presence of atrophy, loss of strength and power, in addition to early muscle fatigue (fatiguability), which explains the exercise intolerance in these patients (ATS/ERS, 1999).

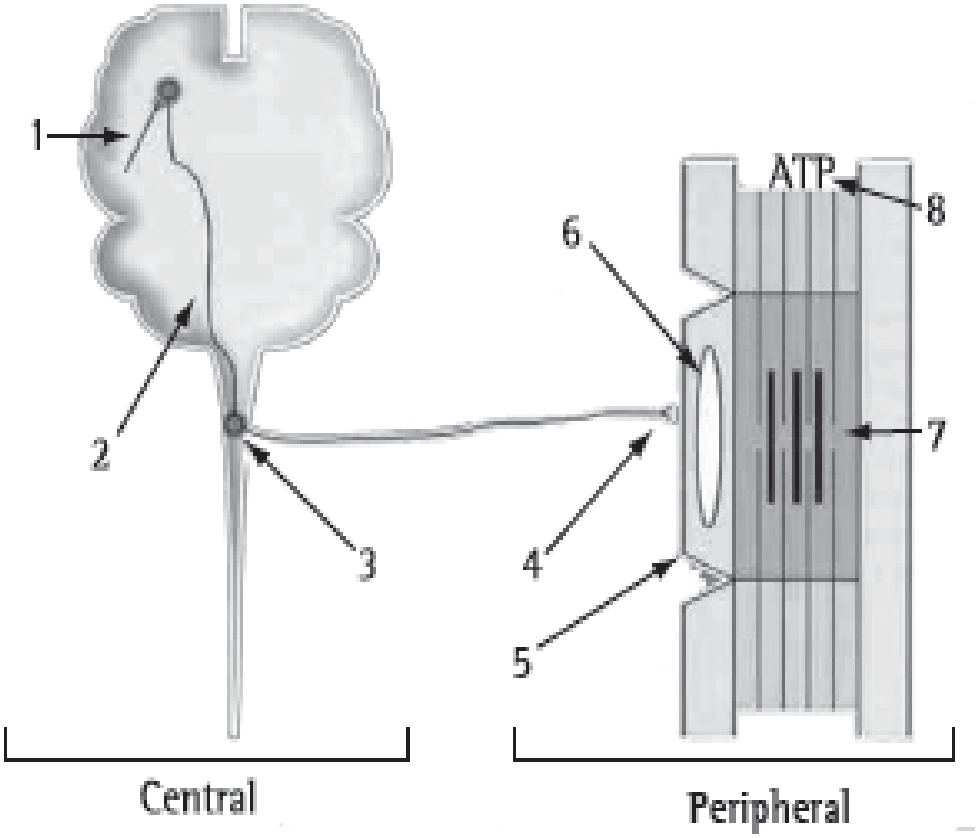
Classically, neuromuscolar fatigue (NMF) is defined as the inability of the muscle to generate or maintain the levels of strength required for a given work rate (Vøllestad NK. 1997). The fact that the capacity to produce maximal force is impaired almost from the time exercise begins has led to a broader definition of fatigue in the neuromuscular research field: fatigue refers to any decrease in the ability to apply muscular force or power caused by exercise, whether or not the task can be sustained (Bigland-Ritchie B, 1984). Impaired quadriceps muscle endurance during isolated muscle exercise is a common finding in patients with COPD, though the magnitude of decline varies considerably (from ~30% to almost 80%) (Coronell C, 1998). These diverging results may arise from discrepancies between testing modalities [e.g. contractile regimen (isometric, isokinetic or isotonic), contraction type (repeated or sustained) or exercise intensity (% of maximal voluntary strength)]. Patients with advanced COPD may suffer from greater impairment in muscle endurance compared to those with less severe disease. For instance, Serres et al. (Serres I, 1998) found a positive correlation between muscle endurance and resting lung function (forced expiratory volume in 1 second (FEVJ % predicted). It is noteworthy, however, that others did not confirm these findings (Allaire J, 2004; Couillard A, 2003).

Van den Borst and colleagues (Van den Borst B, 2013) found that quadriceps endurance was reduced compare to control even in patients with mild-to-moderate COPD (FEVt = 58 ± 16% predicted). Interestingly, Gouzi et al. (Gouzi F, 2011) reported a 40% lower quadriceps endurance in COPD in comparison to healthy controls matched by the current level of physical activity. These results suggest that mechanisms other than physical inactivity may be involved in the impairment of muscle endurance in these patients. Of note, muscle endurance in the upper limb has been found to be preserved in patients with COPD in comparison to healthy controls (Clark CJ, 2000;Franssen FM, 2005;Newell SZ, 1989).

Muscle fatiguability can be divided into two components: central and peripheral. This terminology is based on the anatomical and functional sites involved in the fatigue process. In central fatigue, muscle activation by the central nervous system is impaired, whereas, in peripheral or contractile fatigue, the involvement occurs distally to the neuromuscular junction (Neder JA, 2003).

A pictorial representation of the structures involved in central and peripheral fatigue is presented in **Figure 4.**

Figure 4: The potential sites of muscle fatigue



Legend: Central fatigue is related to changes in one of more that : 1) excitatory drive to the upper motor centers, 2) lower motor neurons, 3) rate of excitability of upper motor centes and motoneurons 4) neuromuscular transmission. Peripheral fatigue occurs when the changes are related to: 5) the excitability of the sarcolemma ; 6) the calcium release and reuptake by the T tubules and sarcoplasmatic reticulum , or 7) to contractile mechanisms, or (8) the energy.

4.3.1 ASSESSMENT OF NMF

Currently, there is a wide range of exercise models, tests and protocols being used in order to identify parameters indicative of NMF. Methods for the assessment involve three basic components:

i) **exercise pattern:** duration and intensity, either involving a single prolonged contraction or a series of repeated contractions muscle;

ii) **exercise condition:** isometric; isoinertial; or isokinetic;

iii) **activation strategy:** voluntary effort or exogenous stimulation;

Here the summary of principal tests used with this aim in COPD population.

In view of the evidence of peripheral muscle function impairment and in view of the different mechanisms determining susceptibility to fatigue in COPD patients, knowledge of the distinct functional assessment methods available (**Table 4**) is absolutely necessary so that it is possible to discriminate the main component involved in the process of peripheral muscle fatigue in these patients. However, some aspects in the choice of the method of assessment, such as the availability and reliability of the equipment, its cost-benefit ratio and its user-friendliness, in addition to patient cooperation, should also be considered.

Table 4: NMF functional assessment methods available.

Method	Assessment	Protocol	Outcome
MVC and submaximal voluntary contraction	Measures MVC and submaximal voluntary contractions until exhaustion	Sustainment of MVC or submaximal voluntary contraction at 20-60% of MVC until failure (↓ 50%)	↓ isometric muscle strength and endurance
Isokinetic measurements	Measures isometric torque, isokinetic torque and total work performed	5 contractions at an angular velocity of 60-90°/s; 15-30 contractions at a velocity of ≈300°/s	↓ isometric PT, ↓ isokinetic PT and ↓ total work generated
Surface electromyography	Analyzes the myoelectrical manifestation of fatigue during muscle contractions	Used during MVC and during submaximal voluntary contraction	↓ in muscle activation; ↓ MF; ↑ SRM and altered M-wave
Twitch interpolation	Differentiates fatigue of central origin from that of peripheral origin	MVC associated with nerve stimulation; failure if the difference between MCV and twitch is >15%	↓ contractile activity and transmission or central activation failure
Critical power	Assesses the ability to sustain exercise under anaerobic conditions	Series of short-duration, high-intensity exercises determines CP (fatigue threshold)	↓ exercise tolerance ↓ fatigue threshold
Borg scale or visual analog scale	Assesses the perception of fatigue using scales	Borg scale (score, 0-10) and visual analog scale (0 -100 mm)	↑ scores for lower limb fatigue
31P-MRS	Directly and noninvasively measures the intramuscular metabolism	Repetitive localized exercise of MMII, in the MRS system, assesses high-energy compounds	↓ levels of high-energy phosphates at rest, during exercise and during recovery
Biopsy	Identifies the microstructural and bioenergy characteristics of the muscles	Collection of vastus lateralis muscle samples	↑ strength/frequency ratio; ↓ % of type I fibers; ↓ CSA fibers; ↓ capillary/fiber ratio; ↓ mitochondrial density
Determination of lactate and ammonia levels	Assesses the inability to convert oxygen into energy in acid situations	Collection of venous, arterial or arterialized blood samples at rest, during exercise and during recovery	↑ lactate and serum ammonia levels during and after exercise
NIRS	Noninvasively measures the indicators of oxygen delivery and oxygen uptake	Detection of variations in the local concentrations of hemoglobin/oxygenated and deoxygenated myoglobin during intense exercise	↑ peripheral muscle O_2 extraction fraction; ↓ estimated muscle perfusion

Legend: MCV=maximal voluntary contraction, PT: peak torque, MF: median frequency, srm: suqre root of the mean, CP. Critical power, 31P-MRS= phosphorus-31 mgnetic resonance spetroscipy, MMLL : lower limb muascles; CSA: cross-sectional area; NIRS: near-infrared spectroscopy, Vo2: oxygen uptake.

Maximal and submaximal voluntary contraction

The assessment of global NMF can be done through the evaluation of maximal voluntary contraction (MVC) and by instructing the patient to generate as much voluntary strength as possible, without changing muscle length. In this assessment, equipment such as tensiometers or dynamometers is used to quantify the isometric strength generated. Since this is a volitional technique, external complicating factors, such as the functional ability and motivation of the patient, can generate contractions using submaximal activation (Allen GM, 1995; Man WD, 2003) However, due to its user-friendliness, the use of verbal encouragement and the experience of the technician, little variability has been described in MVC. In COPD patients, the loss of the capacity to generate or maintain MVC during knee extension exercise has been representative of NMF (Gosselink R, 1996).

Studies have used series of submaximal voluntary contractions in the assessment of muscle fatigue in COPD patientsm (Serres I, 1998; Gosker HR, 2007; Schols AM, 1993; Kim HC, 2008).

Typically, it is required that fatiguing task has to be performed approximately at 20-60% of MVC (repetitive isometric od isotonic muscle contractions) or at 60-80% of peak power output (PPO) (cycling or walking tasks) , and sustained until exhaustion. Endurance is measured by how long the subject can maintain the task and it can be considerate an indirect measure of fatigue.

Twitch interpolation method technique

The current gold standard to evaluate NMF is the twitch interpolation method. In this technique, the individual is asked to perform a MVC, and, in addition, a stimulus is applied to the nerve. It has been demonstrated that the muscle responses evoked by supramaximal electrical and magnetic stimulation are comparable in demonstrating (quadriceps) fatigue (Verges S, 2009).

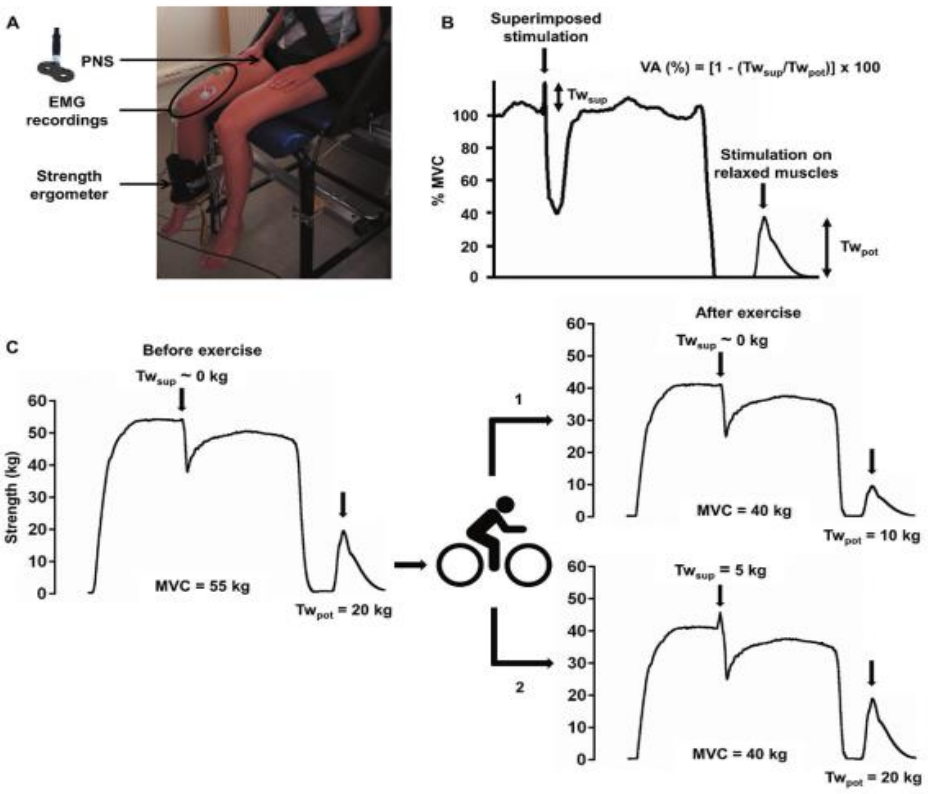
Peripheral fatigue can be demonstrated by stimulation of the relaxed muscle via either the trunk of the motoneurons or the muscle itself. Identical stimulation before and after exercise is used to objectively show an exercise-induced decrease in the evoked muscle strength (Kufel TJ, . 2002; Merton PA, 1954). Additional information regarding the mechanisms underlying NMF (e.g., impairment of neuromuscular propagation of the action potentials, impaired excitation-contraction coupling, etc.) can be obtained by combining measurements of muscle force production with electromyography, and by using combinations of single stimulation, doublets (with 10-100 ms between both stimulations) or stimulation trains (i.e., several stimulations at different frequencies, typically between 10 and 100 Hz). Concomitantly, electrical activity recording will show the additional recruitment of motor units by using twitch. A greater difference between MVC alone and MVC combined with twitch in terms of the muscle activity generated the outcome measure about NMF. A difference > 15% between MVC and QTwpot is characterized as contractile fatigue. In the scientific field, twitch is being currently used to further the understanding of the effects of dynamic exercise (Man WD, 2003) and localized exercise on contractile fatigue of the quadriceps muscle in COPD patients (Verin E, 2004; Swallow EB,. 2007;Mador MJ, 2006;.Allen GM, 1995). In addition, to allowing the differentiation between central fatigue and peripheral fatigue, this interpolated technique, in association with the M-wave, applied during the MVC makes it possible to detect transmission failure or central activation failure.

A major advancement in the evaluation of the central component of fatigue occurred when Merton (Merton PA. 1954) demonstrated that the additional supplementary force provided by electrical neural stimulation during a maximal voluntary contraction can determine the deficit in central motor drive to induce maximal muscle contraction. This technique, twitch interpolation, enables assessment of the participant's ability to voluntarily contract their muscle maximally, i.e., the level of voluntary activation [Percentage of maximal Volontary Activation (MVA%)] (Allen GM, 1995). While once can typically voluntarily activate limb muscles near-maximally before exercise (voluntary activation >90%), exercise can induce an impairment in the ability of the central

nervous system to induce a motor command allowing maximal muscle activation. This exercise-induced central deficit is named central fatigue and can occur in healthy subjects following exercise of sufficient intensity and duration or in specific conditions (e.g. in hypoxia) as well as in patients (Verges S, 2012; Marillier M, 2018). Further insight into the mechanisms of central fatigue can be provided by stimulations applied at the cerebral or spinal levels (Gruet M, 2013). Central motor command can also be evaluated during voluntary muscular contractions from the electromyography (EMG) activity, for instance by using the root mean square of the EMG signal recorded during a maximal contraction.

Figure 5 proposes an explanation of neuromuscular fatigue assessment using peripheral nerve stimulation.

Figure 5. Assessment of the peripheral and central component of neuromuscular fatigue by 'twitch interpolated technique.



Legend:

Panel A describes the experimental setting required to assess neuromuscular fatigue by peripheral nerve stimulation. A pulse is delivered to the peripheral nerve (magnetic stimulation oe electrical stimulation) and the evoked muscle strength is recorded with an ergometer (strain gauge). Strength measurements may also be coupled with EMG recordings.

Panel B depicts the measurement of voluntary activation using the 'twitch interpolated technique'. Specifically, a pulse is delivered over the nerve that innervates the muscle under investigation during a maximal voluntary contraction to measure the amplitude of the superimposed twitch. A second pulse is delivered ~ 2 s after the contraction while muscles are on a relaxed state to determine the amplitude of the potentiated twitch. The amplitudes of the superimposed and potentiated twitch are then compared to determine voluntary activation. A reduction in voluntary activation during or following exercise demonstrates the presence of central fatigue. Meanwhile, a post-exercise reduction in the potentiated twitch indicates the presence of peripheral fatigue.

Panel C shows illustrative examples of peripheral and central fatigue. Before exercise, a participant developed a strength of 55 kg during a maximal voluntary contraction. The superimposed twitch amplitude is close to 0 kg, indicating a near-maximal voluntary activation. After exercise (e.g. cycling), maximal voluntary contraction decreased to about 40 kg in both situations (1 and 2), indicating the development of neuromuscular fatigue. In the situation 1, the superimposed twitch remained close to 0 kg, indicating that no central fatigue has developed. However, the potentiated twitch decreased from 20 to 10 kg, indicating the development of peripheral fatigue. Conversely, in the situation 2, the superimposed twitch reached 5 kg while the potentiated twitch remained 20 kg. Voluntary activation is thus about 75%, indicating the presence of central fatigue but no peripheral fatigue was produced (modified from Marillier, 2021).

In their seminal study using magnetic stimulation in COPD, Mador et al (Mador JM, 2000) showed that almost 60% of patients developed a significant amount of peripheral fatigue following high-intensity cycling exercise to symptom limitation. The occurrence of peripheral fatigue following exercise was detected in up to 81% of patients with COPD when relying on potentiated twitch, a more sensitive index than unpotentiated twitch (prevalence -50%) (Mador MJ, 2001). In fact, post-exercise fatigue originating from the exercising muscles may be anticipated, as it is also observed in healthy controls in response to higher exercise intensities (Polkey Ml, 1996). The limited available evidence indicates that peripheral muscle fatigue is commonly seen in patients with COPD (Marillier, 2021).

The intensity of the observed fatigue is likely to be influenced by a variety of factors, including patients' phenotypes (e.g. severity of airflow obstruction or exercise-induced hypoxemia), exercise modality, exercise intensity and duration, and differences in the procedures used for neuromuscular fatigue investigation (e.g. time delay between exercise cessation and assessment) (Bachasson D, 2013). Larger decreases in the potentiated twitch force in patients than controls after a cycling exercise of equivalent duration and metabolic demand [oxygen (02) uptake] strongly support greater susceptibility to fatigue in COPD (Mador MJ, 2003). However, despite being currently considered the gold standard in this assessment, this method is not yet available in clinical practice.

Isokinetic dynamometry

Isokinetic movement consists of muscle contractions at a constant velocity throughout the movement. This type of contraction is only obtained by using isokinetic equipment, in which resistance is variable and accommodative, adapting itself to the strength applied. With this equipment, it is possible to determine the strength developed at each angle of movement and the duration of the contraction. Therefore, in addition to strength, it is possible to determine the variable *work*, which is the product of strength multiplied by velocity and power (i.e., work performed per unit of time). When isokinetic assessment is performed, peak torque is the most appropriate term to express the maximal strength generated, since strength occurs due to the rotational movement of the joint in

relation to an axis. In order to assess strength, lower angular velocities, typically 60-90º/s, are recommended (Gleeson NP, 1996). In order to assess endurance, the most widely used angular velocities are 180º/s and 300º/s. Greater torque is generated when low angular velocities are applied. Therefore, in the assessment of strength, 3-5 repetitions are used, and the highest value obtained corresponds to peak torque. In the assessment of endurance, 15-30 successive repetitions are used, since lower peak torques are generated and a greater number of muscle contractions are possible. Endurance test results can be interpreted in two ways: total work, which corresponds to the sum of the area under the muscle contraction curve, or a decrease in peak torque or work during 15, 20, 30 or 50 repetitions (Malaguti C, 2006). The decrease is calculated by dividing the peak torque or the work of the last five contractions by that of the first five, and this result is expressed in percentage. A greater decrease translates to greater fatigue.

In clinical populations, it is strongly recommended that total work be used, since the peak torque generated in each contraction when these patients start the test is already lower, and, therefore, its reduction is not pronounced.

The most obvious advantage of using isokinetic assessment, whose reliability and reproducibility are higher than those of conventional techniques, is the control of the velocity and angle of the movement (Malaguti C, 2006). Conversely, the disadvantages are related to the excessive cost, the need to train raters and the extremely limited external validity, since constant angular velocity does not constitute a physiological movement (Mador MJ, 2001). Typically, in comparison with healthy controls, COPD patients were found to present lower isometric torque, lower isokinetic torque and lower total work (Malaguti C. 2006; Neder JA, 2000).

Surface electromyography

Surface electromyography (sEMG) is a widely used noninvasive method for the assessment of muscle function through the placement of electrodes on the skin. The study of muscle function through sEMG results from the analysis of the electrical activity of the muscle by determining the sum of the action potentials of

all muscle fibers. (De Luca CJ, 1997;13(1):135-63 Duchêne J, 1993). In addition to determining the electrical activity of the muscle, sEMG has been used to analyze fatigue, assess the training, determine the sEMG signal/strength ratio and identify pathological condition (Hausswirth C, 2000; Soderberg GL, 2000)

During muscle contraction, the electromyographic record basically provides two parameters: square root of the mean (SMR) and median frequency (MF). The SRM represents the electromyographic signal amplitude, that is, it quantifies the electrical activity during contraction. The MF is related to the firing rates of motor units. Therefore, muscle fatigue is present when, in the electromyographic analysis, there is (Man WD, 2003).

• higher SRM, which results from greater muscle activation due to a reduction in the capacity to sustain a contraction

• lower MF due to a reduction in the action potential of the fibers during muscle contraction

The electromyographic signal resulting from this method is an action potential designated M-wave. The M-wave is proportional to the number of depolarized motor units and, consequently, is a reflex of the extent of the activation of muscle fibers produced during a muscle contraction. A reduction in contractile strength with unchanged M-wave is indicative of contractile fatigue, that is, excitation-contraction coupling failure (Farina D, 2004). However, when the reduction in contractile force is associated with a decrease in M-wave amplitude, transmission failure can be suspected. Therefore, the possible sites of muscle dysfunction during exercise can be determined.

In pulmonary rehabilitation, sEMG has been widely used to assess muscle function, including during exercise (Saey D, 2006). In this context, one group of authors compared, through sEMG, the electrophysiological changes in the quadriceps femoris of COPD patients, who were slightly hypoxemic during exercise, with those of healthy individuals during cycle ergometer incremental exercise. The COPD patients presented lower MF and higher SRM than did the control group patients (Gosselin N, 2003). Subsequently, in a randomized study,

another group of authors revealed changes in the electromyographic responses of the quadriceps femoris during exercise performed using oxygen. The same group suggested that those changes would be associated with improved aerobic metabolism, delayed fatigue, greater muscle excitability and greater muscle activation at a given level of exercise when using oxygen (Gosselink N, 2004.)

In another study, COPD patients presented a lower capacity to sustain an isometric contraction of the quadriceps femoris at 60% of voluntary contraction until exhaustion than did healthy individuals (42 s and 80 s, respectively; $p < 0.05$). Despite the lower muscle resistance, the decrease in MF was similar in both groups (Allaire J, 2004).

Critical power

A physiological approach in the assessment of fatigue is the test of anaerobic capacity or power. This method attempts to assess the organic ability to provide energy regardless of the oxygen supply or of the use of oxygen, that is, the capacity to sustain predominantly anaerobic work. In this context, the concept of Critical Power (CP) involves the performance of high-intensity activities of short duration, and the limits of exercise tolerance are determined using a mathematical model. The clinical importance of this test consists in quantifying the workload at which fatigue occurs, that is, in determining the fatigue threshold (Neder JA, 2000). Despite involving a series of dynamic and exhausting exercise tests, this protocol was feasible in COPD patients (Malaguti C, 2006). Therefore, one group of authors demonstrated that, in these patients, CP and anaerobic work capacity present different determinants from those observed in healthy controls, being dependent on airflow limitation and the consequent dyspnea sensation in COPD patients (Neder JA, 2000).

Fatigue Rating of perception scales

The assessment of the subjective perception of fatigue by the patient during exercise tests or training tests has been commonly performed using scales. Although more than 30 scales can be found, the most widely used are the modified Borg scale (Borg GA, 1982) and the visual analog scale (Hayes M, 1921).

Although these scales are user-friendly, their outcomes can be influenced by various factors, such as motivation and understanding. Therefore, despite being widely used, these scales should be used in combination with other objective assessments.

Phosphorus-31 magnetic resonance spectroscopy

Phosphorus-31 magnetic resonance spectroscopy (31P-MRS) is a method for the direct and noninvasive measurement of muscle bioenergy [ATP, PCr, inorganic phosphate (IP) and intracellular pH], repetitive localized exercise and during the subsequent recovery period. This method has been clinically used in the treatment of patients with severe COPD, with evidence of pronounced changes in their muscle metabolism. These changes are revealed by lower aerobic capacity [decrease PCr/PI and decrease PCr/(PCr +PI)] during exercise, as well as by lower intracellular pH and lower PCr resynthesis during the recovery period, when compared with those observed in controls (Kutsuzawa T, 1995; Tada H, 1992;Lévy P, Wuyam B, 1997). It has also been shown that acute oxygen administration partially improves theses indices (Lévy P, 1997) suggesting that factors other than hypoxemia affect muscle metabolism.

Muscle biopsy

Reports of muscle biopsy in this population have shown changes in enzymatic and metabolic activity, as well as changes in the proportion of muscle fiber types and in the relationship with exercise intolerance (Whittom F, 1998; Maltais F, 1996).

A study using techniques of vastus lateralis muscle biopsy revealed a higher strength/frequency ratio in patients with severe COPD, that is, these patients required a higher frequency of stimulation to produce the same relative vastus lateralis muscle strength than did normal controls (Debigaré R, 2003). This measure describes indirectly the early development of NMF.

Determination of lactate and serum ammonia levels

Another marker to monitor fatigue in these patients is the level of serum ammonia, which typically accompanies the response to lactate during exercise. In one study, it was observed that, in comparison with healthy individuals, 60% of the COPD patients showed an increase in serum ammonia levels during exercise. It is likely that this event is due to the degradation of the AMP deaminase enzyme, subsequently converted into inosine monophosphate and ammonia, with a consequent reduction in the production of ATP, making its level insufficient to meet the energy demand (Calvert LD, 2008). Blood lactate levels determined during dynamic exercise and during the recovery period indicate that the COPD patients who interrupted the exercise complaining of lower limb fatigue tended to present significantly higher lactate levels than did those who interrupted the exercise complaining of dyspnea. Therefore, one group of authors observed that, in patients with fatigue, there was a relationship between increased lactate levels and decreased quadriceps twitch after dynamic exercise (Saey D, 2005).

The early onset of lactic acidosis observed in these patients occurs mainly due to the reduced mitochondrial density and the reduced muscle oxidative capacity, leading to the decrease in pH and the accumulation of acid lactic resulting from the inability to convert oxygen into energy in acid situations (Saey D, 2006).

Near-infrared spectroscopy

Reduced muscle perfusion and hypoxemia have been considered potential factors for the development of contractile fatigue. Near-infrared spectroscopy (NIRS) constitutes a state-of-the-art method for noninvasive measurement of indicators of peripheral perfusion, such as muscle oxygenation. In this technique, the oxygen-dependent differences in the absorption spectrum of iron (in the heme prosthetic group of hemoglobin) or copper (in cytochrome oxidase) make it possible to estimate the changes in the quantity of these metals, providing the local volumes of oxyhemoglobin and deoxyhemoglobin, as well as the sum of both volumes in the local muscle blood flow (Borghi-Silva A, 2008. Chiappa GR, 2008). Using this technique in COPD patients, one group of authors showed that increased

ventilatory work during moderate to intense exercise promotes blood flow redistribution, preferably to the respiratory muscles, reducing skeletal muscle perfusion and consequently increasing lactacidemia and muscle fatigue (Borghi-Silva A, 2008). Recently, using NIRS, another group of authors showed more eloquently that, in comparison with control group patients, COPD patients present higher peripheral muscle O_2 extraction fraction accompanied by lower estimated muscle perfusion during intense exercise (Chiappa GR, 2008). Therefore, the evident imbalance between oxygen delivery and oxygen uptake also plays a negative role in exercise tolerance in these individuals (Borghi-Silva A, 2008).

4.3.2. PHYSIOPATHOLOGY OF NMF

The interest in studying peripheral muscle fatigue in COPD patients is very recent, since the scientific focus has always been on the contributions of respiratory muscle fatigue to and on its implications for exercise tolerance. A study conducted in the early 1990s can be considered the precursor of subsequent studies on muscle fatiguability, having made a contribution in terms of exercise limitation, since lower limb fatigue was the predominant system when maximal exercise was interrupted in 43% of the sample of COPD patients of that study. At that time, the authors reported that it was an unexpected result (Killian KJ, 1992). In that same decade, another group of authors demonstrated that quadriceps muscle strength was an important determinant of physical capacity in this population (Gosselink R, 1996). These findings had a significant impact, furthering the study of the relationship between muscle performance and exercise capacity. More recently, one group of authors demonstrated that, in patients with moderate to severe COPD, quadriceps muscle strength is a better predictor of mortality than are age, body mass index and FEV_1 (Swallow EB, 2007).
In literature there are a some major findings on the metabolic and bioenergy determinants of muscle fatigue, as well as the methods for its identification and quantification use in this population.

Bioenergetic and metabolic determinants of peripheral muscle fatigue in COPD

Cronic respiratory diseases leads significantly to peripheral muscle fatigue. The impact of this dysfunction on muscle performance stems from abnormalities in muscle function (Gosselink R, 1996), structure (Whittom F, 1998), and bioenergy (Maltais F, 1996).
The etiology of these abnormalities seems to be multifactorial, involving factors such as deconditioning, hypoxia or hypercapnia, oxidative stress, senescence, hormonal dysfunction, systemic inflammation, chronic or repetitive use of drugs (corticosteroids) and nutritional depletion (ARTS/ERS, 1999).

In stable COPD patients, increased levels of C-reactive protein (CRP), fibrinogen, circulating leukocytes and proinflammatory cytokines, including TNF-α, IL-8 and IL-6, have been observed. Recently, increased serum IL-18 levels have also been identified in patients with moderate to severe COPD (Dourado VZ, J Bras Pneumol. 2006; Schols AM, 1996; Dentener MA, 2001; Gan WQ, 2004; Spruit MA, 2003).

The involvement of inflammatory mediators in COPD is suggested by the observation that systemic inflammatory markers are related to poor contractile muscle performance in COPD. For instance, quadriceps muscle strength was negatively associated with IL-8 levels during disease exacerbation (Spruit MA, 2003; Yende S, 2006), and with IL-6 and TNF-α levels in elderly individuals (Yende S, 2006). Conversely, another study revealed that severe quadriceps muscle weakness was significantly related to the mean daily dose of steroids used by patients during acute disease exacerbation. The deleterious effects of steroids on skeletal muscle function have been attributed to the inhibition of protein synthesis and the increase in protein degradation. However, due to the fact that patients receive corticosteroids for the treatment of acute inflammation, it is difficult to differentiate the muscle effect of steroid administration from the direct deleterious effects of COPD exacerbation (Decramer M, 1994).

Other evidence suggests the participation of oxidative stress in muscle dysfunction in COPD patient (Spruit MA, 2003). An imbalance between antioxidants and oxidants can be hypothesized. One group of authors established an inverse relationship between the magnitude of oxidative stress and quadriceps muscle endurance in COPD patients. In addition, that same group showed that short-term therapy with high doses of N-acetylcysteine (an antioxidant) prevent oxidative stress and significantly improves quadriceps muscle endurance (Koechlin C, 2004).

Senescence seems to be an important factor related to loss of muscle strength in healthy individuals. There is approximately a 30% decline in muscle strength and a 40% decline in muscle mass between the second and the seventh decade of life (Lexell J, 1995). This decline in muscle strength is associated with the degree of type II fiber atrophy and, usually, is not limited to the lower limbs. Since COPD patients frequently have advanced age, the effects of this disease on skeletal

muscle function should be considered. Finally, the sedentary lifestyle adopted to prevent or minimize the sensation of dyspnea and muscle fatigue promotes muscle deconditioning, which results in weakness due to a reduction in motor neuron activity. This cascade culminates in a decrease in the proportion of type I fibers, an increase in the proportion of type IIx fibers and a reduction in the oxidation potential. Similarly, a significant correlation has been reported between physical inactivity and quadriceps muscle endurance in COPD patients (Serres I, 1998).

It is worthy of note that these changes are more pronounced in the locomotor muscles in these patients. (Gosselink R, 1996) A recent systematic review has established that, based on reference values, there usually is a 27% reduction in the proportion of type I fibers and a 29% increase in the proportion of type IIx fibers in patients with severe COPD (Gosker HR, Thorax. 2007).

The elevated baseline energy expenditure in activities of daily living suggests a high cost due to the increase in ventilatory demand. In addition, the low protein-calorie intake, caused by symptoms of dyspnea, fatigue and early satiety, results in an imbalance between energy demand and energy consumption in these patients, contributing to an increase in their daily energy expenditure. The reduction in body mass index in COPD patients correlates with a poor muscle contractile performance, suggesting that nutritional aspects play a key role in muscle function in these patients (Kim HC, 2008).

One group of authors demonstrated that COPD patients with muscle mass depletion complained more of lower limb fatigue during the six-minute walk test than did COPD patients with preserved muscle mass (Pelegrino NR, 2009). From a microstructural point of view, the histochemical and bioenergy changes observed in skeletal muscle can be summarized as follows: maintenance or increase in glycolytic enzyme activity; reduction in oxidative stress; decrease in capillary density; reduction in the cross-sectional area of slow and fast fibers; reduction in mitochondrial activity; and reduction in the capillary/fiber ratio. These changes increase the contribution of the anaerobic system to the generation of energy, resulting in early lactacidemia (Malaguti C, 2006). This peripheral muscle fatigue can be intensified in cases of disease exacerbation (Gosselink R, 1996).

Table 5 presents a summary of the metabolic and bioenergy determinants of muscle fatigue in COPD patients.

Table 5. Metabolic and bioenergy determinants of muscle fatigue in COPD patients.

Determinants	Abnormalities	Dysfunction	Clinical outcomes
Inflammatory stress	↑ proinflammatory cytokines: IL-8; CRP; and IL-6	↓ muscle performance during exacerbation	
Prolonged use of corticosteroids	↓ protein synthesis ↑ protein degradation	↓ muscle performance during exercise	worsening of the symptoms of fatigue and dyspnea on exertion
Hypoxemia	↑ inflammatory mediators ↓ ATP, PCr and muscle glycogen	↓ muscle endurance	↓ performance on activities of daily living
Oxidative stress	oxidant/antioxidant imbalance	↓ resistência muscular	↓ quality of life
Deconditioning	↓ type I fibers ↑ type IIx fibers (hypotrophied) ↓ oxidative enzymes	↓ muscle performance during exercise	↑ use of health care services
↑ BEE due to ↑ ventilatory work and ↓ protein-calorie intake	↓ BMI ↓ LMI	↓ muscle performance during exercise	worse prognosis

Legend: CRP: C-reactive protein; PCr: phosphocreatine; BEE: basal energy expenditure; IMC : body mass index, LMI:Lean mass index .

4.4. FATIGUE IN COPD WITH CHRONIC RESPIRATORY FAILURE

In patients with Chronic Respiratory Failure has been shown that systemic inflammation and hypoxemia are strongly associated with increased oxidative stress (Boots AW, 2003) and that chronic hypoxemia also seems to be involved in the reduction in muscle strength and endurance, increasing atrophy and attenuating mitochondrial enzymatic activity. In addition, the levels of ATP, glycogen and phosphocreatine (PCr) are significantly reduced in the quadriceps muscle fibers in hypoxemic COPD patients (Jakobsson P, 1990).
It is also suggested that these effects are rapidly reversed by oxygen supplementation (Faucher M, 2004).
Jakobsson at al. described a significant correlation between muscle metabolites and arterial blood gas values with the strongest correlation between muscle glycogen and arterial PO2 ($r = 0.70$; p less than 0.001). They found, trought a muscle biopsy, a very low percentage of "oxidative" type I muscle fibres in this population.
Regarding the fatigue phenomenon, very few studies are perfomed in this population. Guidelines for the prescription of long-term oxygen therapy (LTOT) in hypoxemic COPD patients are based on two landmark studies in which survival was the primary outcome. Such patients are importantly symptomatic with poor health-related quality of life (HRQL) but the effect of LTOT on HRQL remains uncertain. Eaton at al. undertook a prospective longitudinal interventional study of hypoxiemic COPD patients. The introduction of LTOT to patients with severe COPD fulfilling standard criteria was associated with early significant improvements in HRQL including fatigue with sustained or further response at 6 months (Eaton T, 2003). In addition, evaluating the quality of life and fatigue (as assessed by Sant Georges Respiratory Questionnaire) in this population,
it appears to be lower in patients who do not adhere to LTOT than in those who do (Mesquita CB, 2018).
About the effect of exercise training in this population we found a randomized controlled study describing that **a** supervised home-based physiotherapy was

effective and safe in improving exercise capacity, dyspnea, perceived fatigue, and health status (Kovelis D, 2020).

Despite these few documents, knowledge of the prevalence and mechanisms underlying the perception of fatigue in this population is currently lacking. Regarding neuromuscular fatigue, we have not found any work focusing on this phenomenon in patients receiving long-term oxygen therapy. There is also a lack of knowledge describing the relationship between the perception of fatigue and its neuromuscular counterpart.

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4.5 PROJECT 1: THE IMPACT OF EXERCISE TRAINING ON FATIGUE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS.

ABSTRACT (Project 1)

Introduction and Objective: Fatigue can be divided in perceived fatigue, the feeling of exhaustion or lack of energy, and performance fatigue, the reduction in muscle force/activation during a given task. This meta-analysis evaluates the impact of exercise training on fatigue, as compared to usual care in patients with COPD.

Material and Methods: We searched randomised controlled trials on MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and CINAHL databases from their inception to December, 31st 2019 using the terms COPD, Fatigue, Fatigability, Muscle activation, Muscle endurance, Muscle Performance, Voluntary Activation, Motoneuron excitability, Force Development, Exercise, AND Rehabilitation.

Results: We evaluated 494 potential articles. Sixteen, all evaluating perceived fatigability, satisfied the inclusion criteria and were included. Twelve studies (463 patients) assessed fatigue by the Chronic Respiratory Questionnaire showing that intervention improved significantly more than the control group [SMD 0.708; 95% CI 0.510, 0.907; $p<0.001$; $I^2 = 34.3\%$; $p=0.116$]. Two studies (68 patients) using the Fatigue Impact Scale, did not find any significant differences between groups [SMD-0.922; 95%CI -2.258, 0.413; $p=0.176$; $I^2 = 83.9\%$; $p=0.013$]. Two studies (82 patients) assessed perceived fatigue by the Fatigue Severity Scale: the intervention improved significantly more than the control group [SMD -2.282; 95%CI -2.870, -1.699; $p<0.001$; $I^2 = 64.6\%$, $p=0.093$]. No study evaluating performance fatigue was found.

Conclusions: This study provided low-quality evidence of a positive impact of different exercise training programs on perceived fatigue in patients with COPD.

Further studies are needed to assess the effects of exercise training on fatigue and to test tailored programs.

Keywords: COPD; Fatigue; Fatigability; Exercise; Rehabilitation

This study has already published on Pulmonology Sep-Oct 2020;26(5):304-313. doi: 10.1016/j.pulmoe.2020.02.004. Epub 2020 Mar 14. Mara Paneroni, i Michele Vitacca [2], Massimo Venturelli Carla Simonelli [1], Laura Bertacchini [1], Simonetta Scalvini [4], Federico Schena [3], Nicolino Ambrosino [5] **The impact of exercise training on fatigue in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis.**

INTRODUCTION (Project 1)

Fatigue is present in more than half of patients with chronic obstructive pulmonary disease (COPD), and may have a substantial impact on functional impairment, physical activity, health related quality of life (HRQL), mortality, morbidity, hospitalization rate and length of hospital stay (Stridsman C, 2015; Finsterer J, 2014)

Lower limb muscles of patients with COPD may show reduced endurance capacity and are more prone to fatigue, due to the disuse, the presence of limb muscle dysfunction (Postma DS, 2016) and the exercise vasoconstriction induced by respiratory muscle fatigue (Sheel AW, 2001; Small S, 1999).
These mechanisms may be responsible for the onset of the symptom fatigue during daily life (Kentson M, 2016).

It can be divided in perceived fatigue or performance fatigue (Gruet M, 2018)
The first one is a normal response to exercise or stress, a multidimensional perception defined as "the subjective feeling of tiredness, exhaustion or lack of energy, which occurs on a daily basis" (Gruet M, 2018). However, fatigue may also occur during the performance of a given task, and is defined as performance fatigue**:** an objective and measurable domain, consisting in the reversible reduction in force generated by the muscle during a given task (Nyberg A, 2016) such as a constant load exercise (Taylor JL, 2016) It could be distinguished in central, defined as a progressive reduction in the voluntary activation of muscle during exercise (Amann M, 2016) and peripheral fatigability, described by the reduction of muscle activation in or distal to the neuromuscular junction (Gandevia SC, 2001).
The reduction of fatigue should be one of the aims of comprehensive management of patients with COPD (Spruit MA, 2017). Exercise training is strongly recommended in COPD, being effective in reducing dyspnoea and improving exercise capacity and Health related quality of life (Spruit MA, 2013; McCarthy B, 2015; Paneroni M, 2017). However, the effects of exercise training on fatigue as primary aim in patients with COPD have been rarely studied (Lewko A, 2012; Van Herck M, 2019), and to our knowledge, a systematic review of the literature about the effectiveness of exercise training on fatigue in patients with COPD is lacking.

Therefore, the aim of this systematic review and meta-analysis of randomized controlled trials (RCTs) in patients with COPD, was to evaluate the impact of interventions including exercise training on perceived and performance fatigue**,** as compared to usual care or education alone.

METHODS (Project 1)

This study conforms to all Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and reports the required information accordingly (Supplementary Checklist, http://links.lww.com/PHM/A364).

Data Sources and Search Strategies

We searched the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature, from their inception to December, 31st 2019, with no language restriction. We also reviewed the references of retrieved articles for additional studies. The search was limited only to RCTs using the terms: COPD, Fatigue, Fatigability, Muscle activation, Muscle endurance, Muscle Performance, Voluntary Activation, Motoneurons excitability, Force Development, Exercise, and Rehabilitation.

Patients

We included RCTs involving patients with COPD according to the Global Initiative for Chronic Obstructive Lung Disease recommendations in all stage of severity (GOLD, 2019). We excluded studies involving patients with (1) an acute exacerbation within 4 weeks before starting the intervention; (2) major comorbidities such as chronic heart failure, asthma, and sleep-related disorders.

We included studies administering exercise training programs, with the following characteristics:

- Involving in- or out-patients, and home- or community-based programs;
- Programs of 2 week minimum duration;
- Endurance and/or strength training of lower and/or upper limbs;

- Comparing exercise training with usual care, (defined as conventional medical care without any prescription of exercise training or physical activity) and/or education.

Outcome Measures

We included any study assessing:

- Perceived fatigue: by means of scales or questionnaires evaluating subjective perception of fatigue;

- Performance fatigue: by means of objective measures evaluating changes in muscle performance after a fatiguing task such as muscle force or electromyography trace during a maximal voluntary contraction (MVC) or stimulated muscle resting Twitch.

Data Collection and Analysis

Two investigators (LB, MP) independently conducted the search of the databases, screening all titles and/or abstracts for the inclusion criteria. Reviewers then retrieved abstracts and/or full-text papers of all potentially eligible studies and maintained records of all studies not meeting the inclusion criteria. They also provided the reasons for their exclusion.

The investigators inserted the data of potentially eligible articles in a Microsoft Excel (2013 version, Microsoft, Redmond, WA) dedicated database. Disagreement between investigators about eligibility was resolved by discussion and consensus. If consensus could not be reached, a third investigator (MV) adjudicated. All data were checked for accuracy. Missing data were requested by e-mail to the authors. An investigator (LB) retrieved the full-text of the included studies and inserted their data into a dedicated electronic database. Another investigator (MP) independently extracted data from the same studies.

The information collected were the background characteristics of the research reports: characteristics of participants in the study; number of participants who dropped out or withdrew from the study; a full description of the exercise training programs (setting, components, duration, and characteristics); assessments, and associated results. If a study reported multiple group comparisons (e.g., exercise training plus free walking vs exercise training alone vs conventional care),

treatment groups performing exercise that could be relevant to outcomes were combined into one virtual intervention group, and this group was compared to the group receiving conventional care.

The investigators assessed papers for bias using the Cochrane Collaboration's tool for assessing risk of bias in RCTs (Higgins JP, 2011). Risk of bias was assessed according to the following domains: sequence generation; allocation concealment; blinding of participants; blinding of personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting, and other biases.

Statistical Analysis

Statistical analysis was performed using STATA version 11.2 software (Stata, College Station, TX). All data were extrapolated from the corresponding full-text studies. For outcome, we recorded mean and standard deviation (SD) of variation from baseline to the end of the study. When SD was not available, we calculated them from standard errors, confidence intervals, or t-values or contacted the trial authors by email for clarification. We excluded studies with data other than mean and SD (Higgins JP, 2011).

The standardized mean difference (SMD) was calculated. Heterogeneity of studies was assessed by performing the Q-test considering values of $P < 0.01$ as significant. The first step of the evaluation was conducted by fixed-effect models using the Mantel-Haenzel method. If a significant heterogeneity among studies was found, a random effect evaluation by the Der-Simonian and Laird method approach was performed (DerSimonian R, 1986).

Forest plots were used to detect publication bias for meta-analysis evaluation including more than 8 studies (Olivo SA, 2008). For the meta-analysis, only the outcome measures included in at least two studies were analysed.

RESULTS (Project 1)

We identified 494 potentially relevant articles. Of these, 405 were excluded after the abstracts were read and 89 full-texts were analysed for inclusion criteria. Sixteen out of the 48 studies evaluating perceived fatigue satisfied the inclusion criteria and were included in the meta-analysis (**Figure 1**).

Table 2 shows the main characteristics of all interventions carried out in the studies included.

Figure 1 (Project 2): Flow chart of the study.

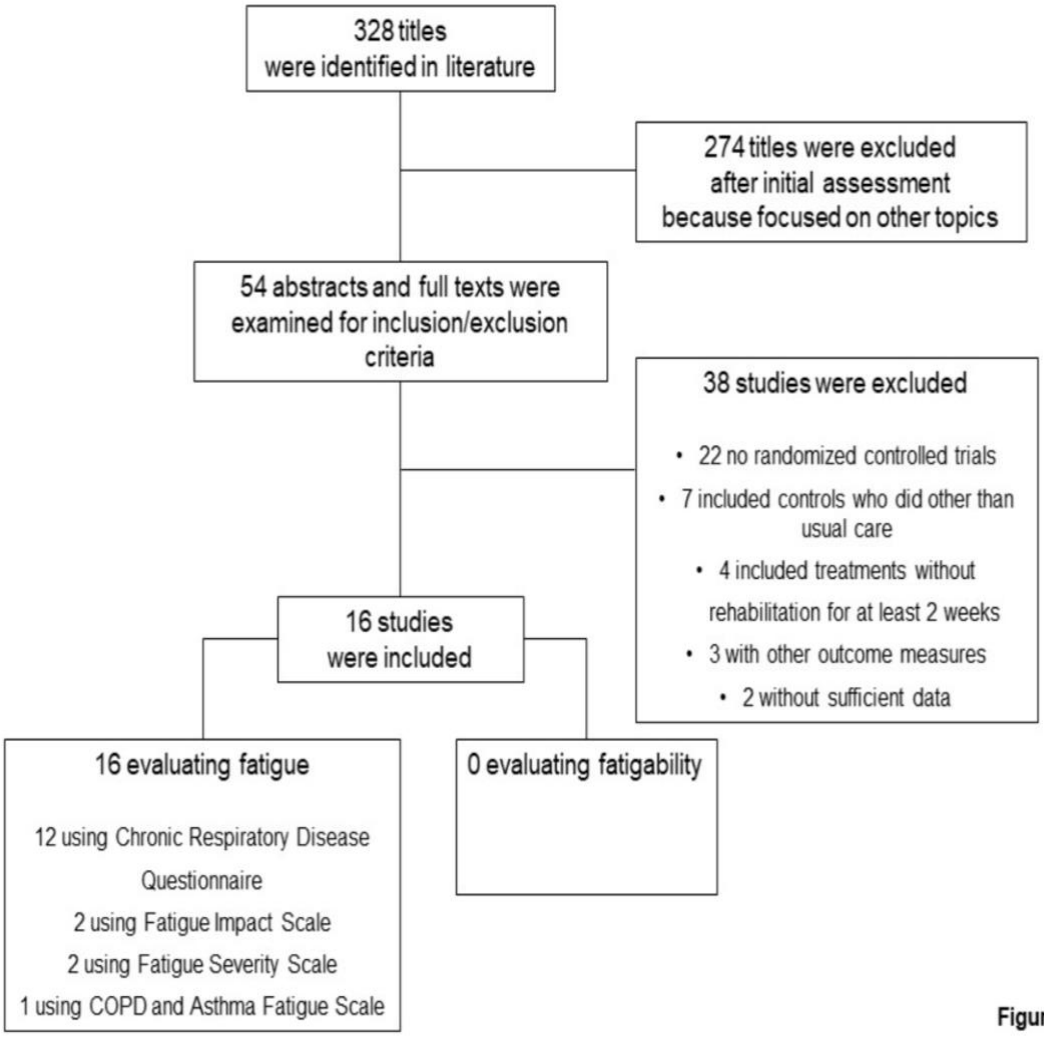


Figure 1

No study out of the other 41 evaluating changes in performance fatigue satisfied the inclusion criteria.

Table 1 shows the baseline characteristics of the included subjects. They suffered from moderate-to-severe COPD.

Table 1 (Project 1): Demographic, anthropometric, and clinical characteristics of included patient.

Clinical characteristics	No. Studies (No. Participants)	Pre-intervention Mean (SD)
Age, years	15 (596)	64.2 (7.7)
BMI, kg/m^2	7 (288)	27.7 (4.7)
FEV_1, % of predicted	13 (481)	45.6 (15.2)
FVC, % of predicted	4 (168)	63.6 (15.6)
FEV_1/FVC, % of predicted	6 (249)	47.0 (11.1)
RV, % of predicted	4 (173)	165.5 (44.1)
PaO_2, mm Hg	3 (124)	72.5 (8.0)
$PaCO_2$, mm Hg	3 (124)	42.8 (5.6)
MIP, % of predicted	2 (86)	77.7 (26.7)
MEP, % of predicted	2 (86)	65.9 (19.3)
6MWT, m	8 (315)	348.3 (77.1)
CRQ fatigue domain	9 (348)	11.1 (3.4)
FIS units	2 (68)	53.5 (32.3)
FSS units	2 (82)	45.3 (11.1)
CAFS units	1 (65)	53.8 (17.1)
SGRQ units	4 (143)	52.6 (14.8)

Abbreviations: BMI, Body Mass Index; FEV_1, Forced Expiratory Volume in the 1st second; FVC, Forced Vital Capacity; RV, Residual Volume; MIP, Maximal Inspiratory Pressure; MEP, Maximal Expiratory Pressure; CRQ, Chronic Respiratory Questionnaire; FIS, Fatigue Impact Scale; FSS, Fatigue Severity Scale; CAFS, COPD and Asthma Fatigue Scale; SGRQ, St. George's Respiratory Questio

Table 2 (Project 1): Characteristics of the interventions.

Reference	Duration, weeks	Withdrawal/ dropouts	Participants, n	Intervention and Control	Intervention Details
Wijkstra[23]	12	2	28	Intervention: outpatient (2 days/week) and home based cycle ergometer and upper limb training , 2 times/day +inspiratory muscle training and education session	30 min of training; cycling at 60% of Wmax, gradually extended to a maximum of 75% of Wmax
			15	Control: usual medical care	
Cambach[24]	12	23	15	Intervention: outpatient training, 3 days/week + education session	90 min of cycle ergometer/rowing machine/stair-walking training (twice a week) at 60-75% Wmax; 45 min of recreational activities such as swimming/cycling/hockey (once a week)
			8	Control: usual medical care	
Larson[25]	16	77	28	Intervention: cycle ergometry training at home, 5 days/week + Inspiratory muscle training	Interval training protocol with 4 work sets of 5 min separated by rest intervals (2–4 min); intensity of 50% of peak work rate, evaluated weekly with progressive increases as tolerated
			12	Control: education	

Guell[26]	24	13	24	Intervention: cycle ergometer training, 5 days/ week + breathing exercise ad education session	30-min of cycle ergometer at 50% of the maximal load (Wmax); load increased in increments of 10 W provided according to symptoms
			23	Control: usual medical care	
Hernandez[27]	12	23	20	Intervention: home-based walking training, 6 days/week	1 hour of walking 67raining at 70% of the maximum speed attained in the SWT
			17	Control: usual medical care	
Man[28]	8	8	18	Intervention: aerobic and strength training, 2 days/week + education session	1 hour walking/cycling and strength training for the upper and lower limb
			16	Control: usual medical care	
O'Shea[29]	12	10	20	Intervention: resistance exercise, 3 days/week (1 at hospital, 2 at home)	6 resistance exercises against elastic bands of increasing resistance; 3 sets of 8 to 12 repetition maximum
			24	Control: usual medical care	
Moore[30]	6	7	10	Intervention: video exercise at home, 4 days/week + education session	30 min of upper and lower limb strengthening and aerobic exercise
			10	Control: usual medical care	
Ghanem[31]	8	0	25	Intervention: home-based endurance and strength training, 7 days/week + breathing exercise	Walking/cycling training + 6 to 10 upper-body and lower-body strength exercises with
			14	Control: usual medical care	
McNamara[32]	8	8	30	Intervention: water-based and land-based exercise, 3 days/week	60 min of exercise at intensity rating of 3-5 on modified Borg scale for dyspnea and perceived exertion

			15	Control: usual medical care	
Roman[33]	12	21	36	Intervention: Low intensity peripheral muscle training and breathing exercises, 3/week + education program	15 minutes breathing exercises and 45 minutes of abdominal and upper and lower limb exercises
			14	Control: usual medical care	
Wadell[34]	8	7	17	Intervention: graduated exercise training for upper and lower limbs, 3 days/week + education session	2.5 hours of graduated walking/cycle ergometer training, arm ergometer and strength exercises for upper and lower limbs, at highest attainable work rate for the longest tolerable duration
			24	Control: education	
Theander[35]	12	4	12	Intervention: multidisciplinary pulmonary rehabilitation programme, 2 days/week + home training programme	10–15 minutes of bicycle training + strength exercise
			14	Control: usual medical care	
Duruturk[36]	6	5	29	Intervention: all-body callisthenic exercise and cycle ergometer training, 3 days/week + education session	20/45 min of exercise and 20–30 min of continuous cycling at 50–70% of VO2max; intensity adjusted to maintain a perceived difficulty level of 4-7 on the Modified Borg Scale
			13	Control: education session	
Arslan[37]	8	15	32	Intervention: individualized exercise home program + walking program, 3 days/week	Walking outdoors on a flat surface
			33	Control: usual medical care.	
Mohammad[38]	7	0	20	Intervention: home-based training program, 3 days/week+ breathing exercise and education session	Walking training
			20	Control: usual medical care	

Settings

Seven studies (Cambach W, 1997 Guell R,2000 McNamara RJ, 2013 Theander K, 2009; Duruturk N, 2016; Roman M, 2013; Man WD, 2004) were conducted mainly in an out-patient setting, six at home (Larson JL, 1999; Hernandez MT, 2000; Moore J, 2009; Ghanem M, 2010; Arslan S, 2016; Mohammadi F, 2013) and three studies (Wijkstra PJ, 1994; O'shea SD, 2007; Theander K, 2009) in both settings.

Schedules

The total duration of programs ranged from 6 to 24 weeks. There were two to seven sessions per week. The duration of each session ranged from 30 to 90 minutes in eleven studies (Wijkstra PJ, 1994; Cambach W, 1997; Larson JL, 1999; Guell R, 2000; Hernandez MT, 2000; O'shea SD, 2007; Man WD, 2004; Moore J, 2009; McNamara RJ, 2013; Roman M, 2013; McNamara RJ, 2013; Roman M, 2013) and lasted two and a half hours in one study (Wadell K, 2013). Four studies (Arslan S, 2016; Mohammadi F, 2013; O'shea SD, 2007; O'shea SD, 2007) did not report any duration.

Interventions

Thirteen studies included exercise training of locomotor muscles: cycling in five studies (Larson JL, 1999; Guell R,2000; Wijkstra PJ, 1994; Theander K, 2009 Duruturk N, 2016), walking in three (Larson JL, 1999; Arslan S, 2016 Mohammadi F, 2013) and a combination of these in five. (Larson JL, 1999; Ghanem M, 2010; Roman M, 2013; Man WD, 2004 Wadell K, 2013)

In three studies the intervention consisted only of calisthenics exercise (Roman M, 2013; O'shea SD, 2007; Moore J, 2009).

All the studies included endurance training. The intensity ranging from 50% to 75% of either the maximum workload or oxygen consumption (VO_2) reached during incremental tests in five studies (Wijkstra PJ, 1994; Cambach W, 1997; Larson JL, 1999; Guell R,2000; Duruturk N, 2016). McNamara et al. (McNamara RJ, 2013) used the Borg scale (Borg GAV, 1982) to set the intensity of the exercise (3 to 5 on modified Borg scale) and Hernandez et al. (Hernandez MT, 2000) used the 70% of the maximum speed attained in the Incremental Shuttle Walking test (ISWT) (Sigh SJ, 1992); nine others studies (O'shea SD, 2007; Moore J, 2009

Ghanem M, 2010; Roman M, 2013;Wadell K, 2013;Theander K, 2009; Arslan S, 2016; Mohammadi F, 2013; Man WD, 2004) reported no training intensity.

In six studies (Wijkstra PJ, 1994; Cambach W, 1997; Guell R,2000; Roman M, 2013; Theander K, 2009; Duruturk N, 2016) patients performed continuous training on a cycloergometer, while only one (Larson JL, 1999) used the interval training.

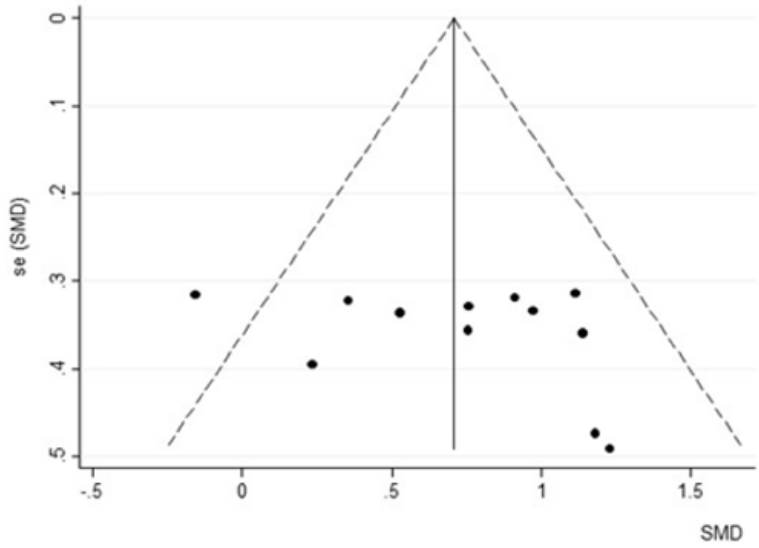
Additional components of exercise training

In four studies (Mohammadi F, 2013, Guell R,2000; Ghanem M, 2010; Wadell K, 2013) breathing exercises were administered in addition to the exercise program (e.g.: pursued lip breathing and diaphragmatic breathing). In eleven studies (Wijkstra PJ, 1994; Cambach W, 1997; Larson JL, 1999; Guell R,2000; Man WD, 2004; Moore J, 2009; Roman M, 2013; Wadell K, 2013; Theander K, 2009; Duruturk N, 2016; Mohammadi F, 2013) was added in two studies (Wijkstra PJ, 1994; Larson JL, 1999).

Outcomes

Twelve studies (463 patients: 271 study group and 192 controls) evaluated perceived fatigue by means of the dedicated domain of the chronic respiratory questionnaire (CRQ) (Guyatt, 1987). Only in three studies (Theander K, 2009; Arslan S, 2016; Mohammadi F, 2013) (18.8%) fatigue measure was the primary outcome. **Figure 2-Panel A** shows the related forest plot: the intervention improved significantly more than the control group [SMD 0.708; 95% CI 0.510, 0.907; $p<0.001$; $I^2 = 34.3\%$; $p=0.116$]. **Figure 1SM** describes funnel plot for studies on fatigue item in CRQ.

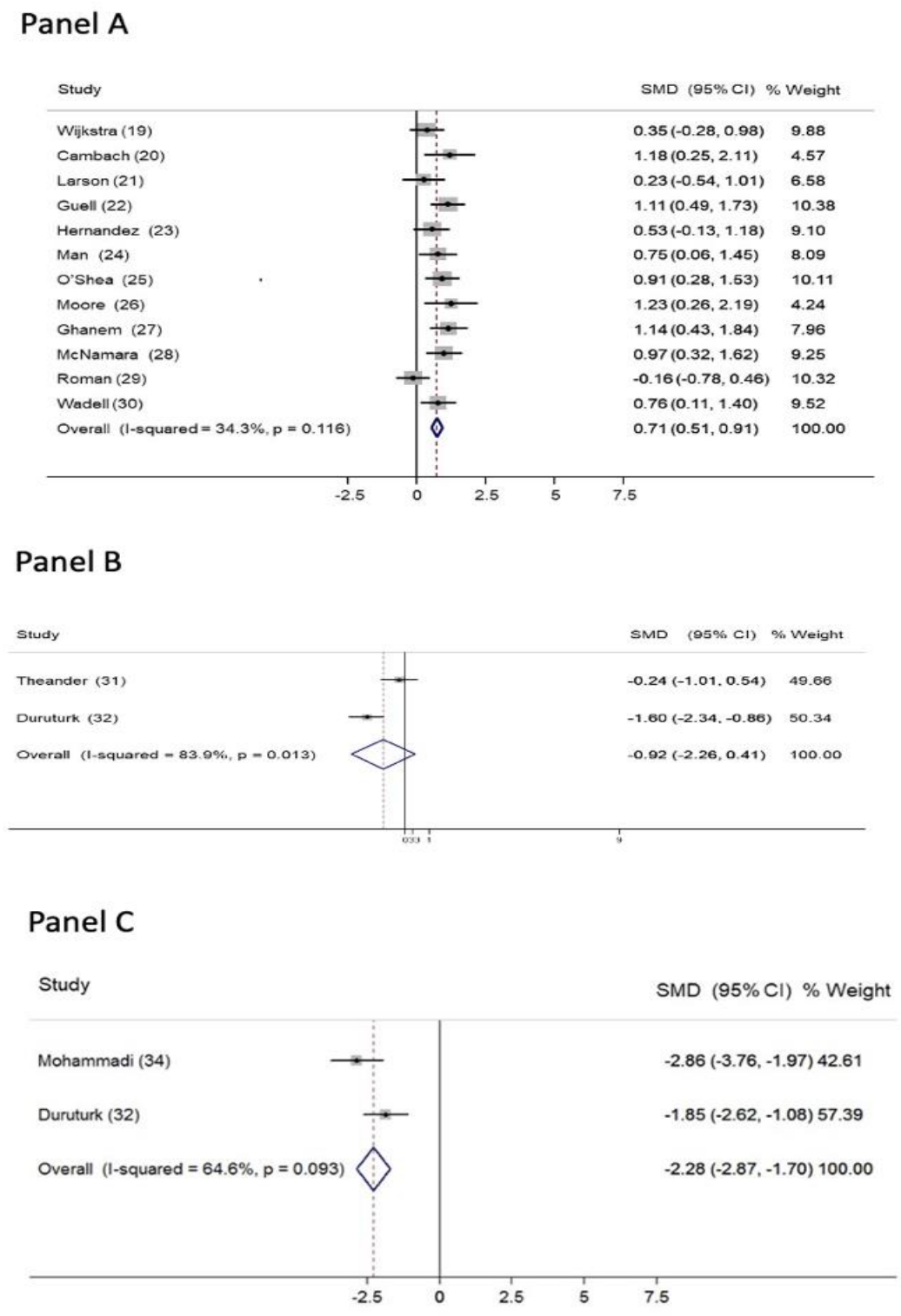
Figure 1SM (Project 1): Funnel plot for studies on fatigue item in CRQ.



Two studies (Theander K, 2009; Duruturk N, 2016) (68 patients: 41 study group and 27 controls) used the Fatigue Impact Scale (FIS), which examines patients' perceptions of their limitations caused by fatigue on the cognitive, physical, and psychosocial domains (Fisk JD, 1994). **Figure 2-Panel B** describes the related forest plot: owing to the high heterogeneity in the "fixed analysis model" (P = 0.0001), a random effect model was performed. No differences between intervention and control group were found. [SMD-0.922; 95%CI -2.258, 0.413; p=0.176; I^2 = 83.9%; p=0.013].

Figure 2-Panel C describes the forest plot for two studies (Duruturk N, 2016; Mohammadi F, 2013) (82 patients: 49 study group and 33 controls) assessing fatigue by the Fatigue Severity Scale **(**FSS), a 9-item scale assessing disabling fatigue. Each question evaluates patients' perception in the form of 7-point modified Likert Scale (Krupp LB, 1989). The intervention group improved significantly more than the control group [SMD -2.282; 95%CI -2.870, -1.699; p<0.001; I^2 = 64.6%, p=0.093]. Only one study (Arslan S, 2016) used the COPD and Asthma Fatigue Scale (Revicki D, 2010)

Figure 2 (Project 1): Forest plot of effect of training on: fatigue item in CRQ scale (Panel A), Fatigue Index Scale (Panel B) and Fatigue Severity Scale (Panel C).



Legend: SMD, Standardized Mean Difference; CI, Confidence Interval.

Risk of bias

The assessment of the risk of bias by funnel plots on CRQ revealed high variability in the results of the included studies. **Table 3** shows results of the risk of bias assessment. Half of the studies did not report any detail on randomization and allocation modalities, and there was a high detection bias rate. Almost all studied included shown a high risk of bias for the blinding of participants and personnel

Table 3 (Project 1): Risk of bias assessment.

Bias	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Modified by Jadad Scale
Wijkstra[23]	Low	Unclear	High	High	Low	Low	2
Cambach[24]	Low	Low	High	High	Low	Low	3
Larson[25]	Unclear	Unclear	High	Low	Low	Low	2
Guell[26]	Low	High	High	Low	Low	Low	2
Hernandez[27]	Low	Unclear	High	Low	High	Low	2
Man[28]	Low	Unclear	High	High	Low	Low	3
O'Shea[29]	Low	Low	High	Low	Low	Low	3
Moore[30]	Low	Low	High	High	Low	Low	3
Ghanem[31]	High	Unclear	High	High	High	Low	1
McNamara[32]	Low	Low	High	Low	Low	Low	3
Roman[33]	Low	Unclear	High	Low	Low	Low	3
Wadel[34]	Unclear	Unclear	High	Unclear	Low	Low	2
Theander[35]	Low	Low	High	High	Low	Low	3
Duruturk[36]	Unclear	Low	High	Unclear	Low	Low	2
Arslan[37]	High	High	High	High	Low	Low	1
Mohammadi[38]	Low	Unclear	High	Unclear	High	High	2

DISCUSSION (Project 1)

This systematic review investigated the current evidence of exercise training on fatigue in patients with COPD. The analysis of the 16 RCTs included evaluating the effects on perceived fatigue shows high heterogeneity of study design, patient sample, exercise training schedules, and outcome measures assessed. All studies showed a high risk of bias. As a whole, the studies showed low-grade evidence of positive effect of exercise training on perceived fatigue. No study evaluated the effects on performance fatigue.

Fatigue is an important debilitating symptom affecting all chronic respiratory diseases, including COPD. A four-year observational study on fatigue in patients with COPD reported that severe fatigue doubled in patients with mild to severe COPD despite optimal care (Revicki D, 2010). Fatigue is a leading cause of consultations with major clinical implications. Despite its well-acknowledged negative impact on patient's life, fatigue is still a misunderstood and underdiagnosed symptom in COPD. As a consequence, there is currently no specific intervention to treat all aspects of this symptom which is rather often considered as a secondary outcome in interventions aiming primarily to increase physical fitness and/or HRQL (Antoniu SA, 2015).

Spruit et al (Spruit MA, 2017) have proposed a model of fatigue in patients with COPD. Moderate to severe fatigue can be the results of systemic, physical, psychological and behavioural factors. Fatigue can be precipitated by infectious COPD exacerbation and its treatment. This model suggests that the fatigue of these patients is not simply the result of COPD and cannot be predicted by the sole degree of airflow obstruction but would be the consequence of multiple factors that may act alone or in interaction, at rest and during/after exercise (Amann M, 2016).

Rather interestingly in our systematic review, the positive impact of pulmonary rehabilitation on perceived fatigue was found in studies using the CRQ and the FSS but not the FIS. Antoniu and Ungureanu (Antoniu SA, 2015) identified 8 multidimensional scales which are commonly used to assess fatigue in COPD but 75% of RCTs included in our analysis evaluated fatigue by means of the dedicated domain of the CRQ (Guyatt, 1987). Houben-Wilke and colleagues recently showed

that the item ‘energy’ of the COPD assessment test improves with the greatest effect size after pulmonary rehabilitation (Houben-Wilke S, 2018) .A commonly used multi-dimensional scale to evaluate fatigue is the subjective fatigue subscale of the checklist individual strength (CIS-Fatigue) (Vercoulen JH, 1994) and Peters and colleagues reported a significant mean improvement in CIS-Fatigue score following 12-week of pulmonary rehabilitation in patients with COPD (Peters JB, 2017). The use of different tools in papers prevents accurate comparisons between studies as the scores produced by the scales show poor to moderate correlations between them (Panitz S, 2015).

It should be noticed that we analysed exercise training, just one (although the main) component of pulmonary rehabilitation which is a comprehensive multidisciplinary intervention including, but not limited to it (Spruit MA, 2013).Therefore the results of our systematic review should not be generalised to pulmonary rehabilitation programs.

On the subject of performance fatigue, it is rather interesting to note that, despite the fact that there are some observational studies describing high prevalence in patients with COPD (Burtin C, 2012), we were unable to include any RCT of the effects of exercise training on this impairment.

Different tests have been used to evaluate performance fatigue, which depends on the ability of the peripheral muscles and the central nervous system to meet the demands of a prescribed task. Both systems can exhibit abnormal changes in response to exercise and contribute to increased performance fatigue (Maltais F, 2014; Rossman MJ, 2013): we can test it by the changes in stimulated resting Twitch for peripheral involvement and by MVC for the central ones (Rossman MJ, 2013). Thereafter, specific methods to train the muscles and reduce the central and / or peripheral component of performance fatigue, such as the maximal strength training (Hoff J, 2007) or neuromuscular electrical stimulation (Maddocks M, 2016), should also be largely investigated in subjects with COPD.

CONCLUSION (Project 1)

This systematic review has provided low-quality evidence of a positive impact of different exercise training programmes on perceived fatigue in patients with COPD. Further studies with better standardisation and scientific validity are needed to assess the effects of exercise training on fatigue and to test dedicated programs. No study of the efficacy of exercise training on performance fatigue was found.

4.6 RELATIONSHIP BETWEEN PERCEIVED AND NEUROMUSCULAR FATIGUE IN COPD PATIENTS WITH CHRONIC RESPIRATORY FAILURE WITH LONG-TERM OXYGEN THERAPY: A CROSS-SECTIONAL STUDY

ABSTRACT (Project 2)

Purpose: To evaluate perceived fatigue (PF) and neuromuscular fatigue (NMF) in the severest stage of COPD, i.e. patients with chronic respiratory failure (CRF) on long-term oxygen therapy (CRF-COPD group), and the relationships between PF, NMF, clinical and functional characteristics, comparing severe COPD patients with patients without CRF (COPD group).

Methods: This cross-sectional study compared 19 CRF-COPD patients with 10 COPD patients attending a rehabilitation program. PF was determined by Fatigue Severity Scale (FSS), while dyspnea by the Barthel Dyspnea Index (BDI). We assessed quadriceps NMF via superimposed twitch technique detecting changes after a Constant Workload Cycling Test (CWCT) at 80% of the peak power output at exhaustion.

Results: CRF-COPD patients showed higher PF (+ 1.79 of FSS score, p=0.0052) and dyspnea (+21.03 of BDI score, p=0.0023) than COPD patients. After the fatiguing task and normalization for the total work there was a similar decrease in the maximal voluntary contraction (CRF-COPD -1.5 ± 2.4 vs COPD -1.1 ± 1.2 % baseline kJ^{-1}, p=0.5819), in the potentiated resting twitch force (CRF-COPD -2.8 ± 4.7 vs COPD -2.0 ± 3.3 % baseline kJ^{-1}, p=0.7481) and in the maximal voluntary activation (CRF-COPD -0.1± 3.9 vs COPD -0.9± 1.2 -2.0 ± 3.3 % baseline kJ^{-1}, p= 0.4354). FSS and BDI were closely related (R=0.5735, p=0.0011), while no correlation between PF and NMF was found.

Conclusion: CRF-COPD patients develop higher levels of perceived fatigue and dyspnea than COPD patients; while neuromuscular fatigue during exercise is similar, suggesting a mismatch between symptoms and neuromuscular dysfunction

Keywords: COPD, fatigue, neuromuscular fatigue, exercise performance, rehabilitation.

INTRODUCTION (Project 2)

Chronic obstructive pulmonary disease (COPD) is a high-prevalence disease (Ruvuna et al.,2020) characterized by airflow limitation that is not fully reversible and by symptoms of chronic cough with sputum production, dyspnea, and reduced exercise capacity (Vestbo et al., 2013). More recently fatigue has been described as a common complaint in COPD patients, as well. It is one of the most important factors contributing to exercise intolerance and a worse quality of life (Spruit et al., 2017).

Patients commonly report a chronic feeling of exhaustion or lack of energy, defined as 'perceived fatigue' (PF) (Gruet M., 2018). In addition, COPD patients frequently show neuromuscular fatigue after a fatiguing task. It can be due to two different components: central (the impairment is from the neural drive to the muscle) and peripheral (the impairment can be ascribed to a biochemical change occurring distal to the neuromuscular junction) (Gandevia 2001). The prevalence of PF in COPD ranges from 17 to 95% and is associated with several physical, psychological and behavioral factors that influence the patient's independence, prognosis, and mortality (Ebadi et al. 2021).

However, it is not yet known if the severity of PF parallels the worsening of pulmonary impairment in patients with severe COPD. The development of neuromuscular fatigue (NMF) observed with the progression of COPD and related to the vicious cycle of chronic muscle disuse is, at least in part, attributable to changes in locomotor muscle properties with decreased muscle mass, strength, and mitochondrial function, increased activity of glycolytic enzymes, and shifting to non-oxidative fibers (Marillier et al. 2021; Maltais et al. 2014). NMF also appears related to impaired oxygen delivery to locomotor muscles due to hemoglobin desaturation (Amman et al. 2006) and an increased sympathetic vasoconstrictor activity of the limbs due to reflex responses evoked by the non-myelinated group III-IV afferents (Dempsey et al. 2006) of fatigued respiratory muscles. It is still not clear if there is a gradual increase of NMF in very severe patients with COPD over time.

In fact, to date, studies on PF and NMF in COPD patients have focused on mild-to-severe COPD (Ebadi et al. 2021; Marillier et al. 2021), but no study has evaluated very severe patients who have already developed chronic respiratory failure (CRF), a condition that results in the inability to effectively exchange oxygen throughout the day, and induces chronically low blood oxygen level with or without chronically high carbon dioxide level (Hardinge et al. 2015; www.aiponet.it/2004).

We focused on very severe COPD patients who had already started the long-term oxygen therapy (LTOT), an elective treatment for them (www.aiponet.it/2004). This growing clinical category of patients is particularly important to study because, while there is evidence of the positive "boost" effect of oxygen in attenuating NMF in normoxemic COPD (Amman et al. 2010; Gosselin et al. 2004), the effect with chronic exposure to oxygen therapy remains to be elucidated. In addition, some clinical studies proposed controversial results about the beneficial impact of oxygen supplementation during pulmonary rehabilitation in patients with and without exercise hypoxia (Freitag et al. 2020; Alison et al. 2019; Neunhäuserer et al. 2016).

Indeed, the side effects of long term oxygen therapy (LTOT), such as increased levels of reactive oxygen species and the subsequent reduction of systemic vascular function combined with severe pulmonary dysfunction, characterized by severe central (lung) limitation, might be responsible for the exacerbation of both PF and NMF. However, current knowledge about the fatigue-related changes in very severe COPD patients is scant.

Therefore, our primary aim in this cross-sectional observational study was to determine if there is a difference in PF and NMF (central and peripheral components) between very severe COPD patients with CRF (CRF-COPD group) on LTOT and severe COPD patients without CRF (COPD group). The secondary aim was to investigate the relationships between PF, NMF, clinical and functional characteristics in these two populations of COPD patients. We hypothesized that the degree of PF, as well as central and peripheral components of NMF, would be more marked in the more severe clinical group.

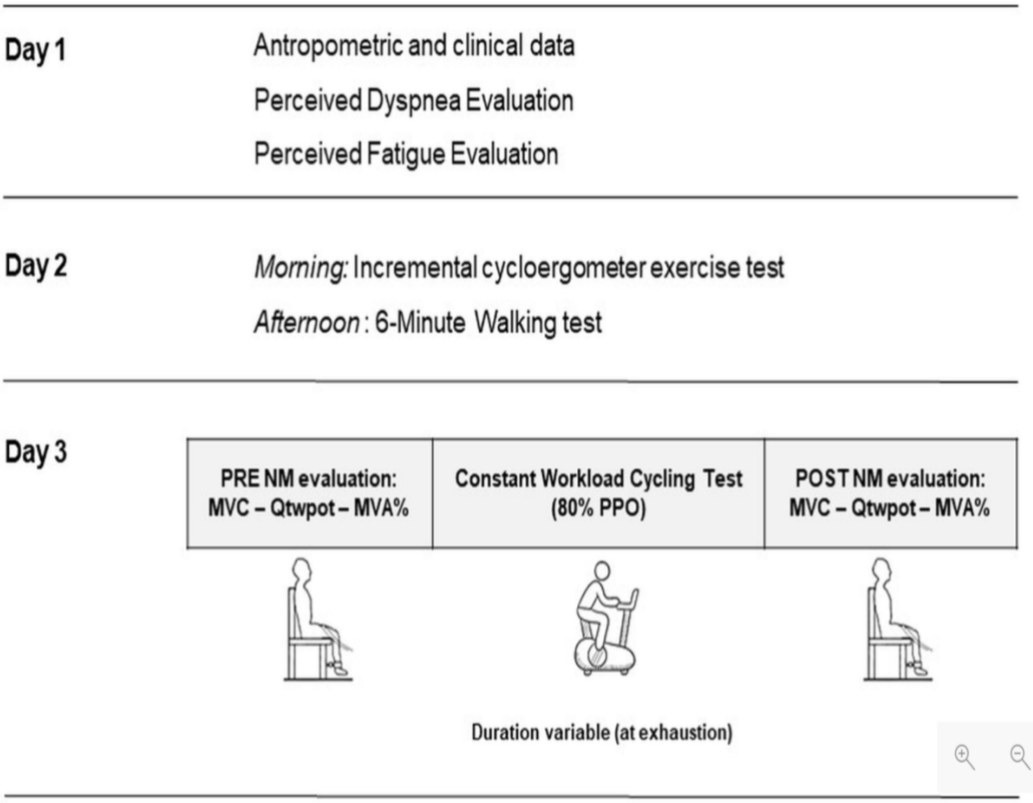
METHODS (Project 2)

In this cross-sectional study, we performed a retrospective analysis on data collected from two groups of severe COPD inpatients admitted to the Respiratory Rehabilitation Unit of the Istituti Clinici Scientifici (ICS) Maugeri of Lumezzane (Brescia), Italy, between June 2020 and September 2021, for a pulmonary rehabilitation attempt. The two groups consisted of severe COPD patients with CRF on LTOT (CRF-COPD group) vs. patients without CRF (COPD group). Inclusion criteria for the CRF-COPD patients were the use of 24 h/day LTOT for at least 3 months according to guideline recommendations (Hardinge et al. 2015; www.aiponet.it/2004); the presence of forced expiratory volume at 1 s (FEV1) <50%, a stable clinical condition (pH>7.35, without change in drug therapy within the last week, and without exacerbations or hospitalizations within the last 3 months) and absence of orthopedic, neurological, cardiac and cognitive impairment. The CRF-COPD group used O_2 supply through nasal prongs as liquid oxygen from a base unit (stationary system) during rest and by means of portable cylinders, either carried by the patient (stroller) or transported by means of a trolley, during daily activities. Patients in the control group (COPD group) had FEV1<50% without CRF (partial pressure of O_2>60 mmHg breathing room air at rest) and were matched to the CRF-COPD group for age, sex, and body mass index (BMI).

The present study represents a sub-analysis of data from two studies conducted in our Institute. Written informed consent was obtained from all participants. Ethics Committees of the ICS Maugeri approved the studies (Pavia, CE 2288 and 2241) and all experimental procedures were performed in accordance with the Declaration of Helsinki.

All anthropometric and clinical characteristics and functional measures of patients were collected by the medical team (doctors and senior physiotherapists) of the rehabilitation center. All evaluations were performed within the first three days of hospital admission, before starting the rehabilitation intervention. **Figure 1** summarizes all evaluation tests performed and described below.

Figure 1 (Project 2) Outline of the study evaluations.



Legend: NM: neuromuscular; MVC: Maximal Voluntary Contraction, Qtwpot: potentiated quadriceps twitch force, MVA%: percentage of Maximal Voluntary Activation, PPO: Peak Power Output, min: minute

On day 1 after admission, the following measures were collected:

- **Anthropometric and clinical characteristics**

A physiotherapist measured the patient's height and body mass with a dedicated stadiometer and a mechanical scale (model 762, SECA, Italy). BMI was calculated as body mass/(height)^2 with body mass recorded in kg and height in meters. Comorbidities (number and severity) were assessed with the Cumulative Illness Rating Scale (CIRS) (Salvi et al. 2008). Arterial Blood Gas (ABG) analysis determined the amount of oxygen and carbon dioxide in the blood at rest (ABL90 series, Radiometer Medical APS, Denmark). Lung function was evaluated by a spirometry test collecting forced volume capacity (FVC)% of predicted, FEV_1% of predicted, and FEV_1/FVC ratio (Miller et al. 2005) (Spirolab, Carefusion, Germany).

- **Perceived dyspnea**

Perceived dyspnea was evaluated with the Barthel Dyspnea Index (BDI) (Vitacca et al. 2020) by an experienced physiotherapist. The total BDI score represents breathlessness during activities of daily living (ADL) and ranges from 0 (no dyspnea) to 100 (maximum level of dyspnea.

- **Perceived fatigue**

Perceived Fatigue during daily life was determined with the Italian version of the Fatigue Severity Scale (FSS) (Ottonello et al. 2016). The questionnaire is self-administered and is composed of 9 items related to the severity of symptoms. Each item consists of a statement about the presence of symptoms over the past week, to which patients express their agreement/disagreement on a 7-point Likert scale from 1 (strong disagreement) to 7 (strong agreement). The total score is the mean of the score of the 9 items, yielding a score range between 1 and 7; a higher mean score indicates greater severity of fatigue symptoms. According to the classification proposed by Johansson et al., an FSS score ≤4.0 indicates no fatigue, from 4.0 to 5.0 borderline fatigue, and above 5.0 fatigue (Johansson et al. 2008).

Maximal exercise capacity

On day 2 **(Figure 1**), maximal exercise capacity was evaluated with an incremental exercise test (IET) to determine the peak work rate capacity defined as peak power output (PPO). The test was performed in the morning and supervised by a senior

physiotherapist and a medical doctor. The IET was performed on an electromagnetically braked cycle ergometer (Ergoline 800; Sensor Medics, Anaheim CA, USA) with the patient maintaining a pedaling frequency of 60 rpm. The protocol consisted of ramp rate increments of 10 W min-1 up to the limit of tolerance (the point at which the patient could not tolerate the work rate due to severe sensations of dyspnea and/or leg discomfort). The Borg scale (Borg 1982) rate of perceived exertion (RPE) of Dyspnea and Leg Fatigue was administered every minute during the test. Heart rate and arterial oxygen saturation (SpO_2) were measured using the R-R interval from a 12-lead online electrocardiogram (Marquette Max; Marquette Hellige, Freiburg, Germany) and a pulse oximeter (Nonin 8600; Nonin Medical, North Plymouth, MN, USA), respectively. The test was stopped when the patient experienced the maximal rate of dyspnea and/or leg muscle discomfort.

In addition, in the afternoon, exercise tolerance was evaluated with the 6-min walk test (6MWT) (Holland et al. 2014). We asked patients to walk as far as they could in the 6-min time limit along a dedicated 30-meter corridor. Patients could stop during the test for dyspnea or leg discomfort and restart as soon as possible, without interrupting the timer (Holland et al. 2014). A physiotherapist recorded the distance walked (meters) and, before and after the test, administered the Borg scale RPE of Dyspnea and Leg Fatigue (Borg 1982) and measured the heart rate and oxygen saturation with a pulse oximeter (Nonin).

Neuromuscular fatigue (NMF)

On day 3 after admission (**Figure 1**) and in the afternoon, ~5 min before and after a constant work rate cycling test (CWCT, see below) the NMF evaluation was performed. Maximal voluntary and electrically evoked muscle contractions of the quadriceps muscle were measured utilizing a custom-made set-up. Subjects were seated in an upright position with back support and a seat belt applied to the pelvis to secure the subject to the chair and prevent movement of other parts of the body. The knee was flexed at 90°, and the ankle of the dominant leg was attached, via a strap and a rigid steel bar, to the force transducer (DBBSE-100kg, A2829; Applied Measurements Ltd, Aldermaston Berkshire, UK). The output from the force transducer was amplified (INT2-L, London Electronics Ltd, Sandy, Bedfordshire,

UK) and recorded with a PowerLab-16/35 data acquisition system (Powerlab, ADInstruments Inc, USA). Electrical stimuli were delivered after positioning self-adhesive electrodes with the cathode positioned over the femoral triangle, 3-5 cm below the inguinal ligament, and the anode placed over the posterior iliac crest. Each test procedure began with the determination of the maximal M-wave and potentiated quadriceps twitch force (Qtwpot) responses in the resting quadriceps muscle. Briefly, the current intensity was progressively increased (+20mA each time) from 25mA to the value beyond which there was no further increase in M-wave peak-to-peak amplitude and resting quadriceps twitch. The value of 125% of the intensity was chosen to evoke the individual maximal M-wave response. The Qtwpot was evoked in the resting muscle using electrical stimulation consisting of single square-wave pulses of 1 ms duration at 350V, delivered by a constant current stimulator (Digitimer mod. DS7HA, Digitimer Ltd, UK). Before starting the trial, each subject was instructed on how to perform the trial correctly. The Qtwpot was evoked 2 s after a 5 s maximal voluntary contraction (MVC) of the quadriceps, and this procedure was repeated 6 times. Hence, it should be noted that Qtwpot was assessed in the potentiated state. The interval between the MVCs was 30 s. Peak torque was evaluated for each MVC and Qtwpot using the lower leg length. Voluntary muscle activation (MVA) of the quadriceps muscle during the MVCs was assessed using the superimposed twitch technique. The force produced during a single twitch superimposed on the MVC was compared with the force produced by the electrically evoked twitch produced, at rest, 2 s after the MVC. The pre-to-post exercise difference after the fatiguing task in MVC defined the global fatigue, in Qtwpot the "peripheral" component, while the reduction in MVA the "central" one (Polkey et al. 1996; Marillier et al. 2021).

The pre-to-post exercise difference in Qtwpot was labeled as exercise-induced locomotor muscle fatigue when there was >15% reduction (Amman and Dempsey 2008). Surface electrodes were used to record M-wave properties of the right vastus lateralis and rectus femoris.

Fatiguing task

The CWCT, executed at 80% of the peak of power output determined during the incremental exercise test, was used to induce NMF. The test was performed on an electromagnetically braked cycle ergometer (Ergoline 800, Sensor Medics, Anaheim, CA, USA) and the time to exhaustion (Tlim) was recorded in seconds. Patients were instructed to exercise for as long as possible, with continuous verbal encouragement. Exercise terminated when dyspnea became intolerable or they were unable to pedal at the required rate (60/min) for more than 10 s. Dyspnea and leg RPE were recorded every 60 s using the modified Borg scale (Borg 1982) ranging from 0 to 10 points. Heart rate was measured using the R-R interval from a 12-lead online electrocardiogram (Marquette Max) and oxygen saturation by a pulse oximeter (Nonin), while blood pressure was measured each minute by a manual sphygmomanometer and the mean arterial pressure (MAP) was calculated as diastolic pressure + 1/3 (systolic pressure - diastolic pressure) (DeMers et al. 2022).

Statistical analysis

Statistical analyses were performed using STATA 11.4 and GraphPad Prism 8.0. Normality of distribution for continuous physiological variables was assessed by the Shapiro-Wilk test. Data were expressed as mean ± standard deviation for normally distributed measures or median (interquartile range) for non-normally distributed measures. For normally distributed data, we used the unpaired or paired t-test for between-group and within-group comparisons, respectively. For data that did not follow a normal distribution, we used the Mann-Whitney U test or Wilcoxon signed-rank test for between-group and within-group comparisons, respectively. We used the $\chi 2$ test to compare differences between groups in categorical and binary variables. Pearson's correlation assessed the relationship between fatigue and dyspnea data and clinical and functional variables. Physiological variables and symptoms (heart rate, mean arterial pressure, oxygen saturation, RPE muscle fatigue, and dyspnea) recorded during the CWCT were analyzed by a two-way analysis of variance (group x time). Exercise time was normalized defining values at 20%, 40%, 60%, 80%, and 100% of the total time for each test. Sidak's posthoc test was applied when this analysis revealed a significant main or interaction effect

A two-tailed alpha level of 0.05 was used as the cut-off for significance. In addition, in order to explain the perceived fatigue (FSS score), we performed a multivariate analysis with a backward stepwise methodology including the following variables: sex, age (years), BMI, $paCO_2$, pH, PaO_2/FiO_2, FEV_1 (%), FVC (%), FEV_1/FVC, quadriceps volume (cm^3), 6MWT (meters), time of CWCT (seconds), quadriceps Maximal Voluntary Contraction (kg), Barthel dyspnea score and CRF presence. Residual distribution and homoscedasticity were checked. P values < 0.05 were considered statistically significant.

The sample size was calculated on NMF considering the change in percentage of MVC after the fatiguing task according to Mador et al. (2003b), who found a reduction in MVC% of 27±7 in severe COPD patients. According to the gap between moderate and severe COPD reported by Mador et al. (2003b), we estimated an additional reduction in MVC of about 10% in the CRF-COPD group (delta MVC%: -37±7). Considering an alpha significance level of 0.05 (2-sided) and a beta of 80%, and a CRF-COPD to COPD ratio of 2:1, a minimum total sample size of 16 participants in the CRF group and 8 in the COPD group was estimated as sufficient to detect significant differences.

RESULTS (Project 2)

The clinical characteristics of the two groups are reported in **Table 1**. Patients in both groups were mainly male, about 65 years old, of normal weight, and having lung hyperinflation. As expected, the time since diagnosis was longer in CRF-COPD patients, who had been on LTOT for 44.8±29.9 months. At rest, CRF-COPD patients were more hypercapnic and presented higher pulmonary obstruction. Blood gases analysis performed in CRF-COPD patients on their usual oxygen supplementation revealed a similar blood oxygen saturation to the control group. No difference in static lung hyperinflation was found.

Table 2 presents data from the exercise tests (IET, CWCT, 6MWT). The CRF-COPD patients performed all exercise tests breathing through nasal prongs under the usual FiO_2 (32±36 %) prescribed during exercise by the pulmonologist. SpO_2 at rest was similar between the two groups. The CRF-COPD group showed a significant reduction in exercise tolerance (total work of CWCT and distance walked at 6MWT) compared to the COPD group.

Table 1 (Project 2) . Clinical and lung function characteristics of patients

	Overall (N=29)	CRF-COPD (N=19)	COPD (N=10)	P
Age, years	65.3 ± 7.6	65.8 ± 7.8	64.4 ± 7.5	0.649
Male, n (%)	19 (66)	14 (74)	5 (50)	0.202
BMI, kg/m^2	24.0 ± 4.5	23.9 ± 5.0	24.2 ± 3.7	0.888
Years since diagnosis of COPD	8.1 ± 5.0	10.7 ± 3.6	3.3 ± 3.3	< **0.001**
CIRS severity index	1.6 ± 0.4	1.8 ± 0.6	1.5 ± 0.2	**0.030**
CIRS comorbidity index	3.0±3.0	4.0±3.0	1.5±2.0	**0.012**
PaO_2/FiO_2, ratio	293.4 ± 46.0	275.9 ± 40.1	326.6 ± 38.8	**0.003**
SpO_2, %	97.0 ± 1.7	97.1 ± 1.7	96.8 ± 1.7	0.708
$PaCO_2$, mmHg	42.4 ± 13.3	43.8 ± 15.0	38.5 ± 5.8	0.007
pH	7.43 ± 0.05	7.43 ± 0.05	7.43 ± 0.03	0.370
FEV_1, % of pred.	29.5 ± 10.2	25.2 ± 8.6	37.6 ± 8.1	< **0.001**
FVC, % of pred.	63.2 ± 14.3	59.1 ± 13.7	70.9 ± 12.7	**0.032**
FEV_1/FVC, ratio	36.0 ± 10.1	33.2 ± 9.3	41.5 ± 9.9	**0.034**
RV, % of pred.	195.2 ± 50.7	204.8 ± 46.2	176.8 ± 56.0	0.160
FEV_1 <50% and >30% of pred., n (%)	12 (41.4)	4 (21.1)	8 (80.0)	< 0.001
FEV_1 < = 30% of pred., n (%)	17 (58.6)	15 (78.9)	2 (20.0)	<0.001

Legend: CRF: Chronic Respiratory Failure; COPD: Chronic Obstructive Pulmonary Disease; BMI: Body mass index; CIRS: cumulative illness rating scale; PaO_2: arterial oxygen partial pressure; FiO2 = inspiratory fraction of oxygen, SpO_2: arterial oxygen saturation; $PaCO_2$: arterial carbon dioxide partial pressure; FEV_1: forced expiratory volume at first second; FVC: forced vital capacity; RV: Residual Volume; pred. = predicted. Data are expressed as mean ± standard deviation for normally distributed measures, median (interquartile range) for non-normally distributed measures.

Table 2 (Project 2).

	Overall (N=29)	CRF-COPD (N=19)	COPD (N=10)	P
Incremental Exercise Test (IET)				
PPO, W	49.0 ± 14.2	45.3 ± 10.7	56.0 ± 17.8	0.052
HR peak, %	107.3 ± 14.2	103.8 ± 14.4	114.0 ± 11.9	0.067
Dyspnea peak, Borg score	10.0 (0)	10.0 (0)	10.0 (0)	0.259
Muscle fatigue peak, Borg score	10.0 (1.0)	10.0 (1.0)	10.0 (5.0)	0.569
Reason for stopping, n (%)				0.556
Dyspnea	6 (21)	3 (16)	3 (30)	
Muscle fatigue	2 (7)	1 (5)	1 (10)	
Both	21 (72)	15 (79)	6 (60)	
Constant Work rate Cycling Test (CWCT)				
Watts endurance test, W	40.0 (8.0)	32.0 (8.0)	40.0 (32.0)	0.139
Time to exhaustion, sec	191.0 (136.0)	180.0 (121.0)	263.0 (387.0)	0.136
Total work, J	7600.0 (7104.0)	7200.0 (4272.0)	14560.0 (12540.0)	0.023
SpO_2 Tlim, %	94.0 (5.0)	94.0 (5.0)	93.5 (7.0)	0.211
HR Tlim, %	108.4 ± 14.0	106.5 ± 13.4	112.1 ± 15.1	0.317
Dyspnea Tlim, Borg score	10.0 (0.0)	10.0 (0.0)	10.0 (3.0)	0.173
Muscle fatigue Tlim, Borg score	10.0 (6.0)	10.0 (3.0)	4.5 (4.0)	0.007
Reason for stopping, n (%)				0.062
Dyspnea	12 (42)	5 (26)	7 (70)	
Muscle fatigue	3 (10)	2 (11)	1 (10)	
Both	14 (48)	12 (63)	2 (20)	
6-Minute Walking Test (6-MWT)				
Distance, m	325.3 ± 97.7	298.7 ± 90.2	376.0 ± 95.3	**0.041**

Legend: IET: incremental exercise test; CRF: Chronic Respiratory Failure; COPD: Chronic Obstructive Pulmonary Disease; PPO: Peak Power Output; W: Watts; HR = Heart rate; sec: seconds; J: Joule; SpO_2: arterial oxygen saturation; Tlim: Time to exhaustion of exercise. Data are expressed as mean ± standard deviation for normally distributed measures or median (interquartile range) for non-normally distributed measures.

Perceived fatigue and dyspnea

Figure 2 shows the differences in perceived fatigue and dyspnea between the groups (panels A and B): CRF-COPD had higher perceived fatigue (FSS score: 5.15±1.31 vs. 3.36±1.85; p=0.0052) and dyspnea (BDI: 35.63±18.14 vs. 14.6±10.45; p=0.0023) than COPD.

Neuromuscular fatigue

Findings for both groups on NMF after CWCT are shown in **Figure 3**. After the fatiguing task, there was a similar decrease in MVC (panel A) with respect to the pre-exercise values in both groups (p=0.6628). Interestingly, the difference between groups remained non-significant after normalization for the total work (panel B, p=0.5819).

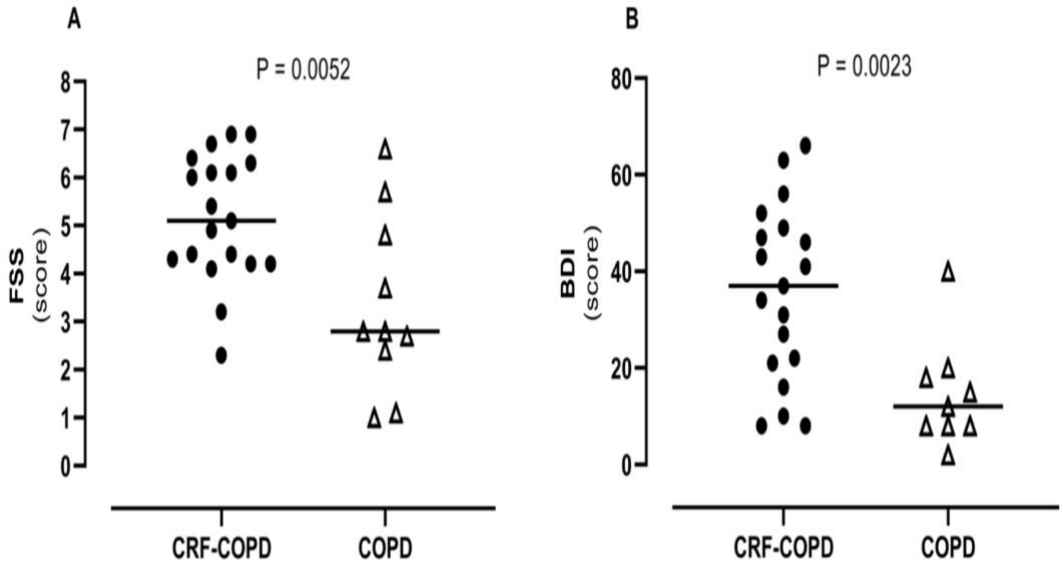
Qtwpot reduction after exhaustion (panel C) showed a similar exercise-induced peripheral NMF in both groups (p=0.2609) and the delta MVA% (panel E) showed a similar development of central fatigue (p=0.3455). No difference between groups was detectable after normalization for the total work for each parameter. **(**panel D [p=0.7481] and F [p=0.4354], respectively).

The occurrence of a significant amount of quadriceps peripheral NMF (i.e. defined as a >15% reduction in Qtwpot) (Johansson et al. 2008) was present in 44.83% of patients overall (36.84% of CRF-COPD vs. 60.0% of COPD group, p=0.233).

CWCT data

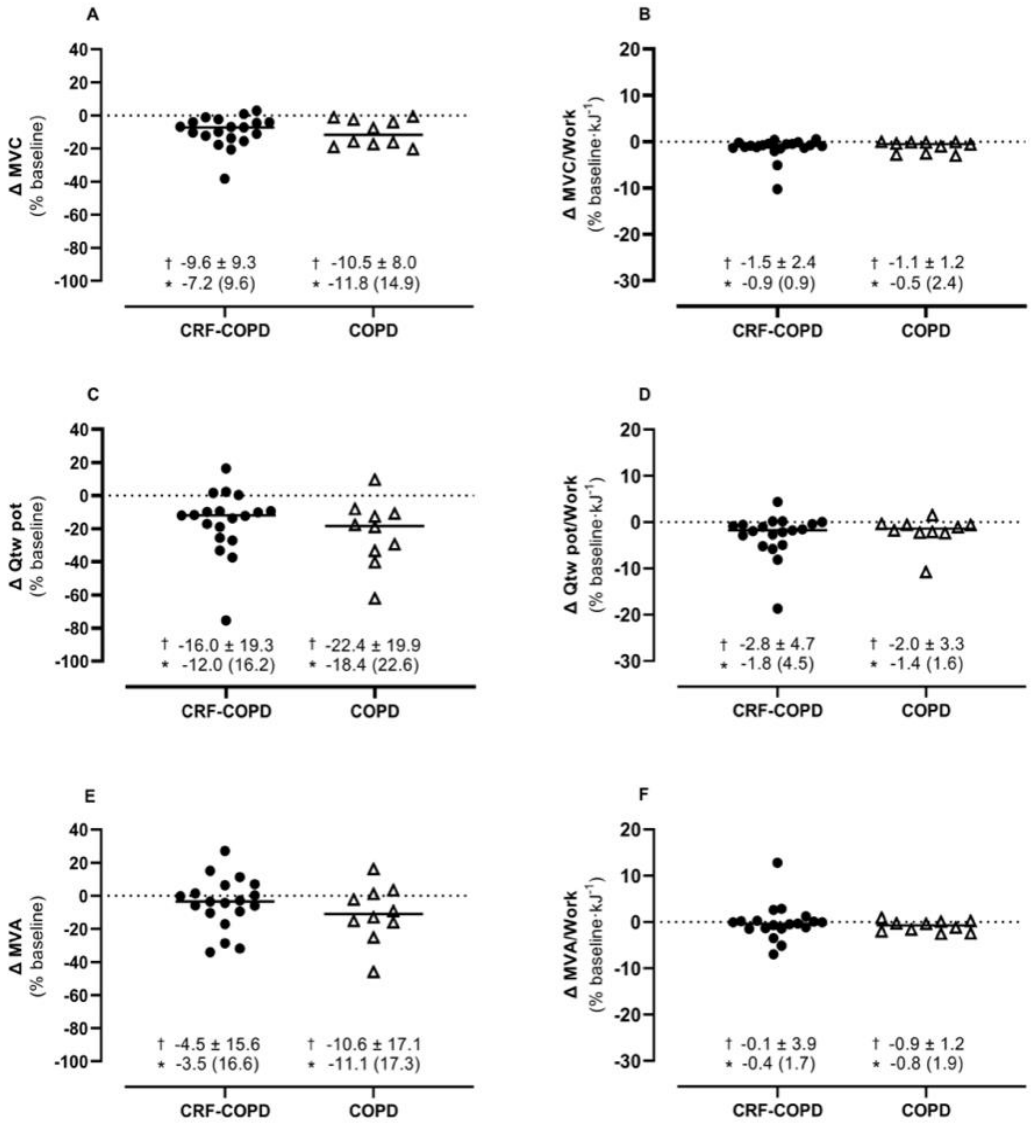
Cardiovascular parameters, SpO_2, and ratings of perceived fatigue during CWCT performed at the same relative work~~load~~ rate (80% of Wmax) are reported in **Figure 4**. During the fatiguing task, CRF-COPD patients showed a similar response in HR and MAP (panels A and B) compared to controls. Conversely, dyspnea and leg muscle RPE were higher in CRF-COPD patients (p=0.0174 and p=0.0062, panels C and D respectively). Interestingly, oxygen saturation was significantly higher (p=0.0475, panel E) in CRF-COPD than in the COPD group.

Figure 2 (Project 2).Differences in perceived fatigue, and dyspnea between CRF-COPD and COPD patients.



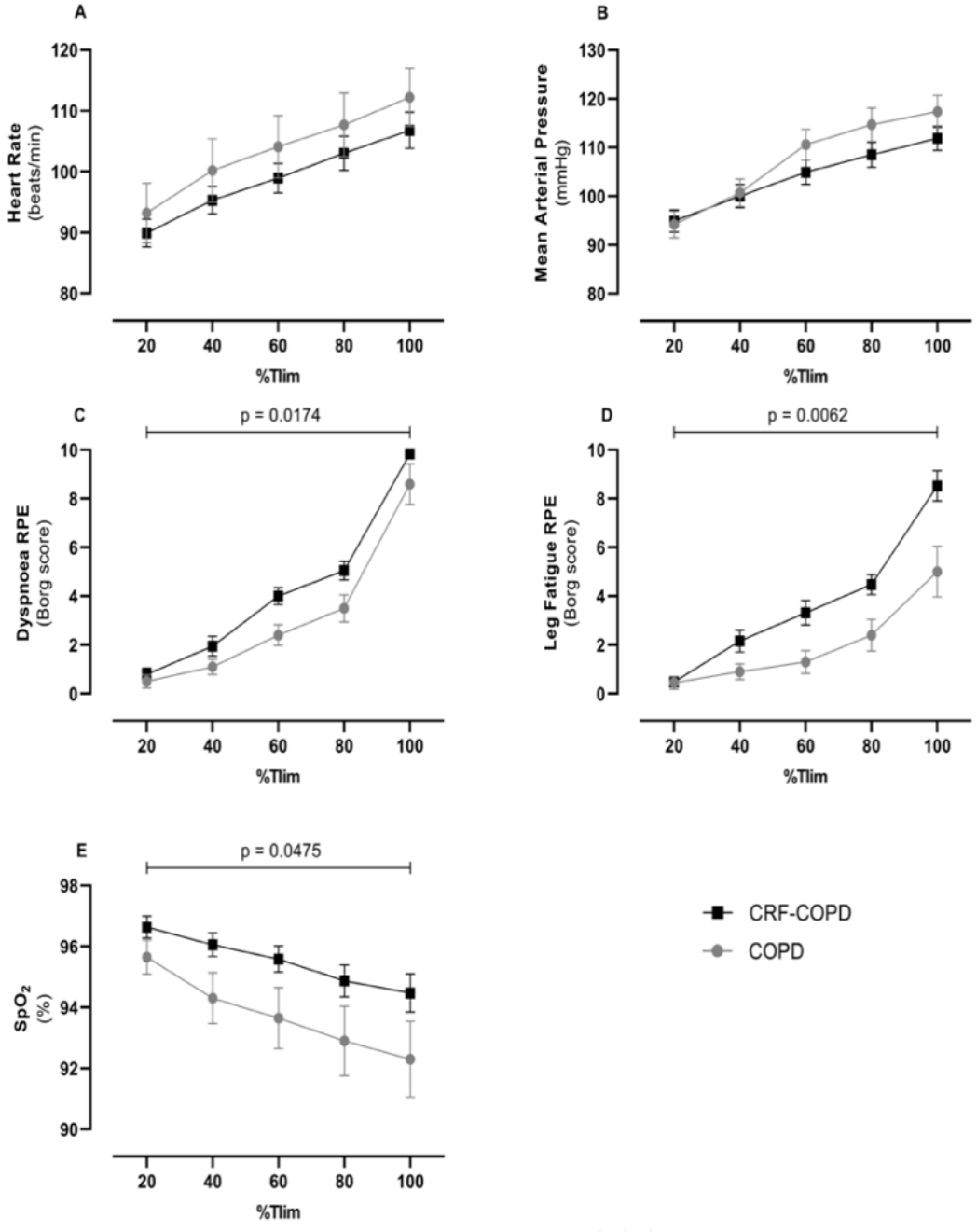
Legend: Panel A: Differences in perceived fatigue (FSS scale) during daily life. Panel B: Differences in dyspnea (BDI scale) during ADL. Black circles: CRF-COPD group, white triangles: COPD group. Abbreviations: CRF: Chronic Respiratory Failure, FSS: Fatigue Severity Scale, BDI: Barthel Index Dyspnea. In all panels, the bar describes the median value

Figure 3 (Project 2). Differences in quadriceps neuromuscular fatigue between CRF-COPD and COPD patients.



Legend: Panel A: Percentage of change in Maximal Voluntary Contraction after CWCT; Panel B: Percentage of change in Maximal Voluntary Contraction after CWCT normalized for total work; Panel C: Percentage of change in potentiated quadriceps twitch force (Resting Twitch) after CWCT; Panel D: Percentage of change in potentiated quadriceps twitch force (Resting Twitch) after CWCT normalized for total work; Panel E: Percentage of change in MVA after CWCT. Panel F: Percentage of change in MVA after CWCT normalized for total work.
Black circles: CRF-COPD group, white triangles: COPD group. Abbreviations: CRF: Chronic Respiratory Failure, MVC: Maximal Voluntary Contraction; Qtwpot: potentiated quadriceps twitch force; MVA: Maximal VoluntaryActivation; In all panels, the bar describes the median value. The values below each graph indicate: †mean ± standard deviation, * median (interquartile range)

Figure 4 (Project 2). Changes in Heart Rate (panel A), Mean Arterial Pressure (panel B), perceived dyspnea (panel C), perceived Leg Muscle Fatigue (panel D), and oxygen saturation (SpO2%, panel E) during constant workload cycling test (CWCT) in CRF-COPD and COPD patients.



Legend: Data expressed as mean±SE. P=ANOVA between groups. Grey dots: COPD group; black squares: COPD group. Abbreviations: CRF: Chronic Respiratory Failure, COPD: Chronic Obstructive Pulmonary Disease, SpO_2: arterial oxygen saturation, %Tlim, percentage of time to exercise intolerance; RPE: rate of perceived exertion

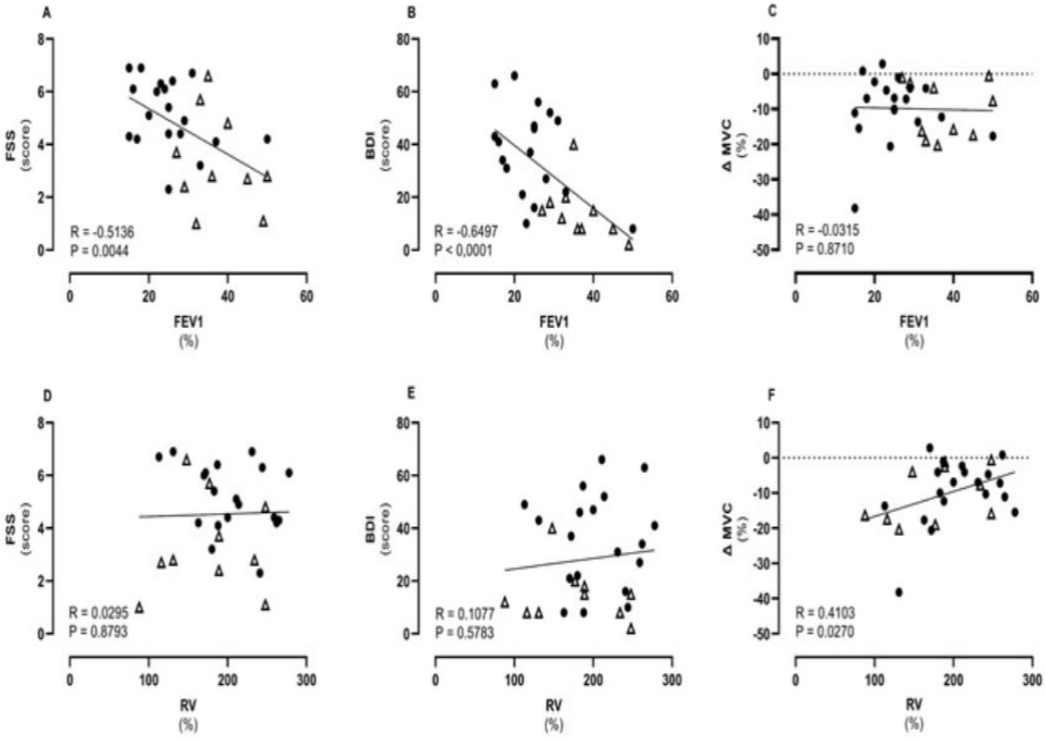
Relationships between variables

No correlation was found between PF and both central and peripheral components of NMF (FSS vs Δ MVC: R=-0.1308, p=0.4988; Δ Qtwpot: R=0.002; p=0.9993, Δ MVA%: R=-0.2262 R=0.2380), neither considering each group (FSS vs Δ MVC: R=-0.0794, p=0.8274; Δ Qtwpot: R= -0.4282; p=0.2170, Δ MVA%: R=- 0.4995; p=0.1416 for COPD group and FSS vs Δ MVC: R=-0.2417, p=0.3187; Δ Qtwpot: R=0.1435; p=0.5578, Δ MVA%: R=-0.2778; p=0.2495 for CRF-COPD group).

The perception of fatigue (FSS score) and perceived dyspnea (BDI score) were closely correlated (R=0.5735, p=0.0011) in both groups of COPD patients. The relationships between lung obstruction (evaluated by FEV_1%) and static hyperinflation (evaluated by RV%) and PF, perceived dyspnea and NMF (change in MVC) are described in **Figure 5.** Lung obstruction was correlated to perceived fatigue and dyspnea ($p<0.01$), but not to NMF (R=-0.032, p=0.871). Instead, a higher static residual volume was inversely correlated to NMF (**Figure 5**, panel F). No significant correlation was found between lung hyperinflation and the peripheral component of fatigue (change in Qtwpot), while it was correlated with the central component of fatigue (change in MVA%) (R =0.410, p=0.027). Dyspnea was correlated with the 6MWT (R=0.495, p=0.006), PPO (watts) (R=- 0.394, p=0.034) and FVC (R=-0.371, p=0.475).

Multivariate analysis evidenced three variables as significantly affecting the perceived fatigue (FSS score) (R^2 adjusted: 0.4627, F test p=0.0003): pH [b = -18.73 (95% IC -34.09; -3.36)], time to exhaustion on CRWT (seconds) [b= -0.003 (95%IC -0.05; -0.0004)] and Barthel dyspnea index score [b= 0.057 (95%IC 0.031-0.084)], beta coefficient 142.6 (95%IC 28.6-256.6).

Figure 5 (Project 2) Correlations of lung obstruction (FEV1%) and static hyperinflation (RV%), respectively, with perceived fatigue (FSS), dyspnea (BDI), and quadriceps neuromuscular fatigue (change in MVC).



Legend: Black circles: CRF-COPD group, white triangles: COPD group. Abbreviations: CRF: Chronic Respiratory Failure, COPD: Chronic Obstructive Pulmonary Disease, FEV_1: forced expiratory volume at first second; RV: Residual Volume; FSS: Fatigue Severity Scale; BDI: Barthel Dyspnea Index; MVC: Maximal Voluntary Contraction

DISCUSSION (Project 2)

The present study evaluated perceived fatigue and the central/peripheral components of neuromuscular fatigue in very severe COPD patients with CRF on LTOT with respect to severe COPD patients without CRF. In the two patient groups, we found, partially in contrast with our hypothesis, that the degree of central and peripheral components of neuromuscular fatigue was similar after a dynamic exercise task executed at the same relative workload. Interestingly, severe COPD patients with CRF on LTOT, despite maintaining a better oxygenation status during the fatiguing task, reported significantly higher levels of perceived fatigue and dyspnea scales, suggesting a mismatch between neuromuscular fatigue and its perception. This notion is also corroborated by the different perceptions of fatigue reported by the more severe patients during daily life activity (FSS score). Taken together, the worse perceived fatigue exhibited by the CRF-COPD group, which was not accompanied by a detectable difference in central and peripheral components of neuromuscular fatigue, suggests that the nature of their exercise intolerance is not associated with neuromuscular dysfunction of the locomotor limbs but that other factors are likely involved in this clinical phenomenon.

Study population

Our study group focused on a category of patients with very severe COPD requiring long-term oxygen therapy: this is a category little investigated in the literature and often neglected by the international scientific community. The prevalence of hypoxemia among COPD patients remains uncertain: in a large trial of general COPD patients, severe hypoxemia requiring the prescription of supplemental oxygen was estimated at around 2% (Tashkin et al. 2008). Conversely, over 80% of the patients with severe pulmonary emphysema disease enrolled in the American National Emphysema Treatment Trial were on some form of oxygen therapy (Martinez et al. 2006). Uncorrected chronic hypoxemia is associated with the development of adverse sequelae including pulmonary hypertension, polycythemia, systemic inflammation, neurocognitive dysfunction, skeletal and respiratory muscle dysfunction, impaired exercise tolerance, reduced quality of life and increased cardiovascular morbidity and death (Kent et al. 2011).

It is known that LTOT can improve pulmonary hemodynamics, reduce erythrocytosis, and improve survival in selected patients with severe hypoxemic respiratory failure (Davidson et al. 1988). Paneroni et al. (2019) showed that COPD patients on LTOT had lower exercise tolerance and daily energy expenditure, longer sedentary time, and took fewer daily steps than COPD patients without CRF. Our study offers a descriptive overview of the perceived and neuromuscular fatigue components in this subgroup of very severe COPD patients helping to broaden the knowledge concerning factors limiting exercise tolerance in these patients.

Fatigue perception

In a recent review on COPD that analyzed 196 studies, PF ranged from 17 to 95%, and several factors could influence it including age, dyspnea, pulmonary obstruction, depression, muscle strength, functional capacity, and quality of life, although there is controversy about what the major causal factors are (Ebadi et al. 2021). Our data indicate, as expected, a higher rating–of perceived fatigue (as assessed with FSS) in CRF-COPD patients compared to severe COPD. These data are also confirmed using the Johansson et al. cut-off for fatigued patients of 4 points (Johansson et al. 2008): 85% of CRF-COPD patients, but only 15% of the COPD group, scored above this proposed threshold ($p<0.001$).

Our report is, to the best of our knowledge, the first study describing this difference in more advanced COPD disease. Considering the differences between the two groups we evaluated, we can speculate that, among other factors, the longer time course of the disease, higher number of comorbidities, worse dyspnea, and lower exercise tolerance could be implicated in the marked worsening of perceived fatigue in our CRF population.

In addition, we considered the correlation between FSS and some possible explanatory factors such as comorbidities, oxygenation, pulmonary obstruction, and exercise tolerance. We found a moderate correlation between the severity of the pulmonary obstruction (FEV_1) and the perception of fatigue evaluated with FSS. Findings in the literature on the relationship between lung obstruction and PF are contradictory, affirming both a significant relationship (Stridsman et al. 2018; Donohue et al. 2018) and a non-significant association (Ebadi et al. 2021).

In addition, we found a moderate correlation between the two main symptoms, i.e. dyspnea and perceived fatigue, suggesting a close link between the complex mechanisms underlying these two factors. Our data support a recent report by Goertz et al. (2019) who found, through multivariate linear regression, that dyspnea was the single factor that accounted for most of the explained variance in perceived fatigue.

According to Goertz et al. (2019) report, also our data describe the dyspnea perception to be implicated in the PF phenomenon. However, in our experience, the multivariate regression performed in order to explain the PF evidenced three factors involved: a lower blood pH at rest, a lower time to exhaustion at CWRT, and a higher level of dyspnea perception were the elements that better explained the fatigue symptom, better than the severity of lung obstruction. This result is in line with the perception of fatigue multifactorial theory and seems to evidence the presence of a particular patient's phenotype more prone to develop it (patients with low effort tolerance, high dyspnea, and blood acidosis).

Neuromuscular fatigue

The presence of increased levels of peripheral NMF in non-hypoxemic COPD compared to healthy people has been reported in a previous study (Mador et al. 2003a). In our investigation, and in contrast with our initial hypothesis, COPD patients with CRF on LTOT experienced the same level of NMF (both peripheral and central components) as COPD patients without CRF when tested at the same relative workload. Our data are in contrast with Mador et al. (Mador et al. 2003b) who reported a worse NMF in severe versus moderate COPD patients. A possible explanation for this discrepancy could be the type of fatiguing exercise task utilized by these authors: a set of ten intermittent maximal isometric single leg contractions. Indeed, this exercise task activates a small amount of skeletal muscle, and, consequently, the severe respiratory limitations of these patients would minimally impact their performance (Rossman et al. 2012). Another difference is the lack of oxygen supplementation in Mador et al.'s study (Mador et al. 2003b), which, interestingly, led to opposite SpO_2 results: exercise-induced desaturation in our study, while no evidence of desaturation in Mador et al.'s. Taken together, the

discrepancy in findings suggests that the CRF-COPD patients recruited in our study were probably more severe than those in Mador et al.'s study (2003b). Indeed, the objectives of his investigation were to evaluate the differences in moderate vs severe severity, while our study focused on the severe *vs* very severe patient comparison.

Regarding non-hypoxemic COPD patients, Amman et al. (2010) experimented a cycle ergometer constant load fatiguing task at the same intensity as in our protocol and found a similar reduction in MVC and Qtwpot to ours. In the same patients, the authors reported that oxygen supplementation delivering a fraction of inspired oxygen of 60%, was able to reduce peripheral NMF by about one-third (Amman et al. 2010). About this, oxygen use may well have influenced our findings in the CRF-COPD group. Patients with CRF would normally spend their lives in chronic hypoxemia, but having a continuous supply of oxygen can lead to a situation of "apparent" normoxia, beneficial for the peripheral muscles for at least two reasons. First, it can compensate for the altered pulmonary gas exchange that characterizes these patients by improving hemoglobin saturation (Amman et al. 2006). Second, it can reduce inspiratory and/or expiratory muscle fatigue leading to less activation of unmyelinated group IV phrenic afferents and consequently to a reduction of sympathetic vasoconstrictor activity in the active limb via a supraspinal reflex (Dempsey et al. 2006). Furthermore, concerning the "cardio-respiratory" involvement, oxygen therapy can decrease minute ventilation, reduce pulmonary arterial pressure and increase cardiac output (through the elimination of hypoxic vasoconstriction) (Kent et al. 2011). All these elements together could be implicated in the non-aggravation of NMF in the CRF group with respect to the control COPD group. Recently, the literature suggested two different theories to explain the fatigue phenomenon. The first is based on the 'critical threshold of peripheral fatigue' concept where a negative feedback loop operates to protect the exercising limb muscle from severe threats to muscle homeostasis. As a consequence, during whole-body exercise, the negative feedback loop protects neuromuscular function, mainly related to III/IV muscle afferents activity, restricting motoneuronal output and muscle activation in proportion to the magnitude of the feedback from these sensory neurons (Hureau et al. 2018). The

second theory called ‘sensory tolerance limit’ extends this idea and suggests that the sum of all feedback and feedforward signals is processed within the central nervous system and ultimately regulates the intensity of the exercise to ensure that voluntary activity remains tolerable. As such, the sensory tolerance limit might be viewed as a more global (i.e., not limited to a single muscle/group) negative feedback loop (Hureau et al., 2018). Based on these theories our studies describe similar responses in terms of peripheral fatigue and central activation between severe COPD patients without CRF and more severe patients with CRF during the oxygen supplementation. This mechanism could be explained by a similar activation of feedback and feedforward signals in these two populations.

Another important finding of our study is the moderate correlation we found between the residual volume at rest and changes in MVC and MVA following the fatigue task, indicating that patients with more static hyperinflation develop less quadriceps NMF, in particular, central fatigue. One possible explanation for this is that patients with higher lung functional residual capacity are more "ventilatory-restricted" and, therefore, terminate the exercise task due to ventilatory limitations before they can truly activate and fatigue the locomotor muscles. Our data highlight a reduction of the central component of fatigue in hyperinflated patients, suggesting less neural drive to a muscle. Direct evidence supporting the assumption of a reduced supraspinal drive (using transcranial magnetic stimulation) following exercise is currently lacking in COPD. A recent report has described that the use of spinal anesthesia can enhance cycling exercise tolerance in patients with COPD, mostly by reducing ventilatory response and dyspnea during exercise; these effects were possibly mediated through the inhibition of group III/IV lower limb sensory muscle afferents (Gagnon P et al. 2012).

However, recent findings indicate a deficit in voluntary activation from the motor cortex in COPD patients who show peripheral muscle weakness (Alexandre et al. 2020). On the contrary, Butcher and colleagues (Butcher et al. 2009) showed an inverse relationship between the magnitudes of ventilatory constraints and skeletal muscle contractile capacity after high-intensity cycling exercise at room air in patients with COPD. In addition, an improvement in exercise time to failure was obtained with heliox administration, a strategy aimed at delaying ventilatory

constraints. Nevertheless, the results of Butcher et al. (2009) are difficult to compare with our data because their study collected no data on central NMF component or oxygen supplementation effect.

Relationship between perceived and neuromuscular fatigue

One of the main findings of our study is the difference in correlation we found between perceived fatigue and NMF in the two groups: in CRF-COPD patients the level of fatigue perceived was worse than that of NMF, whereas in the COPD group the levels were not different. To date, the relationship between PF and NMF has not been evaluated in COPD patients. Previous reports have more extensively investigated the correlation between PF and other physical components, such as exercise tolerance and muscle strength (Ebadi et al. 2021). Most papers indicated that lower exercise capacity and strength correlated with higher fatigue (Ebadi et al. 2021), but none explored the relationship between them.

Our results show a mismatch between the subjective perception of fatigue and the objective physiological muscle fatigue components in patients with very severe COPD, suggesting that the degree of NMF is not a major, let alone the primary, underlying cause of perceived fatigue in these patients. This means that the causes of perceived fatigue should be sought in other physical, psychological and behavioral factors.

Implication of the fatiguing exercise task

We proposed a cycle ergometer constant work-rate exercise test at 80% of the PPO as a fatiguing task. The cycle ergometer exercise stresses respiratory, cardiac and muscular systems involved in the patients' routine exercise performance such as walking, rise stairs, and leisure activities. In COPD the cardio-respiratory involvement can produce a premature interruption of exercise due to dyspnea related to hyperinflation and mechanical constraint when ventilatory requests increase (Neder et al. 2017).

Our data show a higher dyspnea and muscle fatigue RPE in the CRF-COPD group compared to the COPD group (Figure 4, panels C and D). Although we did not dynamically evaluate the inspiratory capacity and minute ventilation, this

finding is presumably due to the greater respiratory involvement (higher respiratory rate and dynamic hyperinflation) in CRF-COPD.

Other studies used different fatiguing tasks, e.g. Mador et al. (2003b) evaluated quadriceps fatigability after isolated maximal voluntary contractions of one leg and found a higher NMF in more severe COPD patients. Their protocol, however, focused specifically on the "muscular" component of exercise and did not consider the cardio-respiratory limitations typical of this disease. Their finding likely reflects the fact that 'central' constraints to exercise limitation may overshadow potential functional impairments in the appendicular muscles. Saey et al. (2003) instead, found NMF to be higher during cycling than walking in COPD patients. They explained this as due to the different exercises performed. Hence, there is a need to contextualize findings in relation to the task performed, avoiding generalization.

Clinical implications

Our results showing a potential mismatch between the subjective perception of fatigue and the objective degree of NMF suggest that it is important for clinicians to evaluate each component since both could have a significant impact on the patient's exercise tolerance and quality of life. These evaluations offer a spectrum of physiological details that can help tailor the rehabilitation program to the individual. For this reason, in the rehabilitation setting, we would recommend a dedicated fatigue assessment battery (both perceived and neuromuscular). About NMF, this evaluation can allow rehabilitative staff to better characterize patients' phenotype because previous studies described a better effort tolerance improvement in patients fatigued at pulmonary rehabilitation admission (Burtin et al. 2012). Our data also supports the use of exercises that can reduce breathlessness and FP for rehabilitation purposes such as small-mass training (eg, using each leg separately through single-leg cycling or quadriceps extension). This type of exercise has been described to be able to improve exercise performance in COPD patients (often better than training both legs at the same time). (Bjorgen et al. 2009; Dolmage et al. 2008; Broxterman et al. 2021).

Limitations

Some methodological features of our study warrant mention. First, we did not have a CRF control group performing oxygen-free exercises. For this reason, the nature of our study can only be descriptive. Further studies would need to compare CRF patients with vs. without oxygen supplementation, although this might be unfeasible for practical (inability to exercise for sufficient time) and ethical (possible deleterious effect of hypoxemia) reasons. Secondly, we calculated neuromuscular fatigue with the same relative load between groups, but with a different absolute workload. We cannot rule out that our findings might have been different if patients had worked at the same absolute workload. Nevertheless, the statistical normalization for the total amount of work confirms our results**.** Given that fatigue appears to be a task-dependent phenomenon, caution is necessary for generalizing our results to everyday life. Third, due to the small sample size, for some of the comparisons where no significant differences were found, the risk of Type-II error could be relevant and considered a main limitation of our study.

In addition, we administered oxygen therapy through a nasal cannula, but some patients could have breathed through the mouth and the real quantity of oxygen administered could have been overestimated. However, our study aimed to reproduce the “real life “of patients and normally our patients used nasal cannula during effort training due to the easy management, comfort, and cost.

Lastly, gas exchange measurement was not possible due to the simultaneous patient’s oxygen supplementation.

CONCLUSION (Project 2)

Severe COPD patients with CRF on LTOT develop higher levels of perceived fatigue and dyspnea when exercising than do severe COPD patients without CRF. In contrast, the extent of neuromuscular fatigue after constant load-cycle exercise performed at 80% of peak power output is similar in both groups. The mismatch between the perceived fatigue and objective neuromuscular fatigue found in COPD patients with CRF on LTOT suggests that the nature of the exercise intolerance in these patients is not due to the neuromuscular dysfunction of the locomotor limbs *per se* but that other factors are likely involved in this clinical phenomenon.

4.7 PROJECT 3: PULMONARY REHABILITATION EFFECT ON FATIGUE IN COPD PATIENTS WITH CHRONIC RESPIRATORY FAILURE.

ABSTRACT (Project 3)

Purpose: To evaluate the efficacy of a rehabilitation program on perceived fatigue (PF) and neuromuscular fatigue (NMF) in patients with COPD with chronic respiratory failure (CRF), submitted to long term oxygen therapy (LTOT). Our hypothesis was that both PF and NMF would have been improved to a similar extent by the rehabilitation program and would have been correlated with the improvement of the other main outcome measures.

Methods: This cohort pre-to-post study in inpatients attending a rehabilitation program, evaluated 32 COPD-CRF in LTOT. PF was determined by Fatigue Severity Scale (FSS), while Quadriceps NMF was assessed via interpolated twitch detecting changes after a Constant Workload Cycling Test (CWCT) at 80% of peak power output. They were submitted to a moderate intensity cycloergometer exercise program with 40-min session/day, 6 times/week.

Results: All outcome measures improved significantly [Barthel dyspnea Index, score -7.01 ± 9.97, Constant Workload Cycle Test +557.9 ± 574.7 seconds, 6-Minute Walking Distance +46.6 ± 47.0 meters; Peak Power Output +5.6 ± 10.8 watts, Maugeri Respiratory Failure (MRF) questionnaire score -2.1 ± 3.1; all P <0.05], except the quadriceps muscle strength. PF decrease significantly (ΔFSS, score: -0.67 ± 1.36, P <0.05), but patients with severe fatigue at baseline had greater improvement than patients without severe PF (-1.62±1.00 vs 0.22±1.01,P <0.001). There was no change in NMF in the overall group, as peripheral NMF improved significantly and to a greater extent in patients with peripheral NMF at baseline than in patients who did not (Δ potential quadriceps contraction + 18.93 ± 14.01% versus -6.59 ± 14.28%; p> 0.001).The same group improved more the 6-Minute Walking Distance (71.7±35.64 vs 31.5±36.17, P = 0.0167). Any relationship between changes in PF and NMF was found (ΔFSS versus change Δ

MVC R = 0.2114, P = 0.2710; ΔFSS versus change Δ Qtwpot R = -0.3003; P = 0.1447; ΔFSS with respect to the change Δ MVA% R = -0.2379; P = 0.2521).

Conclusion: A clear mismatch between the perception of fatigue and the objective neuromuscular fatigue with regard to the change obtained after rehabilitation is evident and a specific assessment for both is mandatory in rehabilitative setting. Further studies about tailored interventions are needed.

INTRODUCTION (Project 3)

After dyspnea, perceived fatigue (PF), "the subjective feeling of tiredness, exhaustion or lack of energy, that occurs on a daily basis", is the second most disabling symptom in COPD patients and it was found associated with physical, psychological and behavioral factors impacting patients' independence, prognosis and mortality (Ebadi Z. 2021).

High levels of PF is common in patients entering Pulmonary rehabilitation (PR), that is defined as "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors". (Spruit, MA, 2013). This intervention is highly effective to reduce perceived fatigue, evaluates with different dedicated questionnaires, as well as dyspnoea, and to improve exercise tolerance, health-related quality of life and reduces the use of healthcare resources (Spruit MA, 2013). The current literature indicates that after a PR intervention, patients with higher PF seems to improve more this symptom and quality of life with clinically significant gains maintained at 1 year (Baltzan MA, 2011).

On the other hand, fatigue could be also described as neuromuscular fatigue (NMF), the reduction in muscle force/activation during a given task (Gruet M. 2018). The exacerbation of NMF it is found in about 60% of COPD patients when performed high intensity exercise. (Saey D, 2003; Mador MJ, 2003). No studies about the efficacy of PR program on NMF are available (Paneroni M, 2020). However, two recent cohort studies (Burtin C , 2012; Mador MJ, 2014) found that those subjects who have develop greater levels of peripheral NMF after an exercise session had a larger improvement in functional exercise capacity and quality of life following an exercise training program. All studies related to fatigue (both perceived and neuromuscular) mainly focused on moderate COPD without Chronic Respiratory

Failure (COPD-CRF), and the current knowledge on the effectiveness of PR in these growing numbers of severe COPD patients is currently unknown.

Therefore, in the present study we aimed to evaluate the effectiveness of a rehabilitative program on the PF and NMF in patients with COPD-CRF. Our hypothesis was that both PF and NMF would be ameliorated at similar extend by the rehabilitative program and would be correlated with the improvement in functional outcome measures.

METHODS (Project 3)

Subjects

This is a prospective cohort study, and this report represent an *in-itinere* analysis of a project funded by *Ministero della Salute Italiano* related to training in patients COPD and CRF. There was a significant delay of enrollment rate due to Covid pandemic (present data referring of about 55% of estimated sample). All patients were enrolled during a in-patients PR attempt at ICS Maugeri Institute Lumezzane (BS)-Italy. Inclusion criteria were the COPD diagnosis, the prescription of 24 h/day LTOT since at least 3 months according to leading guidelines (Hardinge M, 2015), the presence of FEV1< 50%, a stable clinical condition (pH >7.35, no change in drugs therapy within the last week, no exacerbations or hospitalizations within the last 3 months) and absence of orthopedic, neurological, cardiac and cognitive impairment. COPD-CRF group used O_2 supply through nasal prongs as liquid oxygen from a base unit (stationary system) during rest and by means of portable cylinders, either carried by the patient (stroller) or transported by means of a trolley, during daily activities. Written, informed consent was obtained from all participants. Ethics Committees approved the studies (CE 2241) and all experimental procedures were performed in accordance with the Declaration of Helsinki. At baseline all patients were assessed by spirometry: static and dynamic lung volumes were measured by a dedicated technician according to the American Toracic Society guidelines (ATS, 2002) collecting Forced Volume Capacity (FVC%) of predicted, Forced Expiratory Volume at 1 s (FEV1%) of predicted, FEV1/FVC ratio and Residual Volume (RV%) of predicted. (Spirolab, Carefusion, Germany). The amount of oxygen and carbon dioxide in the blood at rest was

evaluated by Arterial Blood Gas (ABG) analysis (ABL90 series, Radiometer Medical APS, Denmark). Maximal inspiratory pressure was measured from residual volume via a dedicated manometer (MicroRPM; CareFusion, Basingstoke, UK) and was compared with reference values (ATS; 2002).

Measurements pre- and post-rehabilitation program

Before to start and after the training program, in 3-day time, patients underwent the evaluation listed below.

Functional exercise capacity was assessed using the **6-minute walk test** evaluating distance (6-MWD) (Holland AE, 2014). We asked patients to walk a longer distance they can in 6-minute time in a dedicated 30-meter corridor. The patients could stop during the test for dyspnea or leg discomfort and re-start the walking as soon as possible without the interruption of time counting. A physiotherapist evaluated, before and after the test, the RPE (Rating of Perception) of Dyspnea and Leg Fatigue by Borg scale (Borg E, 2010), and the heart rate and oxygen saturation by a dedicated pulse oximeter (N8500, Nonin Medical, North Plymouth, MN). We evaluated meters walked and percentage of patients that improved above the minimal clinical important difference (MCID) of 30 m (Holland, AE, 2014).

Maximal exercise capacity was evaluated using an incremental cycle ergometer (Ergometrics 900; Ergoline, Bitz, Germany). **Cycloergometer Incremental Exercise Test (CIET)** utilized for the determination of subject's peak work rate capacity defined as Peak Power Output (PPO) (Wpeak). The test was supervised by a senior physiotherapist and a medical doctor. The incremental exercise test was performed on an electromagnetically braked cycle ergometer (Ergoline 800; Sensor Medics, Anaheim CA) with ramp load increments of 10 W min-1 to the limit of tolerance (the point at which the work rate could not be tolerated due to severe sensations of dyspnea and/or leg discomfort) with the patients maintaining a pedaling frequency of 60 rpm. Borg scale (Borg E, 2010) related to the rate of perceived exertion (RPE) of Dyspnea and Leg Fatigue were administered every minute during the test. Pulse oximetry (SpO_2) was collected via a dedicated pulse oximeter (N8500, Nonin). The heart rate and SpO_2 were measured using the R-R interval from a 12-lead online electrocardiogram (Marquette Max; Marquette Hellige, Freiburg, Germany) and a pulse oximeter (Nonin 8600; Nonin Medical,

North Plymouth, MN), respectively. The test was stopped when patient experimented the maximal rate of dyspnea and /or leg muscle discomfort.

The perceived dyspnea was evaluated with the **Barthel Dyspnea Index (BDI)** (Vitacca M, 2020) by an experienced physiotherapist. The total BDI evaluates breathlessness during activities of daily life (ADL) and scores from 0 (no dyspnea) to 100 (maximum level of dyspnea). A decrease in BDI score represents an improvement, whereas an increase in score represents a worsening in symptoms. The Perceived Fatigue evaluation during daily life was determined by Italian version of **Fatigue Severity Scale (FSS)** (Ottonello M, 2016). The questionnaire is self-administered and is composed of 9 items related to the severity of symptoms. Each item consists of a statement about the presence of symptoms over the past week and is rated on a 7-point Likert scale, from 1 (indicating strong disagreement) to 7 (strong agreement). The total score is the mean of the score of the 9 items, yielding a score range between 1 and 7; a higher mean score indicates greater severity of fatigue symptoms. According to the classification proposed by Johansson et al (Johansson S, 2008), patients were classified as severe fatigued if had a FSS > 5 (**SPF group**). We named no-SPF group patients that had less or equal than 5 point of FSS scale at admission.

The **Maugeri Respiratory Failure (MRF) Questionnaire** was used to assess health-related quality of life (Vidotto M, 2007). This 26-item questionnaire scores quality of life and it is dedicated to respiratory patients withCRF. The total score can range from 0 to 26: higher scores indicating worse quality of life.

In addition, we assessed **quadriceps neuromuscular fatigue**: before (∼5 min) and 5 min after a Constant Workload Cycling Test (CWCT, see below) the NMF evaluation was measured as follow. Maximal voluntary and electrically evoked muscle contractions of the quadriceps muscle were measured utilizing a custom-made set- up. Subjects were seated in an upright position with back support and a seat belts was applied to the pelvis to secure the subject to the chair and prevent movement of other parts of the body. The knee was flexed at 90°, and the ankle of the dominant leg was attached, via a strap and a rigid steel bar, to the force transducer (DBBSE- 100kg, A2829; Applied Measurements Limited). The output from the force transducer was amplified (INT2- L, London Electronics Limited,

Sandy Bedfordshire, United Kingdom) and recorded with a PowerLab-16/35 data acquisition system (ADI Instruments). Electrical stimuli were delivered after positioning self- adhesive electrodes (50×90mm, MyoTrode PLUS, Globus G0465) with the cathode positioned over the femoral triangle, 3- 5 cm below the inguinal ligament, and the anode placed over the posterior iliac crest. Each test procedure began with the determination of the maximal M-wave and potentiated Resting Quadriceps Twitch (Qtwpot) responses in the resting quadriceps muscle. Briefly, the current intensity was progressively increased (+20mA each time) from 25mA to the value beyond which there was no further increase in M-wave peak- to- peak amplitude and resting quadriceps twitch. The 125% of the intensity was chosen to evoke the individual maximal M-wave response. The Qtwpot was evoked in the resting muscle using electrical stimulation consisting of single square-wave pulses of 1 ms duration at 350V, delivered by a constant current stimulator (Digitimer mod.DS7HA, Digitimer Lmd, UK). Before starting the trial, each subject was instructed on how to perform the trial correctly. The Qtwpot was evoked 2-second after a 5-second Maximal Voluntary Contraction (MVC) of the quadriceps, and this procedure was repeated 6 times. Hence, it should be noted that Qtwpot was assessed in the potentiated state. The interval between the MVCs was 30s. Peak torque was evaluated for each MVC and Qtwpot. Voluntary Muscle Activation (MVA) of the quadriceps muscle during the MVCs was assessed using the superimposed twitch technique. The force produced during a single twitch superimposed on the MVC was compared with the force produced by the electrically evoked twitch produced, at rest, 2s after the MVC. The pre to post exercise difference in Qtwpot was labeled as quadriceps peripheral NMF (QNMF) exercise-induced locomotor muscle fatigue when >15% reduction (19) **(QNMF group).** Surface electrodes were used to record M-wave properties of the right vastus lateralis and rectus femoris.

Fatiguing task: Constant Workload Cycling Test (CWCT) executed at 80% of the peak of power output determined during the incremental exercise test was used to induce NMF. The test was performed on an electromagnetically braked cycle ergometer (Ergoline 800, Sensor Medics, Anaheim, CA) and the time to exhaustion (Tlim) was recorded in seconds. Patients were instructed to exercise for as long as possible, with continues verbal encouragements. Exercise terminated when dyspnea

became intolerable or the required pedaling rate (60/min) was not achieved for more than 10 s. Dyspnea and leg RPE were recorded every 60 s using the modified Borg scale (17) ranging from 0 to 10 points. The heart rate was measured using the R-R interval from a 12-lead online electrocardiogram (Marquette Max; Marquette Hellige, Freiburg, Germany) and oxygen saturation by a pulse oximeter (Nonin 8600; Nonin Medical, North Plymouth, MN), while blood pressure was measured each minute by a sphygmomanometer and the Mean Arterial Pressure (MAP) was calculated as systolic pressure + diastolic pressure / 2.

At the end of the rehabilitative program the CWCT was repeated twice: the first test at the same time reached at the beginning (iso-time) in order to evaluate differences on NMF, and the second one asking the patient to reach the exhaustion in order to evaluate the Tlim (time to exhaustion) .

Comprehensive Pulmonary Rehabilitation Program

Patients were enrolled in a comprehensive and multi-professional rehabilitation program. The health professionals involved were pulmonologists, physiotherapist, nurses, phycologists, and nutritionists. All interventions are personalized and tailored on patients' need. Regarding to the physiotherapy intervention: all patients performed exercise training consisting of 20 supervised cycle-ergometer sessions (6 sessions/week) lasting 30 minutes each one, according to ATS/ERS guidelines (Radtke T, 2006). Initial workload was 60% of the PPO evaluated during CIET. Increases or reductions by 10 W in intensity were performed according to Maltais et al. protocol (Maltais F,1997). The workload was increased the session after when patients scored their dyspnea and/or leg fatigue as <5 on a modified 10-point Borg Scale of Perceived Exertion at the end of exercise session. (Borg E, 2010). The workload was unchanged if the Borg score was 5 or 6 and was reduced by 10 watts for scores >6. (Maltais F,1997). Patients were asked to maintain a cycling rate between 50 and 60 rate per minute. Patients performed sessions with oxygen through a nasal cannula and the change of oxygen flow was allowed in case of patients showing SpO_2 values <92%, and it was delivered at a flow sufficient to maintain an SpO_2 value >92%. All exercises sessions were supervised by a trained physiotherapist, blinded about assessment measures. Medication was optimized before starting the training program and any changes were recorded during the

study period. An educational program was implemented, trough group lessons, performed by different health professionals, in order to describe healthy lifestyle, bronchial hygiene technique, correct drugs administration and COPD related psychological issues.

Statistical analysis

All statistical analyses were performed with STATA 11.2 software (Stata, College Station, TX). Data are expressed as mean ± standard deviation for continuous variables and as percentage for categorical or binary ones. Pre-to-post changes was evaluated using paired t-test. Between-group differences were evaluated using unpaired t-test. Differences between groups during time were evaluated using repeated measures two-way ANOVA. Chi-squared tests was used to compare proportions. Pearson correlation coefficients were used to evaluate relationships between variables. The level of significance was 0.05 for all statistical tests.

RESULTS (Project 3)

This report describes the first 32 enrolled patients in this ongoing study, between June 2020 and October 2021.

Baseline characteristics are reported in **table 1.**

Table 1 (Project 3): Baseline characteristics of 32 enrolled patients.

MALE, n (%)	21 (66)
AGE, years	65.9 ± 8.4
BMI, kg/m^2	24.3 ± 5.6
FEV1, % , prd	31.6 ± 14.5
FVC, % prd	65.9 ± 15.6
FEV1/FVC, ratio	36.4 ± 11.2
RV, % prd	205.9±58.7
PAO_2/FIO2, ratio	285.6 ± 45.6
$PACO_2$, mmhg	44.5 ± 7.7
PH	7.421 ± 0.031
CIRS, score	1.7 ± 0.4
MIP, cmh20	58.7 ± 19.6
MEP, cmh20	87.6 ± 34.7
BARTHEL DYSPNOEA, score	26.9 ± 16.9
MRF, score	12.4 ± 7.0
FSS, score	4.6 ± 1.7
6MWD, meters	311.1 ± 89.0
6MWD, % prd	
PPO, watts	50.9 ± 17.3
CWCT, seconds	262.2 ± 165.7
MVC, newton	269.2± 82.9
QTW_{POT}, newton	52.7 ± 47.6

Legend: Body mass index: BMI; cumulative illness rating scale: CIRS; arterial oxygen partial pressure: PaO2; arterial carbon dioxide partial pressure: PaCO2; forced expiratory volume at first second: FEV1; forced vital capacity: FVC; Residual Volume : RV; Maximal Inspiratory pressure: MIP; Maximal Expiratory pressure : MEP; MRF : Maugeri Respiratory failure questionnaire; FSS: fatigue severity Scale ; 6MWD: 6-minute walking distance; m: meters, PRD: predicted; PPO: Peak Power Output; CWCT: Constant Workload Cycling Test; MVC: Maximal voluntary Contraction; Qtwpot: potentiated Resting Quadriceps Twitch.

Patients are mainly male, with severe lung obstruction and severe hyperinflation. They evidenced a moderate reduction of inspiratory muscles and sensible level of dyspnea and perceived fatigue in activity of daily life.

No significant differences were found in baseline characteristics between QNMF group and no-QNMF group, while SPF group had worse Tiffenau Index, higher dyspnea, and worsen quality of life in comparison to patient without baseline severe perception of fatigue **(table 2).**

At the beginning, exercise induced-reduction in MVC and Qtwpot were 8.34±7.51% (P<0.001) and 15.86±17.89 % (P<0.001) respectively, while MVA% remained unvaried -3.13±17.47 (P = 0.3186). The Fraction of Inspirited Oxygen (FiO2%) during exercise at the start of training program was 33.5±5.81%.

Training effect

After PR program, the whole group showed a significant improvement in PF [FSS score of - 0.67 ± 1.36] (P= 0.0131) , 6MWD + 557.9 ± 574.7 meters (P< 0.001) , maximal exercise capacity [PPO of +5.6 ± 10.8 watts (P< 0.001)], dyspnea [BDI score of -7.01 ±9.97 (P< 0.001)], and quality of life [MRF questionnaire of -2.1 ± 3.1 (P< 0.001)] . No significant improvement was found in peripheral muscle strength.

Table 2 and **Table 3** describe clinical and functional measures before and after PR program according to the presence of baseline presence of severe PF and peripheral quadriceps NMF, respectively.

Table 2 (Project 3): Baseline characteristics and outcome measures before and after PR program, according to baseline presence of severe PF.

	QNMF PRE (16)	NO QNMF PRE (16)	P	QNMF POST	NO QNMF POST	P
Male, n (%)	9 (56)	12 (75)	0.264			
Age, years	64.38 ± 9.10	67.38 ± 7.73	0.3228			
BMI, kg/m^2	24.42 ± 4.73	24.21 ± 6.43	0.9154			
FEV1, % prd	27.56 ± 13.35	36.63 ± 14.82	0.4248			
FVC, % prd	63.63 ± 18.42	68.13 ± 12.47	0.0641			
FEV1/FVC	32.75 ± 7.99	40.02 ± 12.86	**0.0117**			
$PaO_{2,\ mmHg}$	68.49 ± 8.87	59.49 ± 10.07	0.1098			
$PaCO_{2,}$ mmHg	46.71 ± 9.38	42.36 ± 4.85	0.3348			
pH	7.415 ± 0.026	7.426 ± 0.035	0.5700			
CIRS1, score	1.76 ± 0.49	1.68 ± 0.28	0.3853			
CIRS2, score	3.25 ± 2.38	2.63 ± 1.54	0.7262			
MIP, cmH2O	60.08 ± 20.28	57.36 ± 19.61	0.2593			
MEP, cmH2O	95.54 ± 41.15	80.21 ± 26.86	0.0603			
Barthel Dyspnoea, score	32.80 ± 19.31	21.44 ± 12.54	**0.0009**	25.20 ± 17.98	14.44 ± 12.52	0.0616
MRF, score	16.40 ± 5.55	8.63 ± 6.13	**0.000**	13.73 ± 6.12	7.13 ± 6.05	0.0060
FSS, score	6.08 ± 0.67	3.28 ± 1.11	0.2437	4.40 ± 1.40	3.47 ± 1.39	0.0828
6MWD, m	292.5 ± 79.98	329.69 ± 96.19	0.0504	340.19 ± 74.33	375.13 ± 103.05	0.2801
PPO, Watts	45.00 ± 13.17	56.88 ± 19.22	0.2219	51.86 ± 11.09	61.25 ± 19.96	0.1109
CWRT (Tlim), s	225.94 ± 150.42	298.38 ± 177.04	0.2219	705.13 ± 516.17	935.06 ± 756.17	0.3231
Leg fatigue RPE						
Incremental exercise	6.44 ± 2.66	7.19 ± 2.07	0.3805	5.31 ± 3.11	6.50 ± 2.42	0.887
Endurance exercise	6.63 ± 2.68	6.44 ± 2.66	0.8438	5.19 ± 2.93	4.94 ± 2.67	0.8024
Dyspnoea RPE						
Incremental exercise	7.38 ± 1.96	7.13 ± 1.86	0.7139	7.81 ± 0.66	7.19 ± 2.40	0.3231
Endurance exercise	8.00 ± 0.52	7.56 ± 1.55	0.2921	6.63 ± 2.63	6.50 ± 2.28	0.2380
MVC, kg	27.02 ± 9.16	28.60 ± 7.72	0.6015	27.48 ± 9.16	28.60 ± 7.22	0.7045
Qtwpot, kg	5.11 ± 5.71	5.64 ± 3.99	0.7626	4.68 ± 3.51	6.37 ± 4.50	0.2761

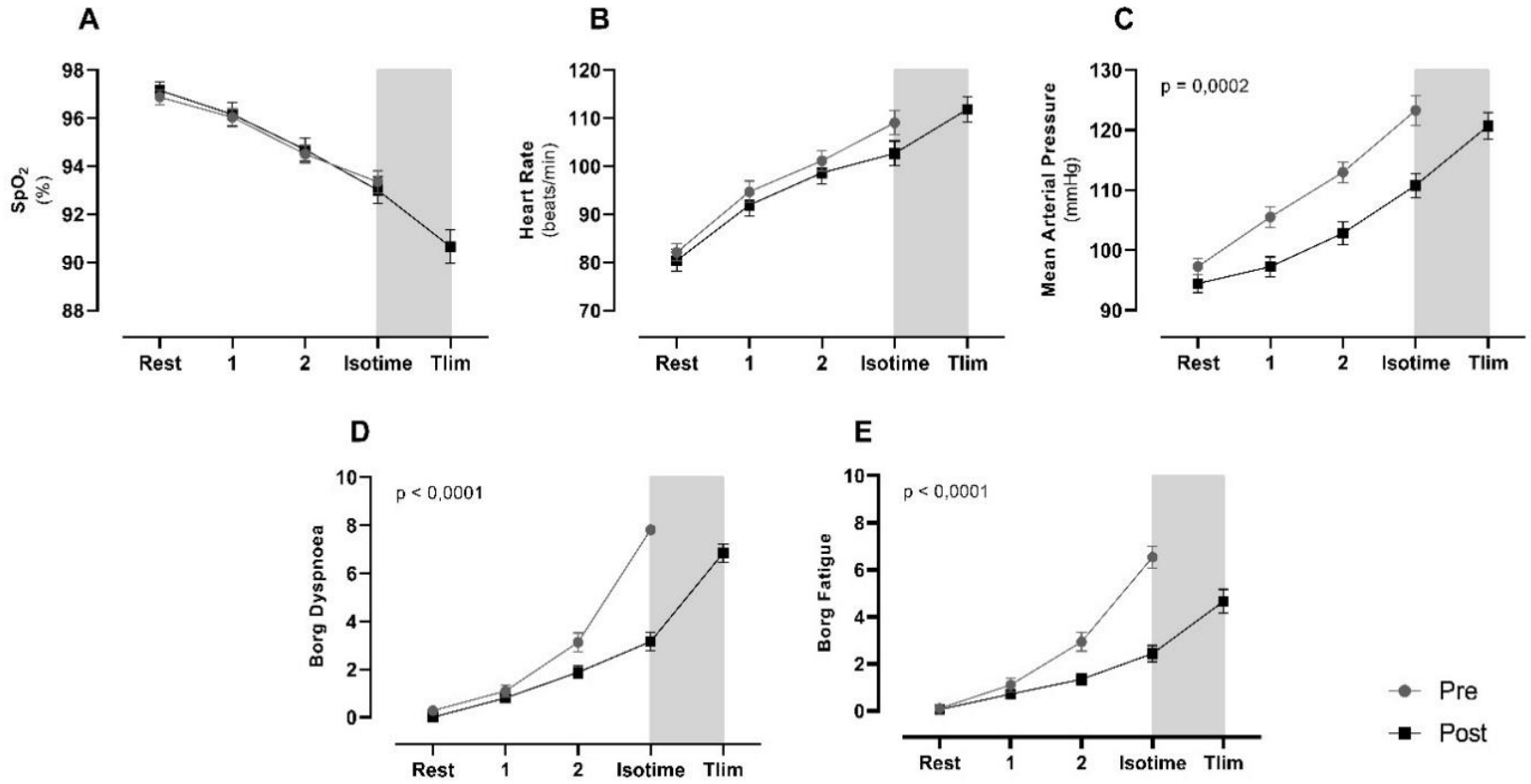
Legend: Body mass index: BMI; cumulative illness rating scale: CIRS; arterial oxygen partial pressure: PaO2; arterial carbon dioxide partial pressure: PaCO2; forced expiratory volume at first second: FEV1; forced vital capacity: FVC; Residual Volume : RV; Maximal Inspiratory pressure: MIP; Maximal Expiratory pressure : MEP; MRF : Maugeri Respiratory failure questionnaire; FSS: fatigue severity Scale ; 6MWD: 6-minute walking distance; m: meters, PRD: predicted; PPO: Peak Power Output; CWCT: Constant Workload Cycling Test; MVC: Maximal voluntary Contraction; Qtwpot: potentiated Resting Quadriceps Twitch.

Table 3 (Project 3): Baseline characteristics and outcome measures before and after the PR program, according to baseline presence of NMF .

	QNMF PRE (12)	NO QNMF PRE (20)	P	QNMF POST	NO QNMF POST	P
Male, n (%)	8 (67)	13 (65)	0.923			
Age, years	65.17 ± 10.07	66.30 ± 7.55	0.7196			
BMI, kg/m^2	22.71 ± 4.24	25.28 ± 6.11	0.2108			
FEV1, % prd	29.92 ± 10.93	32.60 ± 16.42	0.6195			
FVC, % prd	62.25 ± 17.39	68.05 ± 14.51	0.3177			
FEV1/FVC	36.43 ± 7.05	36.36 ± 13.21	0.9854			
$PaO_{2,\ mmHg}$	63.46 ± 9.93	64.31 ± 10.90	0.8267			
$PaCO_{2,}$ mmHg	44.33 ± 9.39	44.66 ± 6.70	0.9094			
pH	7.429 ± 0.029	7.416 ± 0.032	0.2297			
CIRS1, score	1.63 ± 0.33	1.78 ± 0.43	0.3380			
CIRS2, score	2.42 ± 1.62	3.25 ± 2.17	0.2603			
MIP, cmH2O	62.67 ± 21.53	56.67 ± 18.88	0.4641			
MEP, cmH2O	81.44 ± 37.89	90.67 ± 33.68	0.5255			
Barthel Dyspnoea, score	31.00 ± 16.65	24.37 ± 17.01	0.2953	21.83 ± 18.30	18.26 ± 14.90	0.5565
MRF, score	13.75 ± 7.41	11.53 ± 6.76	0.3970	11.17 ± 8.09	9.94 ± 6.10	0.6407
FSS, score	4.86 ± 1.59	4.49 ± 1.78	0.5548	3.87 ± 1.47	3.95 ± 1.48	0.8779
6MWD, m	278.75 ± 76.19	330.50 ± 92.29	0.1127	350.42 ± 77.42	362.00 ± 96.67	0.7311
PPO, Watts	48.33 ± 16.97	52.50 ± 17.73	0.0504	55.83 ± 20.21	57.00 ± 14.55	0.8508
CWRT (Tlim), s	279.58 ± 199.82	251.70 ± 146.26	0.6225	743.83 ± 615.55	865.85 ± 677.33	0.6139
Leg fatigue RPE						
Incremental exercise	7.00 ± 2.45	6.70 ± 2.39	0.7355	6.67 ± 2.31	5.45 ± 3.03	0.2418
Endurance exercise	6.92 ± 2.61	6.30 ± 2.68	0.5292	5.42 ± 2.23	4.85 ± 3.07	0.5821
Dyspnoea RPE						
Incremental exercise	7.25 ± 1.96	7.25 ± 1.89	0.999	7.33 ± 1.83	7.60 ± 1.76	0.6852
Endurance exercise	8.08 ± 0.67	7.60 ± 1.35	0.2591	6.33 ± 2.39	6.70 ± 2.49	0.6855
MVC, kg	27.45 ± 9.78	28.03 ± 7.67	0.8534	27.16 ± 7.96	28.57 ± 8.39	0.6427
Qtwpot, kg	5.46 ± 3.68	5.33 ± 5.34	0.9434	4.79 ± 3.44	6.08 ± 4.49	0.4165

Legend: Body mass index: BMI; cumulative illness rating scale: CIRS; arterial oxygen partial pressure: PaO2; arterial carbon dioxide partial pressure: PaCO2; forced expiratory volume at first second: FEV1; forced vital capacity: FVC; Residual Volume : RV; Maximal Inspiratory pressure: MIP; Maximal Expiratory pressure : MEP; MRF : Maugeri Respiratory failure questionnaire; FSS: fatigue severity Scale ; 6MWD: 6-minute walking distance; m: meters, PRD: predicted; PPO: Peak Power Output; CWCT: Constant Workload Cycling Test; MVC: Maximal voluntary Contraction; Qtwpot: potentiated Resting Quadriceps Twitch.

Figure 3 (Project 3).:Pre-to-post Constant Workload Cycling Test responses



Legend: SpO2: Oxygen saturation; Tlim: time to exhaustion; mmHg: millimeter of mercury; RPE : rate od perception.

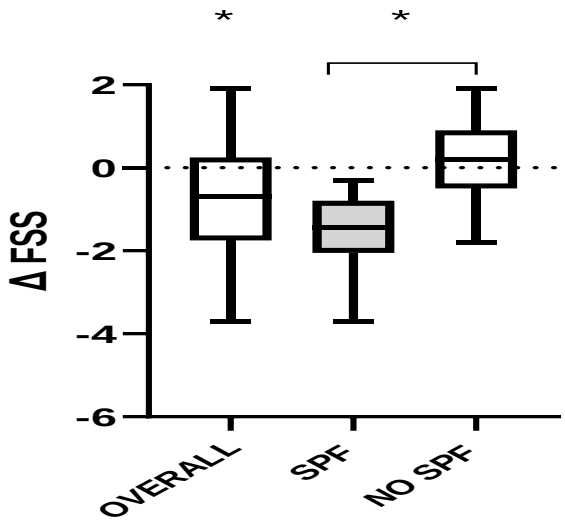
The **figure 3** describes the pre-to-post responses during CWRT regarding RPE of dyspnea and fatigue, as well as SpO2 , heart rate and Mean Arterial Pressure (MAP) due to PR. We can see, at iso-work, a huge and significant reduction of RPE of dyspnea (P< 0.001) and fatigue (P< 0.001), and blood pressure (P< 0.001).

The grade of oxygen desaturation was the same al well as the heart rate increase. No significant differences of changes in all variables between QNMF / no QNMF gropus and between SPF /no SPF groups were found.

Changes in PF

The decrease of PF (delta FFS score : -0.67 ± 1.36) was significant in the overall group, and it was larger in SPF group compared to those who did not [P < 0,001)] **(figure 4)** .

Figure 4 (Project 3): Changes of Perceived Fatigue after PR, according to baseline condition



Legend: FSS: Fatigue Severity Scale, SPF: Severe Perceived Fatigue group; NO SPF = no severe perceived fatigue group**.** * = P< 0.005

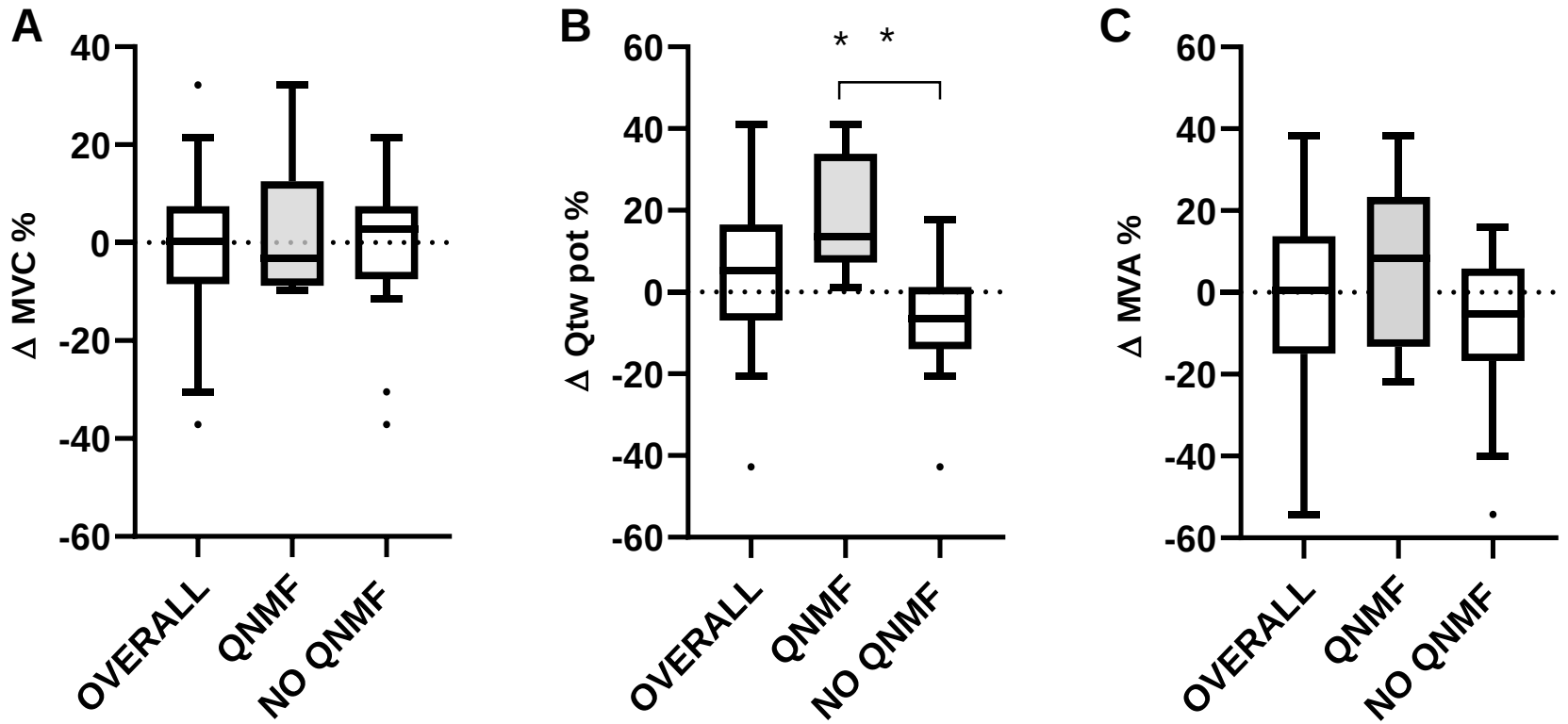
Changes in NMF

Not significant changes in NMF, both in central and peripheral components, were found after PR at iso-work (CWRT at isotime) in the overall group : the variation in ΔMVC was +0.08±13,3 % (P= 0.9725), in ΔQtwpot was +4.35±18.94% (P= 0.2353) and in ΔMVA % was +1.23±20.01% (P=0.7479).

Nevertheless, only QNMF group improved peripheral fatigue over time (P<0,001), and in a larger magnitude compared to no-QNMF group [ΔQtwpot 18.93±14.01 % versus -6.59±14.28 %; p>0.001]. No significant differences were found between the two group in relation to ΔMVC (2.03±13.67 % versus -1.08±13.97 %; p>0.5440) and ΔMVA % (6.93±18.97 % versus -7.34±19.09 %; p=0.0605) **(Figure 5).**

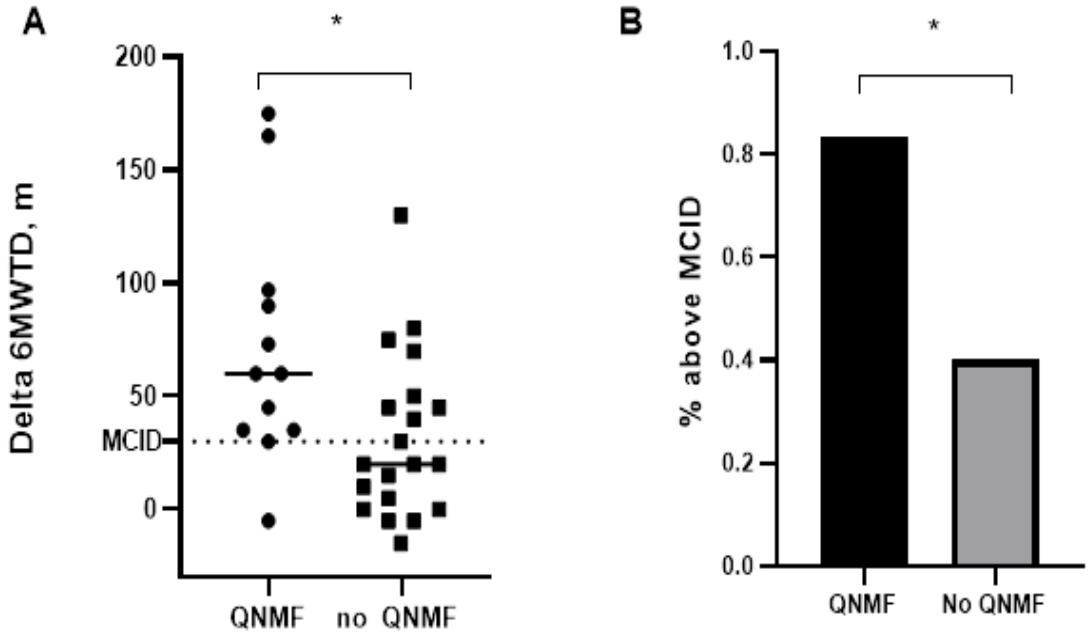
The increase in 6MWD was significantly larger in the QNMF group compared to those who were not fatigued at baseline. 83,3 % of QNMF group showed an improvement in 6MWD exceeding the proposed minimal clinically important difference (MCID) of 30 meters (Holland, 2014) compared with 40 % of no-QNMF group [OR 2.01 (0.25-3.78), P=0.013] **(figure 6).**

Figure 5 (Project 3): Changes in Neuromuscolar Fatigue after PR, according to baseline condition



Legend: QNMF : quadriceps peripheral neuromuscolar Fatigue. MVC: Maximal voluntary Contraction; Qtwpot: potentiated Resting Quadriceps Twitch; MVA%: Rate of Maximal Voluntary Activation. * = P< 0.005

Figure 6 (Project 3): Changes of 6MWT according to the presence of QNMF.



Legend: 6MWTD: 6-minute walking test distance; m: meters; MCID: minimal clinical important difference; % : percentage; QNMF :peripheral Neuromuscolar fatigue. . * = P< 0.001

Correlations

Any relationship was found between changes in PF and NMF (ΔFSS vs change Δ MVC R= 0.2114, P=0.2710; ΔFSS vs change Δ Qtwpot R=-0.3003; P=0.1447; ΔFSS vs change Δ MVA% R=-0.2379; P= 0.2521).

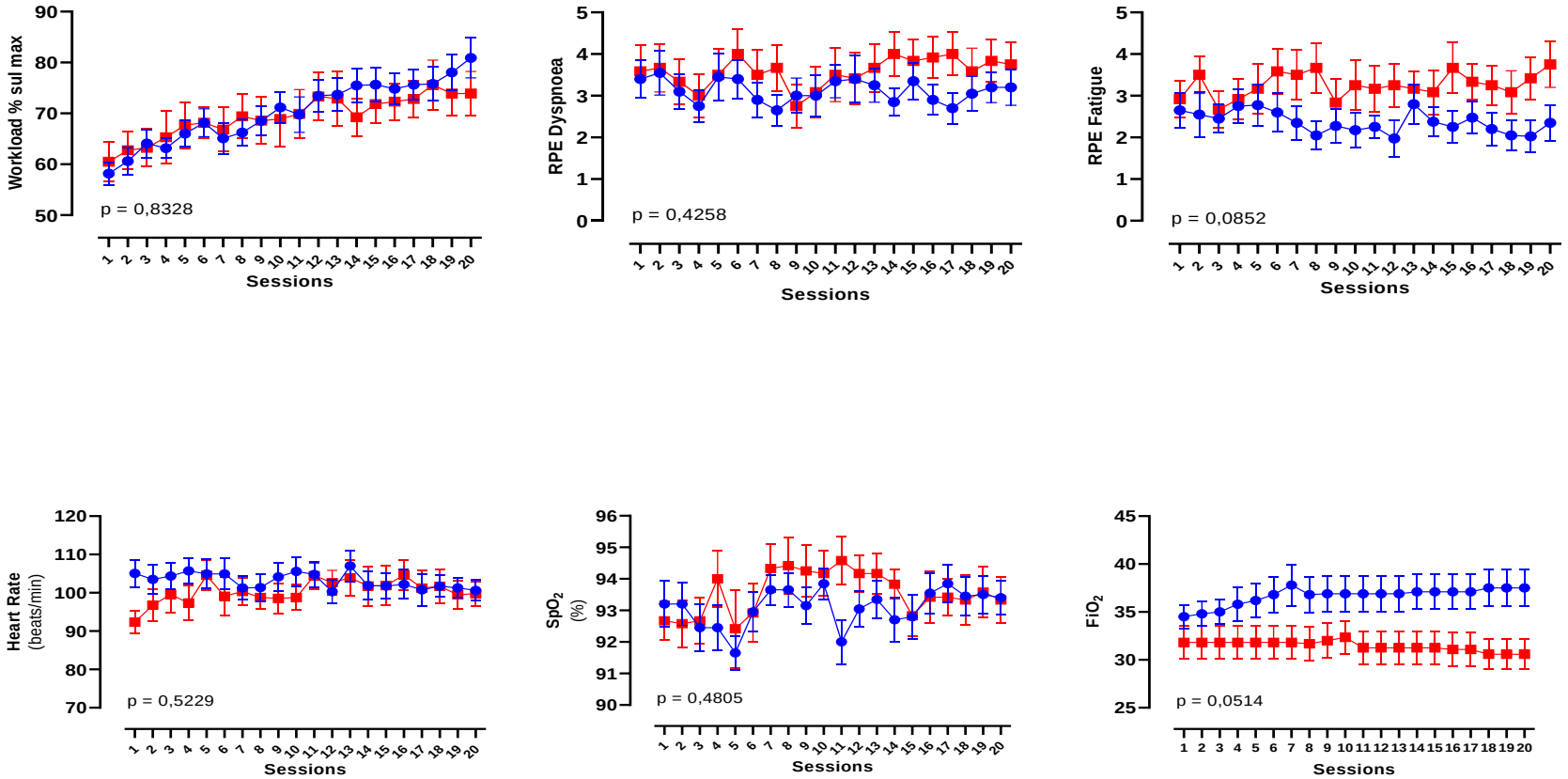
Training course

The mean initial training workload in the overall group was 30.09±11.84 watts (59.03±11.32 % of PPO) and the final was 39.91±16.55 watts (78.28±16.82 % of PPO) (P< 0.001). 37.5% of patients were trained by continuous training, while 63.5 % with interval training modality.

The day-by-day trend of modification of percentage of workload / PPO, rate of perception of dyspnea and fatigue, heart rate, oxygen saturation and FiO2 according to the baseline presence of QNMF are describe in **figure 7**. The trend of increment of workload, as well as heart rate, oxygen saturation and RPE of dyspnea. was similar between QNMF and no QNMF groups. There was a tendency to have higher RPE of fatigue and a significant lower need of increase of oxygen flow in QNMF compared to no QNMF group.

No difference of trend for all the variables described was found between SPF and no-SPF grou

Figure 7 (Project 3). Sessions-by-session trend of exercise training.



Legend: blue line: QNMF group; red line: no QNMF group.

DISCUSSION (Project 3)

This study describes the high prevalence of both PF and NMF in COPF-CRF patients attending a PR program and confirm the beneficial effect of PR in reducing perceived fatigue and dyspnea, and in improving exercise tolerance and quality of life. No change in NMF was detected in the general group, however only patients who initially had peripheral NMF improved it and had a double improvement of 6MWT compared to those who did not. This subset of patients appears to have less need of increase oxygen therapy during training progression. PF improved most in patients with severe PF at baseline, while no correlation was found between PF and NMF changes suggesting a mismatch between symptoms and the objective physiological component of fatigue.

PR effect

A recent metanalysis including 10 RCT studies describes the ability of exercise training to improve perceived fatigue, exercise tolerance and health-related quality of life in patients with very severe COPD although a huge variability in the outcome measures used has been found (Paneroni M, 2017): in this metanalysis only half of the included patients had already developed CRF. Our study on COPD-CRF patients confirms and reinforce the beneficial effect of PR in improving several outcome measures as dyspnea, fatigue, effort tolerance and quality of life after a short-term inpatient PR attempt. This results confirm a previous large cohort study of our network where COPD patients with and without CRF improved equally several outcomes (Carone M, 2007), including fatigue.

In addition, it is remarkably to note we found the absence of improvement in peripheral muscle strength. This results can be referred of the specificity of training: (Ketelhut S, 2020; Liao WH, 2015) in fact, we propose only endurance aerobic reconditioning training.

Another very important aspect is the great improvement in CRWT at iso-work after rehabilitation **(figure 3)** in terms of RPE of dyspnea and fatigue, as well as in the reduction of mean arterial pressure. Casaburi et al. (Casaburi R, 1991) using a constant load test, described the lowering of exercise-induced lactic acidosis

and ventilation at iso-work as a result of physical training in patients with COPD without exercise induced desaturation. Although we did not evaluate the reduction in respiratory capacity (CI) and ventilation, we are confident that the reduction in RPE of dyspnoea and muscle fatigue was closely related to the expected decrease in lactic acidosis and, consequently, of ventilation and hyperinflation. Our study is the first to highlight this finding in COPD-CRF.

Fatigue perception modification

Our report describes that half of patients COPD-CRF admitted for an in-patients PR program had severe PF. Literature data are quite controversial: in less severe population (mean FEV1 %: 41-45 %), Baltzan at al. (Baltzan MA, 2011). describes the presence of severe fatigue in about 40% of patients included in a PR program, while Van Herck et al. (Van Herck M, 2019) in about 70%. However, they have used other fatigue questionnaires (SF-36 viability domain and CIS-fatigue questionnaire) with different cut-off theshold: this fact could over or underestimating the final data interpretation. Regarding the improvement after rehabilitation, our results describe a significant PF improvement on the overall population and a reduction in patients with severe subjective perception of fatigue from 50% to 37.5%. In a recent meta-analysis, Paneroni et al. (Paneroni M,.2020) reports benefits of PR with regard to PF symptoms. The metanalysis concluded on a positive impact of different exercise training programs on perceived fatigue in the general COPD population. Only two studies (82 patients) (McNamara RJ, 2013; Wadell K, 2013) evaluated perceived fatigue using the Fatigue Severity Scale: the intervention group improved significantly more than the control group being the Standard Mean Difference - 2.29 points . Our FSS change was less impressive despite similar baseline conditions. Otherwise, our PR duration was shorter (4 weeks vs 8 weeks) and our population was more severe being difficult to compare the two populations.

In addition, Balzan's and Van Herck's studies (Balzan MA, 2011) described that patients with higher fatigue at baseline experienced greater improvements, and our results described the same phenomenon. At the best of our knowledge, this study is the first describing this result in COPD-CRF patients.

NMF modification

Although some papers document the presence of NMF in COPD patients (Marillier M, 2021), at the moment only 2 cohort studies evaluated the rate of NMF in rehabilitative setting. Mador et al. described the presence of significant peripheral NMF in approximately 60% of COPD patients after high-intensity constant load exercise, while Burtin et al. found the same amount of impairment after an exercise session. The rate of peripheral NMF in our sample is lower, being about 40% before rehabilitation. One possible explanation is that our group of patients is more severe (FEV1 30% vs 45%) and thus may stop exercising due to ventilatory limitations before they can overload their muscles being exercised. This fact might be suggested by the increase in pulmonary obstruction and by static hyperinflation at baseline, but we have no data on ventilatory limitation ($\dot{V}E/MVV$ ratio) and decrease in inspiratory capacity during exertion, so this hypothesis may be only speculative.

The abovementioned studies described only change in MVC and Qtwpot after fatiguing task, but they did not evaluate central component of NMF by the changes in MVA%. Our study, being the first evaluating this aspect, highlights the major involvement of peripheral component of fatigue (higher rate of decrease) respect to the central one.

According to our results other studies in COPD patients, by using the twitch interpolated method, have failed to observe an activation deficit in COPD during maximal voluntary contractions (Alexandre F, 2014; Alexandre F , 2020).

At present, these aspects remain controversial, and further studies are needed to better evaluate this subject. In addition, we evaluated the absence of a significant change of NMF after rehabilitation in the overall group. At present, we have not found any study about COPD describing the change in NMF after PR by using a CWRT at iso-work (iso-time of constant load exercise) as fatiguing task. Our results are only partially in line with the literature on healthy people. Zghal at al. describes that, after an endurance training, the adaptation principally translates into improved tolerance of peripheral neuromuscular fatigue, while central fatigue only partially adapts to this kind of training (Zghal F, 2015). Interestingly, the only patients who

improved peripheral NMF (delta Qtwpot) were those who were fatigued at baseline, establishing a close inverse relationship between baseline delta Qtwpot and its improvement (R = -0.5380, P = 0.0031). Notably, the same patients had a more pronounced (approximately double) 6-MWT improvement than the group without QNMF. Our results are strictly in line with Mador and Burtin's studies regards on 6-MWT improvement (Burtin C , 2012; Mador MJ, 2014).

The link between peripheral NMF and 6-MWT changes in the QNMF group has never evaluated before and may suggest the implication of NMF on effort intolerance in this subgroup of patients.

Unfortunately, we have not measured the ventilatory parameters during exercise and we do not know if this aspect can be related to the modification of muscle fibers or to the improvement of other aspects that may be involved in the development of peripheral muscle fatigue (e.g. system activity, response of vasodilation, etc ...). Another aspect that can be difficult to explain is the different response between 6MWT and other functional exercise tests. In contrast with the results on 6MWD, we did not found significant difference in PPO and CWRT outcomes between patient with peripheral QNMF at baseline and who did not. Principally, the 6-MWT differs to the others because it is submaximal and because patients walk. Literature data describes that during cycling COPD patient have an higher Pao_2 minimizing the magnitude of oxyhemoglobin desaturation compared with walking, and that the reduced walking capacity is associated with an excessively high ventilatory demand (Mahler DA, 2011; Palange P, 2000).
This fact describes that the wider improvement of the QNMF in terms of exercise tolerance is most evident during tasks of higher ventilatory demand that involve more muscle mass. Relating to the training session-by-session trend, we found it similar between the QNMF group and the non-QNMF group, and out report is similar to those highlighted by Burtin's at al (Burtin , 2012). The only difference we found between groups was the need for higher oxygen flow in non-fatigued patients. The explanation for this finding remains only speculative and could be related to different muscle characteristics or mitochondrial function, autonomic responses or pulmonary exchange impairment between the two groups.
Individuals with COPD during cicling have been described to have a mismatch

between muscle oxygen delivery and utilization, characterized by more rapid increases in vastus lateralis (VL) deoxygenated hemoglobin; lower increases in total hemoglobin (tHb) and blood flow; and lower muscle tissue saturation (StO_2). Different peripheral muscle phenotypes could be implicated in fatigue development (Miles M, 2021).

Clinical implications

The present study highlights some relevant clinical implications: first, it describes the mismatch between the perception of fatigue and the objective neuromuscular fatigue, both at baseline and with regard to the change obtained after rehabilitation. Second, it shows that patients who exhibit severe perceived fatigue and neuromuscular fatigue at baseline are more likely to improve their impairment than the general population. These elements support the fact that both areas need to be evaluated and these assessments are not interchangeable. Another important aspect concerns the possibility of making the measurement of neuromuscular fatigue more usable in clinical setting, being it a predictive index for 6MWT improvement and because it can give important information on peripheral muscle function. Future studies will also have to verify whether different training methods can give different results.

Limitations

This study suffers from important limitations: first of all the sample is small and the analyzes will have to be confirmed at the end of the study. Secondly, we do not have an untreated control group that could confirm the efficacy of intervention. Another important limitation is the lack of metabolic data and gases exchange evaluations during the CWCT because they could have provided important elements regarding the genesis of NMF. Finally, our study represents a real-life study and the therapeutic dosage of oxygen during exercise was carried out in order to maintaining an oxygen saturation greater than 92%. We do not exclude that the administration of oxygen with different reference targets would have given different results.

CONCLUSIONS (Project 3)

COPD-CRF patients present high prevalence of both PF and NMF while PR is able to reduce PF, improving exercise tolerance and quality of life. Patients with baseline

PF and peripheral NMF improved them and who had peripheral NMF had a double improvement of 6MWT compared to those who did not. In this population, a clear mismatch between the perception of fatigue and the objective neuromuscular fatigue, both at baseline and with regard to the change obtained after rehabilitation is evident and a specific assessment is mandatory.

5.CONCLUSIONS

In conclusion of this PhD work, I can summarize the following key points:

- Severe COPD patients with CRF on LTOT develop higher levels of perceived fatigue and dyspnea than COPD patients without CRF, while the extent of neuromuscular fatigue is similar in both groups.
- Pulmonary rehabilitation, including exercise training, can reduce PF, improving exercise tolerance and quality of life in COPD with CRF.
- Patients with baseline severe PF and peripheral NMF improved after rehabilitation more than not fatigued patients. Patient with peripheral NMF at baseline had a double improvement of 6MWT compared to those who did not.
- A clear mismatch between the perception of fatigue and the objective neuromuscular fatigue at baseline and regarding the change obtained after rehabilitation is evident. A better knowledge of the determinants of fatigue will permit to design new individualized strategies with the aim to increase acute muscle loading during a given exercise training session and counteract the negative influences of fatigue on daily life.
- A specific assessment for both aspects of fatigue should be mandatory in clinical and rehabilitative setting.
- Further studies following this PhD work about tailored interventions are needed.

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