RESPIRATORY MUSCLE ENDURANCE TRAINING IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

INFLUENCE ON DAILY VOLUNTARY PHYSICAL ACTIVITY, DYSPNOEA AND PHYSICAL WORKING CAPACITY.

Dissertação apresentada com vista à obtenção do grau de mestre em Atividade Física e Saúde, da Faculdade de Desporto da Universidade do Porto ao abrigo do Decreto de Lei nº.74/2006 de 24 de Março, orientada pelo Professor Doutor José Alberto Ramos Duarte.

Ivo Neto Silva

Porto, 2013

Neto Silva, I. (2013). **Respiratory muscle endurance training in chronic obstructive pulmonary disease: influence on daily voluntary physical activity, dyspnoea and physical working capacity.**

Dissertação de Mestrado em Atividade Física e Saúde. Faculdade de Desporto da Universidade do Porto, Porto.

Key Words: COPD; skeletal muscle dysfunction; symptoms; inspiratory muscle training; expiratory muscle training.

To my family

To my one of a kind Daniela,

for her love, support, strength and motivation

Acknowledgments

Since my undergraduate education, passion and curiosity about respiratory diseases have rising up inside of me. This never stepped out of my head. I invested in continuous formation on this field since that time. Along with a work which gave me the pleasure of experience and deal with respiratory patients, two years ago I define for myself the academic goal of enter in a master degree related with exercise and health, to try direct it to the respiratory disease field and formulate a hypothesis for my thesis where in some way I could improve quality of life to respiratory patients. Now here I am… with one more stage of my own academic maturation accomplished. These two years have never been easy, with a great amount of night with few sleepy hours in order to give an adequate response to work and academic obligations. Despite I put all my efforts into this journey and sometimes a certain overcoming spirit, I could not forget the people who help me, support me and challenge me.

First, I would like to thank Professor José Alberto Ramos Duarte for his guidance, patience and wise advices. It was an honor to be oriented by him. In fact, and for the first time I say this, he was one of the biggest reasons for me to enter this specific master degree due to a magnificent experience with his classes in my undergraduate formation. In my mind was always present that if you want to be good, you need to be near the very best minds. It was a very big pleasure Professor!

To Dra. Maria José Guimarães, Dra. Célia Durães and Dra. Daniela Ferreira for their advices and patience. Without their clinical collaboration this project could never have lived. Three friends and true references for me. I hope this connection never ends. From all my heart, I'm thankful for the rest of my life.

Also I would like to thank, Dra. Maria Manuel Figueiredo for her support, understanding and for being an admirable leader; Dr. António Santos Costa for his readiness to help; and to all Pneumology department from the Alto Ave Hospital Center in Guimarães which always receive me with open arms.

A very big acknowledgement to all patients who integrated this research. Only with their availability, self-sacrifice spirit and will to collaborate, this project could proceed. Also, I wish to thank Cláudia Ferreira from Teprel, S.A. and Cristina Seixas from Philips Respironics, S.A. for their support to the research by supplying half of the threshold devices needed.

To my professors and colleagues in respiratory physiotherapy field, which are always present in my mind for the enthusiasm they planted in me to treat respiratory patients in the way they deserve.

To Alberto, André, Miguel Fi and Tiago, for their real childhood friendship. Your support in all phases of my life, good or bad, have been extremely important.

…

I wish to dedicate this work to my Father and Mother, who made me who I am, raising me with all their economic efforts and always educating with the principles but also with the idea that dreams can become true and heaven is the limit for a dreamer.

To my brother João who never fail to give me his support and help, even in moments where I couldn't collaborate in several issues. I know that your're proud of me as I am confident on you.

To my 3 years-old sister Matilde, the light of my life.

Finally, to my muse, my inspiration… Daniela!

This was one of the biggest challenges of my life, but with the help and support of everyone who cares about me it was possible. I'm forever grateful! Now some new challenges are approaching and… I'm ready!

Index of Contents

Resumo

A Doença Pulmonar Obstrutiva Crónica (DPOC) é uma doença respiratória com efeitos sistémicos já descritos, que derivam da inflamação sistémica assim como das comorbilidades associadas à doença; um destes efeitos é a disfunção do músculo-esquelético. Na DPOC, esta disfunção não têm as mesmas consequências biológicas para os músculos periféricos e respiratórios, devido aos diferentes factores locais intervenientes. Também a Actividade Física Diária (AFD) está geralmente comprometida nos sujeitos com DPOC. Esta limitação deve-se sobretudo à presença de dispneia, o principal factor limitante do exercício na DPOC. A par com a fraqueza muscular periférica, os músculos respiratórios poderão ter uma contribuição para esta limitação através de uma reduzida capacidade para tolerar a dispneia assim como uma maior fatigabilidade. Muita investigação tem sido realizada sobre o efeito do treino dos músculos inspiratórios, mostrando melhorias significativas na força, dispneia, capacidade para realizar trabalho físico (CRTF) e qualidade de vida; treino este maioritariamente de força. Para além disto, uma grande variedade de protocolos de treino tem sido descrita. O treino de endurance dos músculos respiratórios através da modalidade de hiperpneia normocapnica também parece apresentar resultados similares. Por outro lado, o treino dos músculos expiratórios apresenta menor evidencia mas também com resultados positivos ao nível da força, dispneia e CRTF. Quanto à relação entre a AFD e os músculos respiratórios, a literatura é muito escassa parecendo no entanto existir algum potencial. Sabendo isto, quisemos analisar o efeito de um treino de endurance dos músculos inspiratórios e expiratórios (RMET) na quantidade e intensidade de AFD desenvolvida, na CRTF e dispneia, em sujeitos com DPOC. Para isso conduzimos um estudo randomizado controlado. Dezasseis indivíduos (média de volume expiratório forçado no primeiro segundo (FEV_1) de 45,5 ± 12,70% de valor predito) realizaram um protocolo de RMET durante seis semanas, com carga a 30% das capacidades inspiratória máxima e expiratória máxima (Pimax e Pemax, respectivamente); no fim da terceira semana foi efectuada uma nova avaliação da Pimax e Pemax de forma a ajustar a carga de treino. O treino decorreu durante 6 dias por semana. Ao mesmo tempo,

treze sujeitos (FEV_1 49,0 ± 13,60 % de valor predicto) não realizaram nenhum tipo de treino (grupo NT). Foram recolhidos os resultados pré e pós protocolo de: testes de função pulmonar, ventilação máxima voluntária (MVV), Pimax, Pemax, prova de marcha dos 6 minutos (6MWT) de forma a CRTF e AFD através de acelerometria. Em termos de resultados e comparando com os valores pré-protocolo, o grupo RMET apresentou melhorias significativas na Pimax (p = 0,006), Pemax (p = 0,024), dispneia (p = 0,043) e 6MWT (p = 0,041); já o grupo NT não apresentou nenhuma diferença significativa, apesar do incremento verificado na Pemax ter estado perto da significância (p = 0,057). Em termos de AFD, diferenças significativas foram encontradas para ambos os grupos, no número de passos por dia (RMET p = 0,045; NT p = 0,040). Quanto ao MVV e níveis de AFD, nenhum tipo de diferenças foi encontrado. Também na comparação entre grupos para os vários parâmetros analisados, nenhuma diferença significativa foi encontrada. Como conclusões, o RMET parece apresentar efeitos benéficos na musculatura respiratória, aumentando a força e a CRTF e melhorando a dispneia. Contudo, estes efeitos parecem ser insuficientes para criar alguma alteração positiva na quantidade e intensidade de AF desenvolvida por sujeitos com DPOC.

Palavras-chave: DPOC; disfunção do músculo-esquelético; sintomas; treino dos músculos inspiratórios; treino dos músculos expiratórios.

Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a respiratory disease with described “extra-pulmonary” effects lying on existing systemic inflammation and comorbidities associated with the disease; atrophy and skeletal muscle dysfunction is one of those. COPD muscle dysfunction doesn’t have the same biological consequences among peripheral and respiratory muscles due to different local factors. Also, Physical Activity (PA) on COPD patients is often compromised. It may be due dyspnoea, the main exercise limiting factor. Along, with peripheral weakness, respiratory muscles might have a contribution to this impairment by showing lower tolerance to dyspnoea and quicker fatigability. Much has been investigated about inspiratory muscle training with significant improvement on strength, dyspnoea, physical working capacity, health related quality of life, mainly through strength training. A great variety of protocols have been used. Endurance training using normocapnic hyperpnea modality shows similar results. In other hand, expiratory muscle training has less evidence but presents also good results on strength, dyspnoea and physical working capacity. The relationship between respiratory muscle strength and PA is sparse of research, but it seems to have a potential rational. Observing this, we aimed to analyze the effects of inspiratory and expiratory muscle endurance training (RMET) on the amount and intensity of physical activity, physical working capacity and dyspnoea in COPD patients. We conducted a randomized controlled trial. Sixteen subjects (mean forced expiratory volume in first second (FEV_1) of 45,5 ± 12,70% predicted value) performed a six-week RMET protocol, at 30% of inspiratory and expiratory maximal pressures (Pimax and Pemax, respectively); in the final of third week inspiratory and expiratory loads were evaluated again for load adjustment. Training occurred 6 days per week. In the same time, thirteen subjects (FEV_1 49,0 ± 13,60 % predicted value) did not perform any kind of respiratory training (No training group). Were obtained baseline and post-protocol measurements for lung function test, maximal voluntary ventilation (MVV), Pimax, Pemax, 6-minute walk test (6MWT) for evaluation of physical working capacity and physical activity through accelerometry. In terms of results, when comparing with baseline values, RMET

group presented a significant improvement on Pimax (p = 0,006), Pemax (p = 0,024), dyspnoea (p = 0,043) and 6MWT (p = 0,041); No training (NT) group didn't present any significant alterations, in spite of Pemax increase had almost reach significance (p = 0,057). In physical activity, a significant differences for both groups were found in Steps per day (RMET p = 0,045; NT p = 0,040). In physical activity levels and maximal voluntary ventilation, no significant changes were observed. Between groups, training effect revealed no statistically differences. As conclusion, RMET could have a positive effect on respiratory muscles, improving strength, dyspnoea and physical working capacity. However, these improvements seem to be insufficient to change positively the amount and intensity of physical activity in COPD subjects.

Key Words: COPD; skeletal muscle dysfunction; symptoms; inspiratory muscle training; expiratory muscle training.

List of Abbreviations

6MWT – six minutes walk test;

AC – activity counts;

ADL – activities of daily living;

ATS – American Thoracic Society;

BMI – body mass index;

COPD – Chronic Obstructive Pulmonary Disease;

EMT – expiratory muscle training;

ERS – European Respiratory Society;

ERV – expiratory reserve volume;

FEV_1 –forced expiratory volume in first second;

FVC –forced vital capacity;

HR – heart rate;

HRQol – health related quality of life;

IMT – inspiratory muscle training;

MRC – Medical Research Council;

MVV –maximal voluntary ventilation;

NT – no training;

ONDR – Observatório Nacional para as Doenças Respiratórias;

Pemax – expiratory maximal pressure;

Pimax – inspiratory maximal pressure;

DPA – daily physical activity;

PEF – peak expiratory flow;

RCT – randomized controlled trial;

RMET – respiratory muscle endurance training;

ROS – reactive oxygen species;

RV – residual volume;

SGRQ-C – St. George Respiratory Questionnaire for patients with Chronic Obstructive Pulmonary Disease;

TLC – total lung capacity;

TLCO SB - diffusing capacity for the lungs measured using carbon monoxide, also known as transfer factor;

TLCO / VA - diffusing capacity for carbon monoxide per unit of alveolar volume;

WHO – World Health Organization.

1. GENERAL INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterized by a progressive and persistent airflow obstruction that is not fully reversible [1]. Nowadays, it's one of the major causes of mortality and morbidity around the world [2].

Until few years ago, definition and approaches to COPD, had mainly focused on the simplified idea that inhalation of particles and gases would mainly affect respiratory tract [3]. Nowadays, COPD is recognized as respiratory disease with systemic implications [4]. One of those is skeletal muscle dysfunction and atrophy [1, 3-7], as result of muscle structure and function alterations. On respiratory muscles, dysfunction is present as result of a combination of local and systemic factors [6], with diaphragm weakness playing a major role [6, 8]. In other hand, investigation has searched for respiratory muscle training effects, mainly focusing on inspiratory muscles [9], and with a variety of protocols.

In COPD, daily physical activity is commonly reduced [10, 11], probably secondary to the related skeletal muscle dysfunction [12]. However, few researches have addressed their main focus on relating respiratory muscle weakness and physical activity. Moreover, until now, none of the known available literature has searched for the possible impact of respiratory muscle training on the amount and intensity of daily physical movement produced by COPD patients.

Therefore, the objective of this study was, through a randomized controlled trial, to analyze the hypothesis that a respiratory muscle endurance training protocol could have a positive effect on daily physical activity, capacity to perform physical work and dyspnoea, in COPD patients.

1.1. Structure of the dissertation

This dissertation is presented according to the Scandinavian model, being divided in four sections:

Section 1: This chapter presents the general introduction to the topic, highlighting the relevance of the study and its objectives.

Section 2: With the title "The relationship between daily voluntary physical activity and respiratory muscles dysfunction in subjects with diagnosis of chronic obstructive pulmonary disease", this chapter reviews the available scientific literature about the impact of respiratory muscles dysfunction and its mechanisms on physical performance of chronic obstructive pulmonary disease diagnosed patients.

Section 3: This chapter is an experimental manuscript entitled "Impact of a six-week inspiratory and expiratory muscle endurance training program on physical activity, physical working capacity and dyspnoea in patients with chronic obstructive pulmonary disease". It constitutes the experimental part of the dissertation, presenting the material and methods used, the obtained results and their discussions.

Section 4: The main conclusions of the dissertation are presenting in this chapter.

The bibliography references supporting concepts, theories, and/or methods are presented at the end of each chapter.

References

1. *Global Strategy for the Diagnosis, Management and Prevention of COPD*. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013.
2. WHO *The Global Burden of Disease: 2004 update*. 2008.
3. Fabbri, L.M. and K.F. Rabe, *From COPD to chronic systemic inflammatory syndrome?*, in *Lancet*. 2007: England. p. 797-9.
4. Barnes, P.J. and B.R. Celli, *Systemic manifestations and comorbidities of COPD*, in *Eur Respir J*. 2009: Switzerland. p. 1165-85.
5. Laveneziana, P. and P. Palange, *Physical activity, nutritional status and systemic inflammation in COPD.* Eur Respir J, 2012. **40**(3): p. 522-529.
6. Gea, J., A. Agusti, and J. Roca, *Pathophysiology of muscle dysfunction in COPD*, in *J Appl Physiol*. 2013: United States. p. 1222-34.
7. *Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society.* Am J Respir Crit Care Med, 1999. **159**(4 Pt 2): p. S1-40.
8. De Troyer, A. and T.A. Wilson, *Effect of acute inflation on the mechanics of the inspiratory muscles*, in *J Appl Physiol*. 2009: United States. p. 315-23.
9. Gosselink, R., J. De Vos, S.P. van den Heuvel, J. Segers, M. Decramer, and G. Kwakkel, *Impact of inspiratory muscle training in patients with COPD: what is the evidence?* Eur Respir J, 2011. **37**(2): p. 416-25.
10. Pitta, F., T. Troosters, M.A. Spruit, V.S. Probst, M. Decramer, and R. Gosselink, *Characteristics of physical activities in daily life in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2005. **171**(9): p. 972-7.
11. Vorrink, S.N., H.S. Kort, T. Troosters, and J.W. Lammers, *Level of daily physical activity in individuals with COPD compared with healthy controls*, in *Respir Res*. 2011: England. p. 33.
12. Donaldson, A.V., M. Maddocks, D. Martolini, M.I. Polkey, and W.D. Man, *Muscle function in COPD: a complex interplay*, in *Int J Chron Obstruct Pulmon Dis*. 2012: New Zealand. p. 523-35.

State of the art

The relation between physical activity and respiratory muscle dysfunction, in subjects with diagnosis of chronic obstructive pulmonary disease.

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a respiratory disease with an airflow obstruction that is not fully reversible as its main feature. Despite COPD respiratory implications, also “extra-pulmonary” effects have been described lying on existing systemic inflammation and comorbidities associated with the disease. Today, two theories approach the relation between disease and systemic inflammation. As one refers to systemic inflammation as a result of a “split-over” of the inflammatory and reparatory events occurring in the lung, the other defends that pulmonary manifestations of COPD are one more form of expression of a “global” inflammatory state with multiple organ compromise. Independently, one comorbidity well identified as a systemic consequence of COPD is atrophy and skeletal muscle dysfunction. For this dysfunction, also an increased oxidative stress may play an important role. However, COPD muscle dysfunction doesn’t have the same biological consequences among peripheral and respiratory muscles due to different local factors. Respiratory muscles face increased ventilatory loads caused by the persistent airflow obstruction. Diaphragm seem to be the most affected muscle by the fact that it’s putted in a mechanical disadvantageous position by commonly presented lung hyperinflation; at the same time, a shift of muscle fibers toward type I fibers is constantly observed. Also other respiratory muscles reveal this type fibers shift like external and parasternal intercostals. About expiratory musculature, reduced strength, endurance and, more recently, resistance to fatigue after high exertion, were described. Much has been investigated about inspiratory muscle training with significant improvement on strength, dyspnoea, physical working capacity, health related quality of life, mainly through strength training. A great variety of protocols have been used. Endurance training through normocapnic hyperpnea modality shows similar results. In other hand, expiratory muscle

training has less evidence but presents also good results on dyspnoea and physical working capacity. Daily Physical Activity (DPA) on COPD patients is often compromised. It may be due dyspnoea, the main exercise limiting factor. Peripheral muscle weakness also contributes to this limitation. The relationship between respiratory muscle strength and DPA is sparse of research, but it seems to have potencial. The objective of this document was to review the available scientific literature about the relation between respiratory musculature and DPA.

Key Words: COPD; systemic inflammation; skeletal muscle dysfunction; respiratory muscle training; dyspnoea.

1. Introduction to Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD), is defined as "*a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lung to noxious particles or gases*". Exacerbations and comorbidities contribute to the overall severity in individual patients [1]. Nowadays, it's one of the major causes of mortality and morbidity around the world, being thought that its incidence has under represented the disease's real impact because most of the times the diagnosis only is made when patient is symptomatic [2].

According to the *World Health Organization* (WHO), in 2004, COPD was responsible for 3 millions of deaths (5,1% total of deaths) in the world, being the 4th leading cause of mortality in that year. In 2030, WHO estimate that COPD become the 3rd major cause of death around the world; moreover, the same organization refer that deaths as consequence of tobacco use (not only COPD), will rise up to 10% of the total [3].

Yet, the *Portuguese National Observatory for Respiratory Diseases* (ONDR) refer that between 2006 and 2010, COPD was responsible for 49.963 hospital stays, being therefore the 2nd major cause of hospital stays in Portugal on that period. The same report reveals that just in 2009, 2859 persons die of COPD. In 2011, the prevalence of COPD in Portugal was about 14,2% [4].

1.1. Pathophysiology

The main feature of COPD is an airflow obstruction that is not fully reversible after brochodilatation [5]. This is caused by a mixture of small airway disease (obstructive bronchiolitis) and emphysema [1, 6]. The first one reflects the remodeling of the small airway compartments as response to inflammation which cause narrowing of the small airways; the second one is the result of lung

parenchyma destruction, also by inflammatory processes, which leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil; in turn, these changes diminish the ability of the airways to remain open during expiration [1, 5, 7]. However, the accumulation of tissue responsible for thickening of small airways (known as exaggerated tissue repair) is a very different process of what is seen on emphysematous destruction of gas-exchanging tissue (known as insufficient tissue repair) [7]. The relative contributions of each one vary from person to person [1, 8]. All this results in a progressive decline of forced expiratory volume in first second (FEV_1) [5]. Airflow limitation, through FEV_1, is best measured by spirometry, as this is the most widely available, gold standard, reproducible test of lung function [1].

The inflammatory process related to COPD, develops in the lungs of everyone who smokes, being found a relationship between this tissue response and extend and severity of airflow limitation in COPD patients [7]. The inflammatory cell infiltration into lung tissue in COPD is bounded to an abnormal repair and remodeling processes that cause an enlargement of bronchial mucus glands, increasing mucus content on epithelial linning the airways lumen, proliferative activity of the epithelial cells and both mucous and squamous cell metaplasia [7].

The course of COPD is frequently aggravated by disease's exacerbations. Those can be defined as a short period (at least 48 hours) of increase dyspnoea and cough, and a production of sputum that can be purulent [5]. Exacerbations might be divided in three categories, mild, moderate and severe; varying on symptoms severity and from subject to subject. A mild exacerbation requires increased doses of bronchodilators; moderate need treatment with systemic corticosteroids, antibiotics or both; and severe exacerbations frequently demand hospital admissions [5]. Thus, COPD exacerbations can range from symptoms to respiratory failure and death, and can result in more rapid declines in lung function and worse outcomes [8]. Recently, in a big longitudinal study with 2138 COPD patients, *Hurst* and colleagues stated that exacerbations become more frequent and more severe as the severity of disease increase. Also, they found that the major relevant factor for frequent exacerbations is the history of exacerbations [9].

1.2. Diagnosis

The clinical diagnosis of COPD should be considered in any patient who has dyspnoea, chronic cough or sputum production, and history of exposure to risk factors of the disease (tobacco smoke, smoke from home cooking and heating fuels, occupational dusts and chemicals) [1].

In clinical context, spirometry is required to make the diagnosis; the presence of a post-bronchodilator $FEV_1/FVC < 0,70$ (FEV_1 – force expiratory volume in first second; FVC – forced vital capacity) confirms the presence of persistent airflow obstruction and thus COPD [1]. This definition is widely accepted because of its practicality, although it may underestimate COPD in the elderly; this can be explained by de faster declining of FEV_1 with age, when compared with FVC. In other hand, some underdiagnosis can be found in younger adults [6]. Therefore, some authors recommend that a lower limit of normal may be applied (fifth percentile of the normal distribution range of FEV_1/FVC) [6].

The *Global Initiative for Chronic Obstructive Lung Disease* (GOLD), classify the severity of lung function of COPD patients, based on predicted FEV_1, in 4 grades: Grade I – FEV1 ≥ 80% (mild), Grade II – 50% ≤ FEV1 < 80% (moderate), Grade III – 30% ≤ FEV1 < 50% (severe), Grade IV – FEV1 < 30% (very severe) [1]. More recently, the same organization adopted a new scheme of disease severity stratification, based on exacerbation rates and symptoms score, in adition to airflow obstruction (as seen above) [1, 6].

1.3. The “extra-pulmonary” impact of COPD

Until few years ago, definitions and approaches of COPD had mainly focused on the simplified idea that inhalation of particles and gases would only affect respiratory tract [10]. However, in many patients the disease is associated with several systemic manifestations that can effectively result in impaired

functional capacity, worsening dyspnoea, reduced health related quality of life (HRQoL) and increased mortality [11].

The most common systemic consequences and comorbidities associated with COPD are: cardiovascular disease, obesity, hypertension, diabetes type II, deconditioning, malnutrition, atrophy and skeletal muscle dysfunction, physical inactivity, osteoporosis, anemia and bone marrow dysfunction [12]. Today is known that this factors are the result of systemic inflammation seen in this patients, mainly during acute exacerbations [12]. Their impact on COPD patients' quality of life is naturally big, assuming the needs of detecting and treating also the comorbilities associated with the disease [1].

Nowadays, yet prevail two types of views relating the association of comorbidities to COPD. Many authors believe that this association results from a "spill-over" of the inflammatory and reparatory events occurring in the lung, with the disease being the centre of process [11, 13]. In the other point of view, pulmonary manifestations of COPD are one more form of expression of a "systemic" inflammatory state with multiple organ compromise [10, 11, 13].

Despite its respiratory consequences, some have proposed the addition of the term "chronic systemic inflammatory syndrome" to the diagnosis of COPD due to the complex chronic comorbidities associated with the disease [10]. Moreover, the differentiation between the concepts of "systemic consequences" and "comorbidities" is difficult to define, and therefore sometimes they are considered together [11].

2. The impact of COPD on the skeletal muscle

Skeletal muscle corresponds to ~40-50% of the total body mass in a male with normal weight [11]. The concept of muscle dysfunction includes the presence of at least one of the following conditions: weakness, reduced endurance, and fatigue. These can be presented simultaneously in the same patient. Moreover, a weak muscle will become fatigued more easily. Muscle

dysfunction in COPD is the end result of a complex interaction between several factors, which, in turn, induce many different molecular and cellular events within the muscle [13].

In COPD patients, skeletal muscle dysfunction and atrophy are, as seen above, other characteristics that can be found [1, 14], as result of muscle structure and function alterations [11, 13, 14]. In severe COPD patients, muscle wasting had a great impact on morbidity, increasing the risk of hospital admission after exacerbation, as well as increases the need for mechanical ventilatory support [11].

For skeletal muscle dysfunction in COPD, it appears that systemic inflammation is the main contributor [11], but not the only one. An imbalance between ROS (reactive oxygen species) and antioxidant productions, gas exchange abnormalities, inefficiency of anabolic hormones, comorbidities and aging, tobacco, exercise and training, and exacerbations, may also play a role [13]. On peripheral muscles (limb muscles), quadriceps weakness was demonstrated in one-third of COPD patients attending respiratory outpatients service, existing also in the absence of severe airflow obstruction and dyspnoea [15]. In other hand, limb muscle dysfunction might not be present in all COPD patients with severe disease [15]. This heterogeneity shows that lung function is not the main factor that causes muscle dysfunction in COPD patients [13].

Nevertheless, skeletal muscle dysfunction in COPD don’t have the same biological consequences among respiratory and limb muscles [13]. Therefore, in the following sections, a more deep approach will be presented regarding respiratory musculature and its relationship with COPD

2.1. Respiratory muscles

The way in what respiratory muscles are divided can diverge from author to author [16, 17]. But generally, respiratory musculature can be divided in: diaphragm and accessory muscles [17].

2.1.1. Diaphragm

Diaphragm is the major muscle of ventilation [17], and has been classically considered as the main inspiratory muscle, at least in healthy and young subjects breathing under resting conditions [13]. The diaphragm has a dome-shaped form [13, 17], located between thoracic and abdominal cavities [17], which is composed by costal and crural portio [13]. Whereas the costal section appears to be more relevant for inspiration, the crural portion also plays a relevant role in the gastroesophageal function [13]. Other authors think that despite being referred as one muscle, this structure is actually composed by two separated muscles known as the right and left hemidiaphragms [17].

When stimulated to contract, this muscle moves downward as the lower ribs moves upward and outward [17], acting mainly by expanding the thoracic cage [13]. This action increases volume of the thoracic cavity [17], generating the negative alveolar pressure that results in inspiratory flow [13]. During normal ventilation on healthy subjects, diaphragm by itself can manage the task of moving gas in and out of the lungs [17].

2.1.2. Acessory Muscles

In turn, the group of accessory muscles can be subdivided in **inspiratory accessory muscles** and **expiratory accessory muscles**.

The **accessory muscles of inspiration** are: *scalenus muscles*, *sternocleidomastoid muscles*, *pectoralis major muscles*, *trapezius muscles* and *external intercostal muscles*. The contraction of external and parasternal (the interchondral extension of the internal interosseus) intercostals muscles mainly enlarges the chest cross-sectional area, while scalenes expand the upper rib cage [13].

In other hand, the **accessory muscles of expiration** are: *abdominis muscles*, *external abdominis obliquus muscles*, *internal abdominis obliquus muscles*, *transverses abdominis muscles* and *internal intercostals muscles* [17].

In cases of increased load on respiratory mechanics, like exercise situations or severe COPD, inspiratory and expiratory accessory muscles are recruited to participate in the breathing effort and assist diaphragm on respiratory mechanics [16, 17], becoming sometimes even more relevant than the diaphragm. In these cases, the external and parasternal intercostals become major players [13].

2.2. Respiratory muscles' dysfunctional mechanisms in COPD

The function of respiratory muscles is frequently impaired in COPD patients [18]. Their dysfunction is caused by a combination of different local and systemic factors [13]. Respecting to systemic factors, those were briefly described above; relating to the local ones, in COPD, respiratory muscles are facing an increase in mechanical ventilatory loads, due to the airflow limitation that characterizes COPD. Simultaneously, pulmonary hyperinflation and increased compliance are also important [13]; Hyperinflation, because it modifies de thorax geometry, shortening the diaphragm length [13].

Diaphragm of hyperinflated COPD patients develops less force than of healthy subjects when they are making effort at their own functional residual capacity [13]. Moreover, lung inflation has a prominent effect on inspiratory muscles by the fact that diaphragm starts its contraction on a shorter position resulting in less force generated [19], and making its costal and crural parts less coordinated [20].

It was shown that diaphragm of patients with severe COPD have a higher proportion of type I muscle fibers when compared with a normal diaphragm which may confer more resistance to fatigue [21, 22]; corroborating with the

findings that with the increasing of airflow obstruction, the activity of oxidative enzymes and the mitochondrial capacity are increased while glycogenolytic activity do not change [23]. This suggests that diaphragm adaptation and consequent atrophy towards a slower muscle profile are present in COPD patients. This was also confirmed by *Testelmans* and coworkers who found an up-regulation of the NF-kB pathway, the ubiquitin-proteasome pathway and myostatin, and a down-regulation of MyoD [22]. Interestingly, despite its certain dysfunction, diaphragm of hyperinflated COPD patients shows even more force than in a healthy group, if this subjects were forced to increase their volumes to similar levels than COPD group [24]. This force's maintenance is probably due to a persistent involuntary training secondary to the increase work of breathing [25].

In other hand, the type fibers shift adaptation of diaphragm in COPD patients, may also occurs earlier than other skeletal muscle structure adaptations, like it was shown in comparison with vastus lateralis; this could support the idea that on early stages of disease, local factors may play a more prominent role than systemic factors like inflammation [26]. This comes in agreement with other findings that postulate a reduced force generating capacity in diaphragm fibers in mild to moderate COPD patients, which was explained by a loss of myosin heavy chain related with an increase of ubiquitin-conjugated proteins that suggest accelerated muscle protein degradation. Moreover, in the remaining contractile proteins were observed signs of impaired function [27]. Also hypoxia and hypercapnia, commonly observed in COPD patients, demonstrated a significant effect on contractile properties and muscle fibers composition of rats' diaphragm [28]. On exertion and when applied an inspiratory muscle loading test, COPD patients diaphragm showed greater injury and also greater susceptibility for additional sarcomere injury [29].

Despite diaphragm major dysfunction as response to COPD presence, also other inspiratory muscles like parasternal intercostals, revealed slow-to-fast profile fibers transformation [30]. However, this transformation's clinical impact remains unclear.

Regarding expiratory muscles, few research has been done and with controversial findings. Some authors have described a decreased strength (maximal expiratory strength, Pemax) [31, 32] and endurance [32], being the last one, proportional to disease severity and with other peripheral muscles weakness, reinforcing the systemic character of COPD. Others, found no statistically significance on cough gastric pressure, when comparing with healthy subjects [33], arguing that Pemax is not the best test to measure expiratory muscle strength, with a 58% predictive value against 94% of cough gastric pressure which detects abdominal weakness [34]. Recently, it was found that abdominal fatigue occurs in COPD patients when exercising to exhaustion, which not happen with diaphragm of same subjects [35]. The authors speculated that lung hyperinflation may be the cause of abdominal muscle lengthening; despite this, the same authors did not find any relationship between hyperinflation and propensity for abdominal fatigue [35]. Finally, it's not available any data regarding fibers type composition of expiratory muscles in COPD patients.

2.3. Respiratory muscles training

In the last years, pulmonary medicine has given some attention to respiratory muscles and to the impact of their weakness/dysfunction on quality of life and functional capacity in COPD patients. A considerable number of randomized controlled trials (RCT) were conducted in order to search inspiratory muscle training impacts on COPD patients' condition [36-65].

Looking to evidence, some controversy can be found about the definition of strength and endurance training, being more frequent in the literature RCT's about the "so called" inspiratory strength training; despite this, some presents low training loads (eg.: 30% of Pimax) [44, 45, 62] which can also be considered as endurance training, depending on training's number of repetitions. Others tried higher intensities, looking sometimes to reach the highest tolerable load, in order to have more strength gains [55]. In the case of

Hill and coworkers study, it was compared high-intensity (H-IMT) versus small-intensity (S-IMT, remained at 10% of Pimax during all protocol); the authors found better statistically differences between groups in maximal inspiratory capacity (Pimax), endurance, health related quality of life (HRQoL) and six-minute walk test (6MWT). In other hand, respiratory muscle endurance training (RMET) has been less studied [47, 54, 56]. The RMET is usually associated with normocapnic hyperpnoea. This type of training consist on breathing to a bag while minute ventilation is constantly monitored in way to subjects reach their target minute ventilation which is set for a determined percentage of maximal voluntary ventilation (MVV) [54, 56]. So, the use of pressure threshold devices has never been taking in account for endurance training purposes.

In 2011, *Gosselink* and colleagues conducted the most recent meta-analysys on inspiratory muscle training (IMT) where they included 32 studies, where 29 tested strength training, while the remaining 3 studies searched for endurance training effects [66]. As main conclusions this recent meta-analysis state that: "*inspiratory muscles training present some evidence about their benefits in respiratory muscle strength and endurance, resulting in reduction of dyspnoea, improvements in physical working capacity and HRQoL; this type of training also shows more effectiveness on COPD patients with more advanced inspiratory muscle weakness (Pimax bellow 60 cm/H_2O) and as a part of a pulmonary rehabilitation program. Moreover, the endurance training seems to be less effective than strength training"* [66]. Also, IMT alone have showed significant structural adaptations in COPD patients. *Ramírez-Sarmiento* and colleagues, found a significant increase on type I fibers proportion (by about 38%) and type II fibers size (by about 21%) in external intercostals muscles, by a 5 weeks with 60% of Pimax load, when compared with a control group [50].

Regarding the training of expiratory muscles on COPD patients, it has been less studied than inspiratory, existing nowadays only 3 studies about this theme [51, 67, 68]. However, some interesting findings could be seen in 6MWT distance, HRQoL and dyspnoea [67]. It was found that expiratory muscle training can improve expiratory muscle strength and endurance [68]. Finally, about the combination of both trainings (inspiratory and expiratory) on COPD subjects, only one study looked to this issue [51]. The authors compared 4

group: 1) inspiratory muscle training (IMT); 2) expiratory muscle training (EMT); 3) combined inspiratory and expiratory muscle training (IMT + EMT); and 4) control group. The authors observed improvements in 6MWT, perception of dyspnoea, and respiratory muscle strength and endurance for both combined IMT and EMT and alone IMT [51]. Despite the good results of combined training, authors conclude that the addition of EMT do not brought any additional benefits for IMT.

In generally, despite of being few the studies about respiratory endurance through specific inspiratory and expiratory muscle training in COPD patients, the evidence seems to indicate for an augmentation on exercise functional capacity (eg.: 6MWT), in other words, for an improvement of capacity to execute tasks. Despite the lack of research about the role of EMT and knowing that expiratory muscles main activity is on exertion levels, the EMT combined with IMT could probably enhance physical working capacity. Consequently, this improvement could have echo in the amount of movement produced and so, on COPD patients' daily physical activity.

3. Physical activity, COPD and respiratory muscles

Physical activity is defined "as any kind of bodily movement produced by skeletal muscles contraction that results in energy expenditure above basal level" [69]. The American College of Sports Medicine and the American Heart Association recommended to all health subjects between 18 and 65 years old, 30 minutes of moderate-intensity aerobic exercise for at least 5 days per week in order to promote and maintain health [70]. Daily physical activity (DPA) can be evaluated by direct observation, energy expenditure, questionnaires and motion sensors [71].

About COPD, *Pitta* and colleagues clearly showed that this patients spend less time walking and standing and more time lying and sitting than healthy subjects [72]. This results were confirmed by a recent meta-analysis performed by *Vorrink* and coworkers which conclude that duration, intensity and counts were significantly reduced when compared with healthy subjects [73].

Moreover, during acute exacerbations which require hospitalization and in the month after, COPD patients present severe limitation on DPA levels [74]. Dyspnoea seems to be the main exercise limitation factor related to lung hyperinflation and mechanical restriction, which causes inefficient tidal volumes and minimal inspiratory reserve volumes, during exertion [75]. In fact, COPD patients increase their neural drive to respiratory muscles at very low exercise levels than healthy subjects. This increase is accompanied by and increase on perceived breathlessness [76].

Relating to the DPA predictors, some studies point out that airflow obstruction on COPD patients is not a good correlation factor for predicting DPA levels [72, 73, 77], while others go in inverse direction [73, 78-80]. In other hand, dynamic hyperinflation correlate well with the amount of physical activity produced by COPD patients [79]. 6-minute walk test (6MWT), according to recent findings, is also a good predictor for inactivity during daily life in this population [72, 79]. This test evaluates the global responses of all systems involved during functional exercise [79, 81].

Interestingly, it was suggested that physical activity practice at moderate to high levels has an attenuation effect on lung function decline and in reducing the risk of COPD, in active smokers [82]. Moreover, in a recent major research, *Waschki* and colleagues suggested that the level of physical activity was the strongest predictor of mortality in COPD patients, when comparing with other prognostic factors [83]. Therefore, physical activity evaluation in COPD subjects has been one of the recent investigation areas inside respiratory medicine because, as said previously, the physical activity reduction plays an extremely important role in what concerns the physical fitness, level of exacerbation and therefore risk associated with the disease, and quality of life [84].

Little research has given special attention to the relationship between respiratory muscles contribution to daily physical activity levels. In 2008, *Pitta* and colleagues show significant correlations between DPA and Maximal Voluntary Ventilation (MVV) [77], as the last one as already being used to test respiratory muscles endurance [47, 54, 56]; these authors didn't test correlation between respiratory muscle force and PA [77]. Previous, it was found that respiratory musculature, in this case inspiratory (Pimax), would have a positive

correlation with the 6MWT, which as previously said, present a good correlation with DPA. This opens the discussion to the fact that, if respiratory musculature performance has an impact on physical working capacity test (like 6MWT) which is a good predictor for DPA, its impairment also could directly influence the amount and intensity of movement performed by COPD patients.

4. Conclusions

Inspiratory muscle strength and endurance are frequently impaired on COPD patients. To this, diaphragmatic weakness plays a major role but also some dysfunction can be found on external intercostals and in parasternal intercostals. About expiratory muscles, remains some controversy, despite its weakness and lack of endurance had been described mainly after intense exercise.

Respiratory muscle training shows sufficient evidence regarding the effects on strength, dyspnoea and HRQoL; however IMT has more research than EMT. A variety of protocols can be found for IMT and EMT, with some controversy on definition of endurance and strength training, and loads applied.

DPA is commonly reduced in COPD patients, being one of the strongest mortality predictors for this population. Airflow obstruction seems to fail a relationship with the amount of movement performed. In other hand, respiratory muscle performance might play a role on influence the amount and intensity of movement performed by COPD patients.

However, research about the direct impact of respiratory muscles and the effect of a respiratory muscle training program on DPA levels in COPD patients is still lacking.

References

1. *Global Strategy for the Diagnosis, Management and Prevention of COPD*. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013.
2. Cooper, C.B., *Airflow obstruction and exercise.* Respir Med, 2009. **103**(3): p. 325-34.
3. WHO *The Global Burden of Disease: 2004 update*. 2008.
4. ONDR *Relatório do Observatório Nacional de Doenças Respiratórias*. 2011.
5. Decramer, M., W. Janssens, and M. Miravitlles, *Chronic obstructive pulmonary disease*, in *Lancet*. 2012: England. p. 1341-51.
6. McDonald, C.F. and Y. Khor, *Advances in chronic obstructive pulmonary disease.* Intern Med J, 2013. **43**(8): p. 854-62.
7. Hogg, J.C. and W. Timens, *The pathology of chronic obstructive pulmonary disease.* Annu Rev Pathol, 2009. **4**: p. 435-59.
8. Mannino, D.M., G. Watt, D. Hole, C. Gillis, C. Hart, A. McConnachie, G. Davey Smith, M. Upton, V. Hawthorne, D.D. Sin, S.F. Man, S. Van Eeden, D.W. Mapel, and J. Vestbo, *The natural history of chronic obstructive pulmonary disease*, in *Eur Respir J*. 2006: Denmark. p. 627-43.
9. Hurst, J.R., J. Vestbo, A. Anzueto, N. Locantore, H. Mullerova, R. Tal-Singer, B. Miller, D.A. Lomas, A. Agusti, W. Macnee, P. Calverley, S. Rennard, E.F. Wouters, J.A. Wedzicha, and C.L.t.I.P.S.E.I. Evaluation of, *Susceptibility to exacerbation in chronic obstructive pulmonary disease.* N Engl J Med, 2010. **363**(12): p. 1128-38.
10. Fabbri, L.M. and K.F. Rabe, *From COPD to chronic systemic inflammatory syndrome?*, in *Lancet*. 2007: England. p. 797-9.
11. Barnes, P.J. and B.R. Celli, *Systemic manifestations and comorbidities of COPD*, in *Eur Respir J*. 2009: Switzerland. p. 1165-85.
12. Laveneziana, P. and P. Palange, *Physical activity, nutritional status and systemic inflammation in COPD.* Eur Respir J, 2012. **40**(3): p. 522-529.
13. Gea, J., A. Agusti, and J. Roca, *Pathophysiology of muscle dysfunction in COPD*, in *J Appl Physiol*. 2013: United States. p. 1222-34.
14. *Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society.* Am J Respir Crit Care Med, 1999. **159**(4 Pt 2): p. S1-40.
15. Seymour, J.M., M.A. Spruit, N.S. Hopkinson, S.A. Natanek, W.D. Man, A. Jackson, H.R. Gosker, A.M. Schols, J. Moxham, M.I. Polkey, and E.F. Wouters, *The prevalence of quadriceps weakness in COPD and the relationship with disease severity*, in *Eur Respir J*. 2010: Switzerland. p. 81-8.
16. Lane, M.A., *Spinal respiratory motoneurons and interneurons*, in *Respir Physiol Neurobiol*. 2011: Netherlands. p. 3-13.

17. Jardins, T.D., *The Anatomy and Physiology of the Respiratory System*, in *Cardiopulmonary Anatomy & Physiology: Essentials for Respiratory Care*. 2008, Delmar Cengage Learning: New York City, USA.
18. Vilaro, J., A. Ramirez-Sarmiento, J.M. Martinez-Llorens, T. Mendoza, M. Alvarez, N. Sanchez-Cayado, A. Vega, E. Gimeno, C. Coronell, J. Gea, J. Roca, and M. Orozco-Levi, *Global muscle dysfunction as a risk factor of readmission to hospital due to COPD exacerbations*, in *Respir Med*. 2010: England. p. 1896-902.
19. De Troyer, A. and T.A. Wilson, *Effect of acute inflation on the mechanics of the inspiratory muscles*, in *J Appl Physiol*. 2009: United States. p. 315-23.
20. Macklem, P.T., D. Gross, G.A. Grassino, and C. Roussos, *Partitioning of inspiratory pressure swings between diaphragm and intercostal/accessory muscles.* J Appl Physiol, 1978. **44**(2): p. 200-8.
21. Levine, S., L. Kaiser, J. Leferovich, and B. Tikunov, *Cellular adaptations in the diaphragm in chronic obstructive pulmonary disease.* N Engl J Med, 1997. **337**(25): p. 1799-806.
22. Testelmans, D., T. Crul, K. Maes, A. Agten, M. Crombach, M. Decramer, and G. Gayan-Ramirez, *Atrophy and hypertrophy signalling in the diaphragm of patients with COPD*, in *Eur Respir J*. 2010: Switzerland. p. 549-56.
23. Wijnhoven, J.H., A.J. Janssen, T.H. van Kuppevelt, R.J. Rodenburg, and P.N. Dekhuijzen, *Metabolic capacity of the diaphragm in patients with COPD*, in *Respir Med*. 2006: England. p. 1064-71.
24. Similowski, T., S. Yan, A.P. Gauthier, P.T. Macklem, and F. Bellemare, *Contractile properties of the human diaphragm during chronic hyperinflation.* N Engl J Med, 1991. **325**(13): p. 917-23.
25. Donaldson, A.V., M. Maddocks, D. Martolini, M.I. Polkey, and W.D. Man, *Muscle function in COPD: a complex interplay*, in *Int J Chron Obstruct Pulmon Dis*. 2012: New Zealand. p. 523-35.
26. Doucet, M., R. Debigare, D.R. Joanisse, C. Cote, P. Leblanc, J. Gregoire, J. Deslauriers, R. Vaillancourt, and F. Maltais, *Adaptation of the diaphragm and the vastus lateralis in mild-to-moderate COPD*, in *Eur Respir J*. 2004: Denmark. p. 971-9.
27. Ottenheijm, C.A., L.M. Heunks, G.C. Sieck, W.Z. Zhan, S.M. Jansen, H. Degens, T. de Boo, and P.N. Dekhuijzen, *Diaphragm dysfunction in chronic obstructive pulmonary disease*, in *Am J Respir Crit Care Med*. 2005: United States. p. 200-5.
28. Shiota, S., T. Okada, H. Naitoh, R. Ochi, and Y. Fukuchi, *Hypoxia and hypercapnia affect contractile and histological properties of rat diaphragm and hind limb muscles*, in *Pathophysiology*. 2004. p. 23-30.
29. Orozco-Levi, M., J. Lloreta, J. Minguella, S. Serrano, J.M. Broquetas, and J. Gea, *Injury of the human diaphragm associated with exertion and chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2001. **164**(9): p. 1734-9.

30. Levine, S., T. Nguyen, M. Friscia, J. Zhu, W. Szeto, J.C. Kucharczuk, B.A. Tikunov, N.A. Rubinstein, L.R. Kaiser, and J.B. Shrager, *Parasternal intercostal muscle remodeling in severe chronic obstructive pulmonary disease*, in *J Appl Physiol*. 2006: United States. p. 1297-302.
31. Gosselink, R., T. Troosters, and M. Decramer, *Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease.* J Cardiopulm Rehabil, 2000. **20**(6): p. 353-60.
32. Ramirez-Sarmiento, A., M. Orozco-Levi, E. Barreiro, R. Mendez, A. Ferrer, J. Broquetas, and J. Gea, *Expiratory muscle endurance in chronic obstructive pulmonary disease.* Thorax, 2002. **57**(2): p. 132-6.
33. Man, W.D., N.S. Hopkinson, F. Harraf, D. Nikoletou, M.I. Polkey, and J. Moxham, *Abdominal muscle and quadriceps strength in chronic obstructive pulmonary disease*, in *Thorax*. 2005: England. p. 718-22.
34. Man, W.D., D. Kyroussis, T.A. Fleming, A. Chetta, F. Harraf, N. Mustfa, G.F. Rafferty, M.I. Polkey, and J. Moxham, *Cough gastric pressure and maximum expiratory mouth pressure in humans*, in *Am J Respir Crit Care Med*. 2003: United States. p. 714-7.
35. Hopkinson, N.S., M.J. Dayer, J. Moxham, and M.I. Polkey, *Abdominal muscle fatigue following exercise in chronic obstructive pulmonary disease*, in *Respir Res*. 2010: England. p. 15.
36. Harver, A., D.A. Mahler, and J.A. Daubenspeck, *Targeted inspiratory muscle training improves respiratory muscle function and reduces dyspnea in patients with chronic obstructive pulmonary disease.* Ann Intern Med, 1989. **111**(2): p. 117-24.
37. Belman, M.J. and R. Shadmehr, *Targeted resistive ventilatory muscle training in chronic obstructive pulmonary disease.* J Appl Physiol, 1988. **65**(6): p. 2726-35.
38. Goldstein, R., J. De Rosie, S. Long, T. Dolmage, and M.A. Avendano, *Applicability of a threshold loading device for inspiratory muscle testing and training in patients with COPD.* Chest, 1989. **96**(3): p. 564-71.
39. Dekhuijzen, P.N., H.T. Folgering, and C.L. van Herwaarden, *Target-flow inspiratory muscle training during pulmonary rehabilitation in patients with COPD.* Chest, 1991. **99**(1): p. 128-33.
40. Weiner, P., Y. Azgad, and R. Ganam, *Inspiratory muscle training combined with general exercise reconditioning in patients with COPD.* Chest, 1992. **102**(5): p. 1351-6.
41. Preusser, B.A., M.L. Winningham, and T.L. Clanton, *High- vs low-intensity inspiratory muscle interval training in patients with COPD.* Chest, 1994. **106**(1): p. 110-7.
42. Wanke, T., D. Formanek, H. Lahrmann, H. Brath, M. Wild, C. Wagner, and H. Zwick, *Effects of combined inspiratory muscle and cycle ergometer training on exercise performance in patients with COPD.* Eur Respir J, 1994. **7**(12): p. 2205-11.
43. Berry, M.J., N.E. Adair, K.S. Sevensky, A. Quinby, and H.M. Lever, *Inspiratory muscle training and whole-body reconditioning in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1996. **153**(6 Pt 1): p. 1812-6.

44. Lisboa, C., C. Villafranca, A. Leiva, E. Cruz, J. Pertuze, and G. Borzone, *Inspiratory muscle training in chronic airflow limitation: effect on exercise performance.* Eur Respir J, 1997. **10**(3): p. 537-42.
45. Villafranca, C., G. Borzone, A. Leiva, and C. Lisboa, *Effect of inspiratory muscle training with an intermediate load on inspiratory power output in COPD.* Eur Respir J, 1998. **11**(1): p. 28-33.
46. Larson, J.L., M.K. Covey, S.E. Wirtz, J.K. Berry, C.G. Alex, W.E. Langbein, and L. Edwards, *Cycle ergometer and inspiratory muscle training in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1999. **160**(2): p. 500-7.
47. Scherer, T.A., C.M. Spengler, D. Owassapian, E. Imhof, and U. Boutellier, *Respiratory muscle endurance training in chronic obstructive pulmonary disease: impact on exercise capacity, dyspnea, and quality of life.* Am J Respir Crit Care Med, 2000. **162**(5): p. 1709-14.
48. Weiner, P., R. Magadle, N. Berar-Yanay, A. Davidovich, and M. Weiner, *The cumulative effect of long-acting bronchodilators, exercise, and inspiratory muscle training on the perception of dyspnea in patients with advanced COPD.* Chest, 2000. **118**(3): p. 672-8.
49. Sanchez Riera, H., T. Montemayor Rubio, F. Ortega Ruiz, P. Cejudo Ramos, D. Del Castillo Otero, T. Elias Hernandez, and J. Castillo Gomez, *Inspiratory muscle training in patients with COPD: effect on dyspnea, exercise performance, and quality of life.* Chest, 2001. **120**(3): p. 748-56.
50. Ramirez-Sarmiento, A., M. Orozco-Levi, R. Guell, E. Barreiro, N. Hernandez, S. Mota, M. Sangenis, J.M. Broquetas, P. Casan, and J. Gea, *Inspiratory muscle training in patients with chronic obstructive pulmonary disease: structural adaptation and physiologic outcomes.* Am J Respir Crit Care Med, 2002. **166**(11): p. 1491-7.
51. Weiner, P., R. Magadle, M. Beckerman, M. Weiner, and N. Berar-Yanay, *Comparison of specific expiratory, inspiratory, and combined muscle training programs in COPD.* Chest, 2003. **124**(4): p. 1357-64.
52. Seron, P., P. Riedemann, S. Munoz, A. Doussoulin, P. Villarroel, and X. Cea, *[Effect of inspiratory muscle training on muscle strength and quality of life in patients with chronic airflow limitation: a randomized controlled trial].* Arch Bronconeumol, 2005. **41**(11): p. 601-6.
53. Beckerman, M., R. Magadle, M. Weiner, and P. Weiner, *The effects of 1 year of specific inspiratory muscle training in patients with COPD.* Chest, 2005. **128**(5): p. 3177-82.
54. Mador, M.J., O. Deniz, A. Aggarwal, M. Shaffer, T.J. Kufel, and C.M. Spengler, *Effect of respiratory muscle endurance training in patients with COPD undergoing pulmonary rehabilitation.* Chest, 2005. **128**(3): p. 1216-24.
55. Hill, K., S.C. Jenkins, D.L. Philippe, N. Cecins, K.L. Shepherd, D.J. Green, D.R. Hillman, and P.R. Eastwood, *High-intensity inspiratory muscle training in COPD.* Eur Respir J, 2006. **27**(6): p. 1119-28.

56. Koppers, R.J., P.J. Vos, C.R. Boot, and H.T. Folgering, *Exercise performance improves in patients with COPD due to respiratory muscle endurance training.* Chest, 2006. **129**(4): p. 886-92.
57. Weiner, P. and M. Weiner, *Inspiratory muscle training may increase peak inspiratory flow in chronic obstructive pulmonary disease.* Respiration, 2006. **73**(2): p. 151-6.
58. Madariaga, V.B., J.B. Iturri, A.G. Manterola, J.C. Buey, N.T. Sebastian, and V.S. Pena, *[Comparison of 2 methods for inspiratory muscle training in patients with chronic obstructive pulmonary disease].* Arch Bronconeumol, 2007. **43**(8): p. 431-8.
59. Magadle, R., A.K. McConnell, M. Beckerman, and P. Weiner, *Inspiratory muscle training in pulmonary rehabilitation program in COPD patients.* Respir Med, 2007. **101**(7): p. 1500-5.
60. Petrovic, M., M. Reiter, H. Zipko, W. Pohl, and T. Wanke, *Effects of inspiratory muscle training on dynamic hyperinflation in patients with COPD*, in *Int J Chron Obstruct Pulmon Dis*. 2012: New Zealand. p. 797-805.
61. Heijdra, Y.F., P.N. Dekhuijzen, C.L. van Herwaarden, and H.T. Folgering, *Nocturnal saturation improves by target-flow inspiratory muscle training in patients with COPD.* Am J Respir Crit Care Med, 1996. **153**(1): p. 260-5.
62. Kim, M.J., J.L. Larson, M.K. Covey, C.A. Vitalo, C.G. Alex, and M. Patel, *Inspiratory muscle training in patients with chronic obstructive pulmonary disease.* Nurs Res, 1993. **42**(6): p. 356-62.
63. Patessio, A., C. Rampulla, C. Fracchia, F. Ioli, U. Majani, A. De Marchi, and C.F. Donner, *Relationship between the perception of breathlessness and inspiratory resistive loading: report on a clinical trial.* Eur Respir J Suppl, 1989. **7**: p. 587s-591s.
64. Covey, M.K., J.L. Larson, S.E. Wirtz, J.K. Berry, N.J. Pogue, C.G. Alex, and M. Patel, *High-intensity inspiratory muscle training in patients with chronic obstructive pulmonary disease and severely reduced function.* J Cardiopulm Rehabil, 2001. **21**(4): p. 231-40.
65. Hsiao, S.F., Y.T. Wu, H.D. Wu, and T.G. Wang, *Comparison of effectiveness of pressure threshold and targeted resistance devices for inspiratory muscle training in patients with chronic obstructive pulmonary disease.* J Formos Med Assoc, 2003. **102**(4): p. 240-5.
66. Gosselink, R., J. De Vos, S.P. van den Heuvel, J. Segers, M. Decramer, and G. Kwakkel, *Impact of inspiratory muscle training in patients with COPD: what is the evidence?* Eur Respir J, 2011. **37**(2): p. 416-25.
67. Mota, S., R. Guell, E. Barreiro, I. Solanes, A. Ramirez-Sarmiento, M. Orozco-Levi, P. Casan, J. Gea, and J. Sanchis, *Clinical outcomes of expiratory muscle training in severe COPD patients.* Respir Med, 2007. **101**(3): p. 516-24.
68. Weiner, P., R. Magadle, M. Beckerman, M. Weiner, and N. Berar-Yanay, *Specific expiratory muscle training in COPD.* Chest, 2003. **124**(2): p. 468-73.

69. Caspersen, C.J., K.E. Powell, and G.M. Christenson, *Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research.* Public Health Rep, 1985. **100**(2): p. 126-31.

70. Haskell, W.L., I.M. Lee, R.R. Pate, K.E. Powell, S.N. Blair, B.A. Franklin, C.A. Macera, G.W. Heath, P.D. Thompson, and A. Bauman, *Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association*, in *Circulation*. 2007: United States. p. 1081-93.

71. Pitta, F., T. Troosters, V.S. Probst, M.A. Spruit, M. Decramer, and R. Gosselink, *Quantifying physical activity in daily life with questionnaires and motion sensors in COPD.* Eur Respir J, 2006. **27**(5): p. 1040-55.

72. Pitta, F., T. Troosters, M.A. Spruit, V.S. Probst, M. Decramer, and R. Gosselink, *Characteristics of physical activities in daily life in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2005. **171**(9): p. 972-7.

73. Vorrink, S.N., H.S. Kort, T. Troosters, and J.W. Lammers, *Level of daily physical activity in individuals with COPD compared with healthy controls*, in *Respir Res*. 2011: England. p. 33.

74. Pitta, F., T. Troosters, V.S. Probst, M.A. Spruit, M. Decramer, and R. Gosselink, *Physical activity and hospitalization for exacerbation of COPD.* Chest, 2006. **129**(3): p. 536-44.

75. Decramer, M., *Response of the respiratory muscles to rehabilitation in COPD*, in *J Appl Physiol*. 2009: United States. p. 971-6.

76. Duiverman, M.L., E.W. de Boer, L.A. van Eykern, M.H. de Greef, D.F. Jansen, J.B. Wempe, H.A. Kerstjens, and P.J. Wijkstra, *Respiratory muscle activity and dyspnea during exercise in chronic obstructive pulmonary disease*, in *Respir Physiol Neurobiol*. 2009: Netherlands. p. 195-200.

77. Pitta, F., M.Y. Takaki, N.H. Oliveira, T.J. Sant'anna, A.D. Fontana, D. Kovelis, C.A. Camillo, V.S. Probst, and A.F. Brunetto, *Relationship between pulmonary function and physical activity in daily life in patients with COPD.* Respir Med, 2008. **102**(8): p. 1203-7.

78. Watz, H., B. Waschki, C. Boehme, M. Claussen, T. Meyer, and H. Magnussen, *Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study.* Am J Respir Crit Care Med, 2008. **177**(7): p. 743-51.

79. Garcia-Rio, F., V. Lores, O. Mediano, B. Rojo, A. Hernanz, E. Lopez-Collazo, and R. Alvarez-Sala, *Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation.* Am J Respir Crit Care Med, 2009. **180**(6): p. 506-12.

80. Bossenbroek, L., M.H. de Greef, J.B. Wempe, W.P. Krijnen, and N.H. Ten Hacken, *Daily physical activity in patients with chronic obstructive pulmonary disease: a systematic review.* COPD, 2011. **8**(4): p. 306-19.

81. *ATS statement: guidelines for the six-minute walk test.* Am J Respir Crit Care Med, 2002. **166**(1): p. 111-7.

82. Garcia-Aymerich, J., P. Lange, M. Benet, P. Schnohr, and J.M. Anto, *Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study.* Am J Respir Crit Care Med, 2007. **175**(5): p. 458-63.
83. Waschki, B., A. Kirsten, O. Holz, K.C. Muller, T. Meyer, H. Watz, and H. Magnussen, *Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study.* Chest, 2011. **140**(2): p. 331-42.
84. Couillard, A., J.F. Muir, and D. Veale, *COPD recent findings: impact on clinical practice.* COPD, 2010. **7**(3): p. 204-13.

Experimental Study

Impact of a six-week inspiratory and expiratory muscle endurance training program on physical activity, physical working capacity and dyspnoea in patients with chronic obstructive pulmonary disease.

ABSTRACT

The present study, we aimed to analyze the effects of inspiratory and expiratory muscle endurance training (RMET) on the amount and intensity of physical activity, physical working capacity and dyspnoea in chronic obstructive pulmonary disease (COPD) patients. Sixteen subjects (mean forced expiratory volume in first second (FEV_1) of 45,5 ± 12,70% predicted) performed a six-week RMET protocol, at 30% of inspiratory and expiratory maximal pressures (Pimax and Pemax, respectively); in the final of third week inspiratory and expiratory loads were evaluated again for load adjustment. Training occurred 6 days per week. In the same time, thirteen subjects (FEV_1 49,0 ± 13,60 % predicted) did not perform any kind of respiratory training (No training group). Were obtained baseline and post-protocol measurements for lung function test, maximal voluntary ventilation (MVV), Pimax, Pemax, 6-minute walk test (6MWT) for evaluation of physical working capacity and physical activity through accelerometry. Comparing with baseline values, RMET group presented a significant improvement on Pimax (p = 0,006), Pemax (p = 0,024), dyspnoea (p = 0,043) and 6MWT (p = 0,041); No training (NT) group didn't present any significant alterations, in spite of Pemax increase had almost reach significance (p = 0,057). In physical activity, a significant differences for both groups were found in Steps per day (RMET p = 0,045; NT p = 0,040). In physical activity levels and maximal voluntary ventilation, no significant changes were observed. Between groups, training effect revealed no statistically differences. RMET could have a positive effect on respiratory muscles, improving strength, dyspnoea and physical working capacity. However, these improvements seem to be insufficient to change positively the amount and intensity of physical activity in COPD subjects.

Key Words: COPD; threshold; 6-minute walk test; accelerometry; symptoms.

INTROCUCTION

Chronic Obstructive Lung Disease (COPD), is defined as "*a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lung to noxious particles or gases*" [1]. Today, COPD is the 4th leading cause of death around the world. World Health Organization (WHO) estimated that it will become de 3rd mortality cause in 2030 [2].

Physical inactivity in COPD patients has been growingly studied. These patients present themselves with less physical activity than healthy subjects [3]. The lack of physical activity presents today as the strongest predictor of mortality in COPD patients when comparing with other prognostic factors [4], and for those who practice regular exercise, hospital admissions and respiratory-cause mortality are reduced [5].

Dyspnoea is usually the main factor that limit exercise capacity on COPD patients [6]. To this, respiratory muscles contribute in the way they are placed in disadvantage position [7-9]; also peripheral muscles contribute to this limitation through their structural and functional alterations and deconditioning [8, 10], related with disease. Here, pulmonary rehabilitation has demonstrated to improve not also dyspnoea, but other symptoms, exercise tolerance and health-related quality of life [11].

For many years, research has explored the impact of inspiratory muscle training on several COPD outcomes [12]. Less frequently, expiratory muscle training (EMT) has been studied in this kind of population but also with good results [13, 14]. Moreover, it's not available information about what impact could respiratory muscle training might have on physical activity levels in relation with physical working capacity.

Therefore, combined inspiratory and expiratory endurance training might produce respiratory increased endurance and strength and could probably enhance physical working capacity and dyspnoea. Consequently, this

improvement could have echo in the amount and intensity of movement produced and so, on COPD patients' daily physical activity.

The purpose of this study was to evaluate the possible changes produced by inspiratory and expiratory muscle endurance training on the amount and intensity of physical activity, physical working capacity and dyspnoea in COPD patients.

MATERIAL AND METHODS

Subjects

Individuals who had medical diagnosis of COPD, a forced expiratory volume in first second ($FEV_{1)}$ bellow 80% of their predicted value (grade II, III and IV from GOLD classification for airflow obstruction severity) and ages between 45 and 75 were recruited. Exclusion criteria included: 1) use of long-term oxygen therapy (LTOT); 2) instable or moderate-to-severe cardiac disease; 3) vascular disease; 4) other types of disease which preclude physical activity execution; 5) cognitive problems; 6) recent abdominal or thoracic surgery; 7) body mass index (BMI) over 35 kg/m^2; 8) use of ambulation aids; and 9) participation in pulmonary rehabilitation or any formal exercise program.

The study was approved by appropriate ethics committee and informed consent was obtained from participants. These were recruited in Pneumology department of Alto Ave Hospital Center in Guimarães, Portugal.

Study Design

A prospective, randomized and controlled design study was used with a treatment group undergoing 6 weeks of respiratory muscle endurance training (RMET) and a control group with No Training (NT) (figure 1).

The study design comprehended 3 phases. The first phase occurred between January and April of 2013. In this period 32 patients meet the inclusion criteria. During this time, the exclusion criteria were verified through patients' interview and hospital informatics system. Baseline assessment integrated the following items: 1) lung function test and respiratory muscle function; 2) perception of breathlessness; 3) physical working capacity through 6-minute walk test (6MWT); and 4) daily physical activity. After the recruitment and

assessment, patients were allocated to RMET or NT group. A manually allocation was performed, with a stratified randomization by sex, age and airflow obstruction severity.

In the second phase of the protocol, it was done a call up of those subjects who were allocated to the RMET group. The main investigator explained the training protocol as well as scheduled the upcoming hospital visits according to the training program.

The third and final phase, which occurred between July and August of 2013, commenced when the first subject of RMET group finalized the training protocol. At the same time, it was started the call up of subjects from NT group.

Importantly to note that between baseline evaluation and post-protocol evaluation, patients maintained their stable status. Three patients from control group withdrew during the study: one for acute vascular problems and two for transportation problems. Also, for the remaining patients in NT group, 2 started nocturnal noninvasive ventilation for sleep apnea treatment. In RMET group, there were nothing to point out.

Measurements

1) lung function test and respiratory muscle function.

Post-bronchodilation measurements of spirometry, body plethysmography and single-breath lung diffusion *(Jaeger® Masterscreen® Body, Wurzburg, Germany)*, were obtained according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations [15-17]; the used reference values are according to the most recent recommendations [18]. Also, maximal voluntary ventilation (MVV) was assessed [15].

Meanwhile, respiratory muscles strength was also tested through maximal inspiratory pressure (Pimax) and maximal expiratory pressure

(Pemax), according to the technique [19] and reference values already described [20-22]. Due to the absence of Portuguese reference values, were used international accepted reference values.

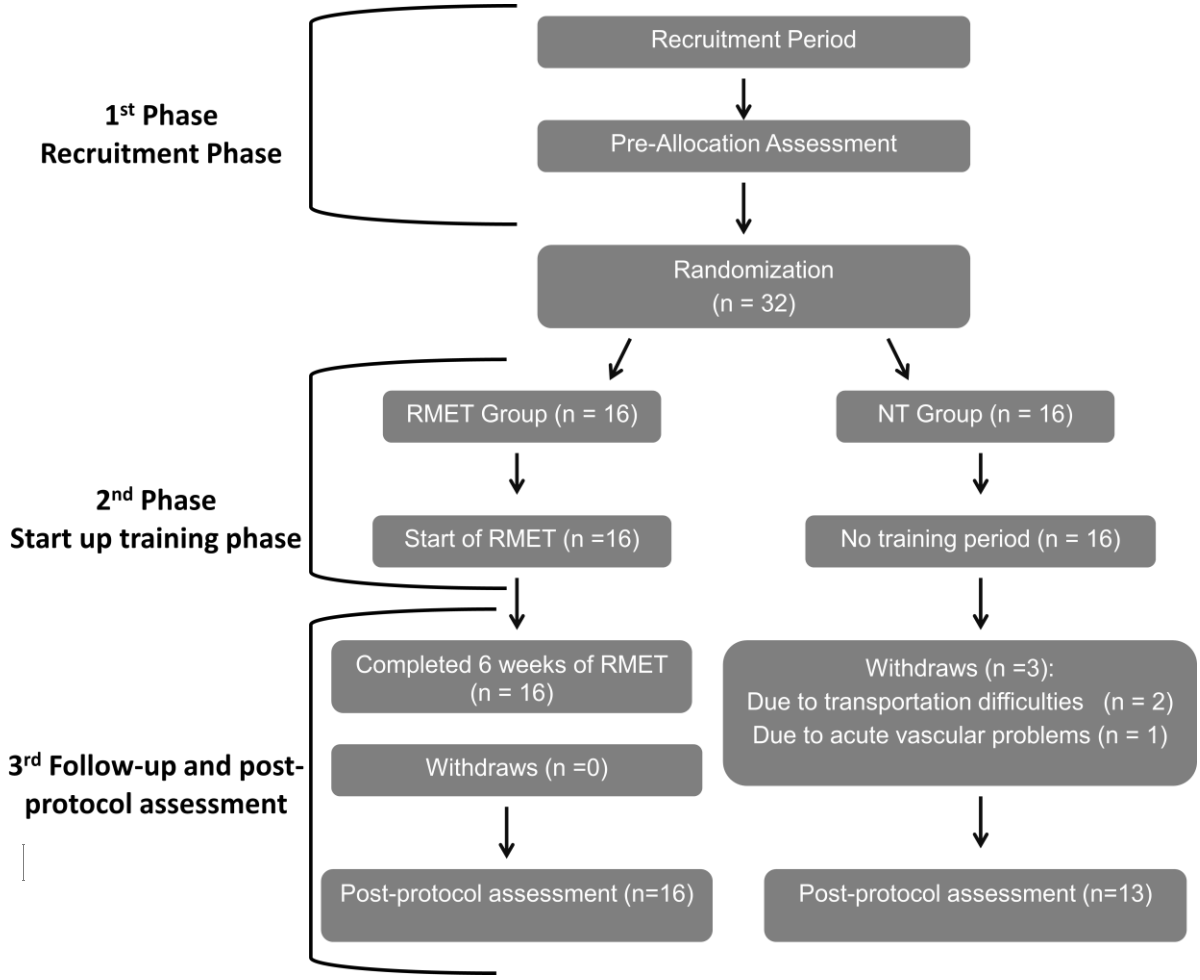

Figure 1 - Study Design. RMET: Respiratory muscle endurance training; NT: No training

2) Dyspnoea

Dyspnoea was assessed with *Modified British Medical Research Council* (mMRC) dyspnoea scale [23]. This is a 5 items scale which evaluates the grade of perceived breathlessness. The subjects are asked to select a grade between 0 and 4 (mMRC grade 0 – *"I only get breathless with stenous exercise"*; mMRC grade 1 – *"I get short of breath when hurrying on the level or walking up a slight hill"*; mMRC grade 2 – *"I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level"*; mMRC grade 3 – *"I stop for breath after walking about*

100 meters or after a few minutes on the level"; mMRC grade 4 – *"I am too breathless to leave the house or I am breathless when dressing or undressing"*). The bigger the value selected, bigger the grade of perceived breathlessness.

3) 6-minute walk test

The 6MWT was used to assess physical working capacity. The procedures were executed according to ATS recommendations [24]. 6MWT is a practical simple test. It evaluates the level of sub-maximal functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. Because most of the activities of daily living (ADL) are performed in sub-maximal levels of exertion, the 6MWT is probably the better field test to reflect the physical working capacity during daily physical activities [24], also presenting good correlation with physical activity in COPD population [3, 25]. The outcome used for analysis was distance.

4) Daily Physical activity.

To evaluate daily physical activity (DPA) levels, it was used the accelerometry through Actigraph GT1M® monitor (*Actigraph®, Pensacola FL, USA*).

Subjects wore the device on the right waist for 5 to 7 consecutive days, with the recommendation to only take off the device during the sleep and for personal hygiene purpose. The reason for this type of prolonged time of device wearing was in order to avoid bias related with a more active behavior adopted by subjects because they know they are being monitored [26].

The registered activity was based on a 60 seconds Epochs. A valid evaluation comprehended a minimum of 500 minutes per day of recorded activity and at least 4 valid days. Periods ≥ 90 minutes of consecutive zero counts were considered as a non-wear time (allowing periods ≤ 2 minutes of non-zero counts).

The main outcome was activity counts and steps per day. In the absence of specific “cut-off” points for COPD patients, it was adopted those proposed by *Freedson* and colleagues for healthy adult subjects [27]. These authors described the following levels of physical activity based on accelerometer counts: *Sedentary, Light, Lifestyle, Moderate, Vigorous and Very Vigorous.* However, despite the absence of values for *Very Vigorous* and an existence of residual values in *Vigorous*, it was adopted to merge levels *Moderate and Vigorous*. *Very Vigorous* was not displayed.

To analyze data, it was used the proper devices software, Actilife© v6.5.1 (*Actigraph®, Pensacola FL, USA*).

Training devices and protocols

After randomization, subjects allocated to RMET group carried out a six weeks non-supervised, home-based, respiratory muscle endurance training using specific inspiratory (*Threshold IMT®*,*Phillips Respironics, Inc.*) and expiratory (*Threshold PEP®* ,*Phillips Respironics, Inc.*) devices; the seventh day of each week was considered as a rest day. The training program initiation was performed at the Hospital. All the training process was properly explained.

Threshold training devices impose a critical pressure through a flow-independent valve; this set up pressure need to be overcome in order to respiratory flow began [28]. These devices present an adjustable resistance which varies between 0 and 41 for *Threshold IMT®*; for *Threshold PEP®* the resistance variation range between 0 and 20. For both devices, resistance pressure is defined in centimeters of water (cm/H_2O).

In training days, subjects performed 7 blocks of 2 minutes intervaled by 1 minute of rest for each respiratory loading device. This results in 21 minutes of training for each respiratory musculature group. During each 2-minute block, subjects breathe through the devices. Also, during training they were free to choose their own breathing pattern [29]. The intensity training chosen for both

devices was 30% of inspiratory and expiratory maximal pressures (*Pimax* e *Pemax*, respectively) [30, 31]. Subjects were advised to execute both trainings always on the same sequence (e.g.: 1st inspiratory and 2nd expiratory, for example) and at different times of day (e.g.: inspiratory training at morning and then expiratory training at afternoon, for example) in order to avoid fatigue influence.

In the specific case of expiratory muscle training device, was created an equation in order to compensate its maximal resistance pressure limitation of 20 cm/H_2O through an augmentation of each cycle time, maintaining endurance training demands. The equation is as follows and its result represents an approximated time for each expiratory training cycle in seconds: *[(30% Pemax – 20) / 20 x 120 + 120 = (seconds)]*. The fixed time for an expiratory endurance time increment was settled in improvements of 30 seconds.

During the training with both devices, subjects used a nose clip to ensure that respiratory pressure was only performed through the respiratory devices [32]. After 3 weeks of training, a new Pimax and Pemax was evaluated in order to adjust new inspiratory and expiratory loads [33]. Along the training, subjects completed a diary in which they reported their training regimen [34]. This diary contained information like training day; number of cycles completed or pressure loading prescription. Training adherence was controlled and encouraged through phone calls at the second and fifth weeks. These contacts also represented a way of taking doubts.

Statistical Analysis

It was used a 95% confidence interval. The significance index was defined as *alpha* = 0,05. Data is present as mean and standard deviation (SD). The Shapiro-Wilk test was used to test the presence of a normal distribution.

Within groups, the t-test for two related samples or the Wilcoxon Signed-Rank test were used to search statistically significant differences in case of

normal or non-normal distributions, respectively. For differences between groups at post-protocol moments, we used the two independent samples T-test or Mann-Whitney test, varying on sample normal distribution presence, based on baseline/post-protocol percentage variation of parameters (Pimax, Pemax, MVV, 6MWT, Steps per day, Counts per minute, DPA levels). Exception for this percentage variation usage was applied for MRC dyspnoea scale in reason of its categorical propriety.

In the same way, it was used *Person* or *Spearman* correlations test (in case of parametric or non-parametric distributions, respectively), in order to assess any relationship between the training effect on respiratory muscles and other functional variables (MVV, 6MWT, *Steps per day* and *Counts per minute*).

IBM SPSS v.20 was the program used for statistical analysis and generating.

RESULTS

Twenty-nine subjects included the study; sixteen (14 males, 2 females) integrated the RMET group with a mean age of 59,9 ± 6,92 years and a FEV_1 (% predicted value) of 45,5 ± 12,70. In other hand, NT group included thirteen subjects (12 males, 1 female) with a mean age of 59,9 ± 8,00 years and FEV_1 (% predicted value) of 49,0 ± 13,60. Anthropometric characteristics and lung function tests are displayed in table 1. No differences were found between baseline and post-protocol values within groups; also between baseline values of both groups, no differences were presented.

Respiratory muscle function

In RMET group, inspiratory and expiratory muscles strength showed significant improvements (p = 0,006 and p = 0,024, respectively). Inclusively, Pimax in RMET group presented significance for a confidence interval of 99%. In other hand, those results were not seen in control group, where also some improvements were observed, mainly in Pémax; despite this, significance was not reached for both parameters (Inspiratory p value = 0,448; expiratory p = 0,057) (see table 2).

Between groups, the training effect resulted in no differences. Despite this, for Pimax (RMET % variation 11,5 ± 15,55, NT % variation 4,4 ± 12,39) significance was almost reached (p value = 0,132,). In the case of Pemax (RMET % variation 9,0 ± 14,44, NT % variation 9,6 ± 17,21) differences for groups resulted in a p value of 0,924(see figure 2).

TABLE 1 Subjects' anthropometric characteristics and lung function tests

	RMET Group (n = 16)		NT Group (n = 13)	
Anthropometric characteristics				
Age (years)	59,9 ± 6,92		59,9 ± 8,00	
Male/Female	14/2		12/1	
Height (m)	1,63 ± 0,673		1,65 ± 0,762	
Weight (Kg)	67,5 ± 12,04		74,5 ± 15,93	
BMI ($m \cdot kg^{-2}$)	25,6 ± 4,40		27,4 ± 4,81	
Current smokers	3		5	
	Baseline	**Post-Protocol**	**Baseline**	**Post-Protocol**
Lung Function Tests				
FVC (L)	3,03 ± 0,758	2,94 ± 0,619	3,19 ± 1,195	3,12 ± 1,060
FVC % pred.	89,6 ± 15,96	87,1 ± 12,10	88,5 ± 20,79	87,3 ± 18,69
FEV_1 (L)	1,21 ± 0,325	1,14 ± 0,309	1,416 ± 0,568	1,38 ± 0,516
FEV_1 % pred.	45,5 ± 12,70	42,7 ± 12,27	49,0 ± 13,60	48,0 ± 12,18
FEV1 / FVC (%)	40,66 ± 8,569	39,24 ± 9,974	44,45 ± 9,082	44,03 ± 8,485
PEF (L/s)	3,46 ± 0,948	3,28 ± 1,046	4,43 ± 1,602	4,26 ± 1,528
PEF % pred.	46,8 ± 11,18	44,3 ± 12,13	57,4 ± 16,41	55,3 ± 15,25
RV (L)	4,19 ± 1,225	4,39 ± 1,065	3,78 ± 0,658	3,90 ± 0,982
RV % pred.	192,3 ± 52,46	201,9 ± 44,72	170,9 ± 25,35	175,7 ± 41,08
TLC (L)	7,37 ± 1,406	7,57 ± 1,470	7,12 ± 1,646	7,19 ± 1,512
TLC % pred.	126,5 ± 16,33	129,9 ± 17,86	117,6 ± 17,77	119,5 ± 18,70
ERV (L)	1,05 ± 0,585	1,04 ± 0,404	0,92 ± 0,436	0,85 ± 0,475
ERV % pred.	101,5 ± 43,77	102,5 ± 34,77	90,6 ± 42,75	80,6 ± 39,17
RV / TLC (%)	56,28 ± 8,993	57,93 ± 7,072	54,11 ± 7,045	54,53 ± 9,273
RV / TLC % pred.	150,2 ± 24,30	154,2 ± 18,06	144,7 ± 13,82	144,8 ± 19,59
TLCO / VA	1,03 ± 0,388	1,03 ± 0,343	1,13 ± 0,394	1,15 ± 0,358
TLCO / VA % pred.	74,3 ± 27,12	73,5 ± 23,63	81,5 ± 26,29	83,2 ± 23,17
TLCO SB	5,51 ± 1,968	5,11 ± 1,489	5,90 ± 2,084	5,93 ± 2,132
TLCO SB % pred.	69,1 ± 25,72	64,00 ± 18,50	69,5 ± 16,77	69,9 ± 16,82

Note: Data are presented as mean ± standard deviation (SD); Predicted values retrieved from [18]; No statistically significant differences were found between groups ($p \geq 0,05$) for anthropometric characteristics; No statistically significant differences were found within groups ($p \geq 0,05$) for lung function tests.

Abbreviations: RMET, respiratory muscle endurance training; NT, no training; BMI, body mass index; pred., predicted; FVC, forced vital capacity; FEV_1, Forced expiratory volume in one second; PEF, Peak expiratory flow; RV, Residual volume; TLC. Total lung capacity; ERV, Expiratory reserve volume; TLCO / VA, Diffusing capacity for carbon monoxide per unit of alveolar volume; TLCO SB, Diffusing capacity for the lungs measured using carbon monoxide, also known as transfer factor.

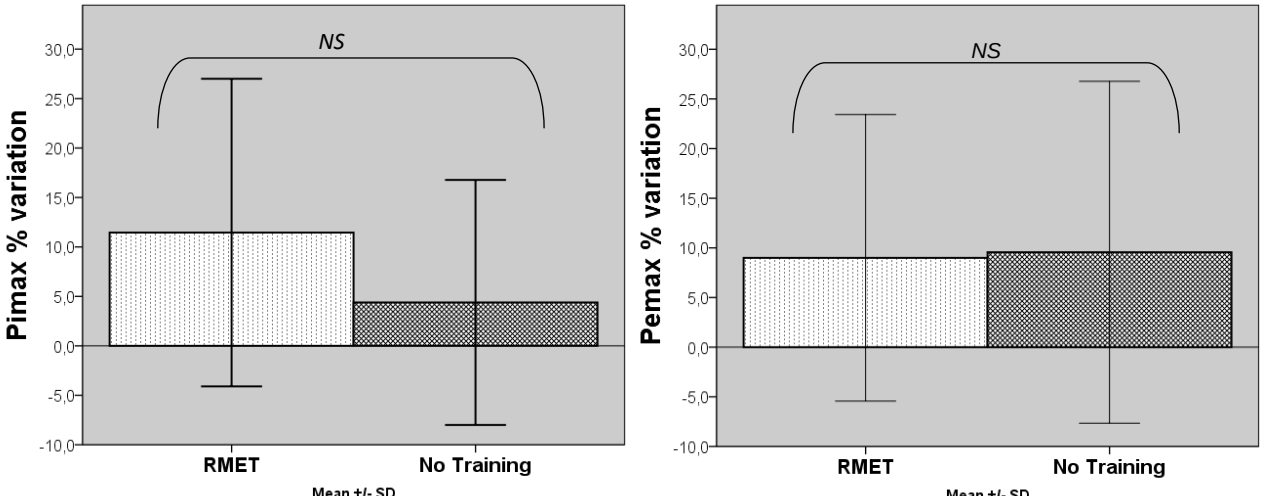

Figure 2 – Mean values (± SD) and statistical differences for groups comparison, in Pimax and Pemax % variations between baseline and post-protocol assessments; *NS* – $p \geq 0,05$.

Abbreviations: SD, standard deviation; Pimáx, inspiratory maximal pressure; Pemax, expiratory maximal pressure; RMET, respiratory muscle endurance training; NT, no training; NS, not significant.

Maximal voluntary ventilation

MVV was analyzed in order to search for some respiratory muscle endurance improvements. Between groups statistical analysis (see figure 3) resulted in non significant values of 0,622 for MVV absolute values (RMET % variation -3,2 ± 19,52, NT % variation -6,7 ± 17,51).

Analyzing data, it was observed a decrease on MVV capacity for both RMET (*p* value = 0,325) and NT (*p* value = 0,237) groups (see table 2).

Dyspnoea

About perception of breathlessness (table 2), our study found statistical significant improvements on RMET group by a decrease on MRC dyspnoea scale (2,1 ± 0,81 points to 1,8 ± 0,87 points; *p* value = 0,043). In other hand, NT group revealed a non significant increase on perception of breathlessness (1,3 ± 0,95 points to 1,4 ± 0,87 points; *p* value = 0,230). Between group comparison

(see figure 4) fail to reveal statistical significance (RMET variation -0,3 ± 0,60 points, NT variation 0,1 ± 0,64; *p* value = 0,156).

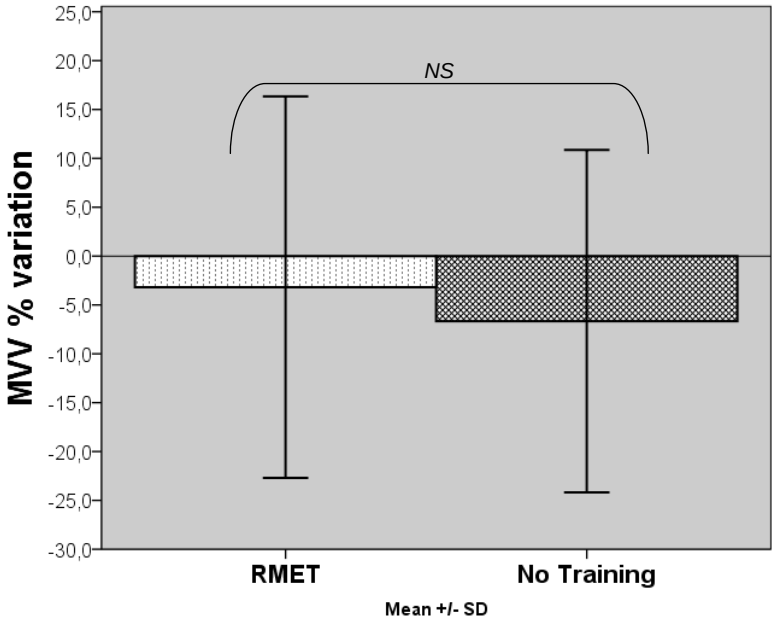

Figure 3 – Mean values (± 1 SD) and statistical differences for groups comparison, in MVV % variation between baseline and post-protocol assessments; *NS* – *p* ≥ 0,05.

Abbreviations: SD, standard deviation; MVV, maximal voluntary ventilation RMET, respiratory muscle endurance training; NT, no training; NS, not significant.

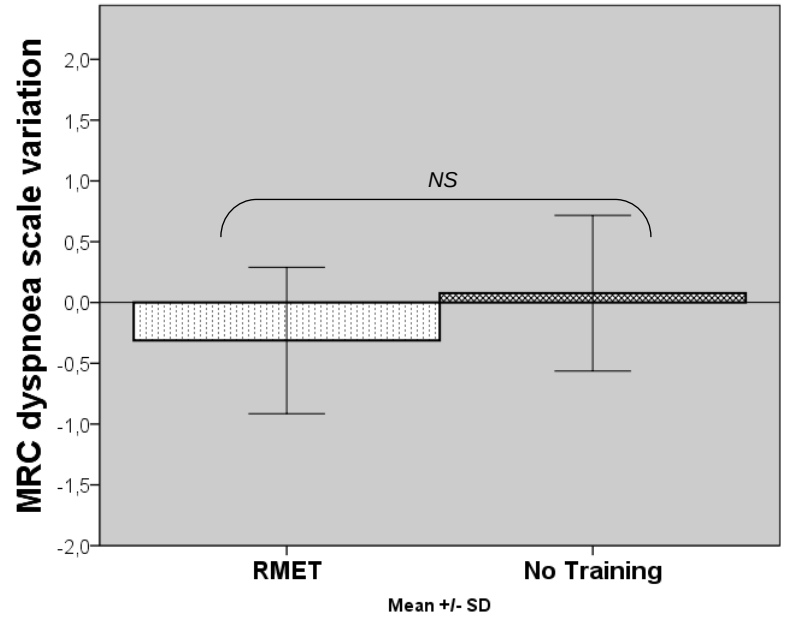

Figure 4 – Mean values (± 1 SD) and statistical differences for groups comparison, in MRC dyspnoea scale difference between baseline and post-protocol assessments; *NS* – *p* ≥ 0,05.

Abbreviations: SD, standard deviation; MRC, Medical Research Council; RMET, respiratory muscle endurance training; NT, no training; NS, not significant.

6-minute walk test

The RMET group showed a significant improvement on 6MWT distance (from 442, 2 ± 58,77 meters to 460,7 ± 46,88 meters; *p* value = 0,041) meanwhile NT group do not show significant differences (437,3 ± 66,51 meters to 447,08 ± 68,07 meters; *p* value = 0,240) (see table 2). Between groups comparison showed no statistical differences (RMET % variation of 4,8 ± 8,31, NT % variation 2,4 ± 7,09; *p* value = 0,402) (see figure 5).

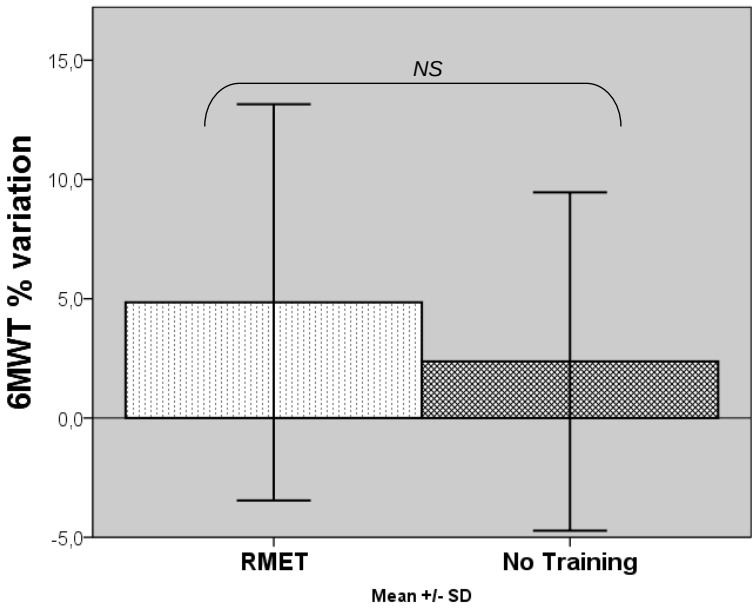

Figure 5 - Mean values (± SD) and statistical differences for groups comparison, in 6MWT % variation between baseline and post-protocol assessments; *NS* – *p* ≥ 0,05.

Abbreviations: 6MWT, six-minute walk test; SD, standard deviation; RMET, respiratory muscle endurance training; NT, no training; NS, not significant.

TABLE 2	Training effect on Pimax, Pemax, MRC dyspnoea scale and 6MWT			
	RMET Group (n = 16)		NT Group (n = 13)	
	Baseline	Post-Protocol	Baseline	Post-Protocol
Pimax (kPa)	7,6 ± 1,70	8,4 ± 1,88 §	8,6 ± 2,40	8,8 ± 1,85
Pemax (kPa)	11,6 ± 2,02	12,6 ± 2,20 *	12,7 ± 2,15	13,8 ± 2,46 #
MVV (liters)	45,2 ± 13,23	43 ± 12,95	58,0 ± 18,57	54,2 ± 21,60
MRC dyspnoea scale	2,1 ± 0,81	1,8 ± 0,87 *	1,3 ± 0,95	1,4 ± 0,87
6MWT (meters)	442,2 ± 58,77	460,7 ± 46,88 *	437,3 ± 66,51	447,08 ± 68,07

Note: Data are presented as mean ± SD; * - $p < 0,05$; § - $p < 0,01$; # - $p < 0,10$; when compared with baseline values.

Abbreviations: RMET, respiratory muscle endurance training; NT, no training; Pimax, maximal inspiratory pressure, Pemax, maximal expiratory pressure, MVV, maximal voluntary ventilation; MRC, *Medical Research Council*, 6MWT, six-minute walk test; SD, standard deviation;

Daily Physical Activity

In what concerns about *steps per day* (table 3), both groups presented improvements when compared with baseline values. This difference was significant for both RMET (p value = 0,045) and NT (p value = 0,040) groups. Relating to between groups comparison (see figure 6), RMET group present a 27,2 ± 41,87 % variation, while NT group presented a 22,8 ± 36,03 % variation; this was not statistically significant (p value = 0,771).

On *activity counts per minute* (see table 3), like on steps per day, both groups improved their values from baseline to post-protocol time but no statistical differences were found (RMET: p value = 0,379; NT: p value = 0,389). This resulted was also a non significant difference for between groups

comparison (RMET % variation of 17,5 ± 38,01; NT % variation of 14,8 ± 39,90; *p* value = 0,853) (see figure 6).

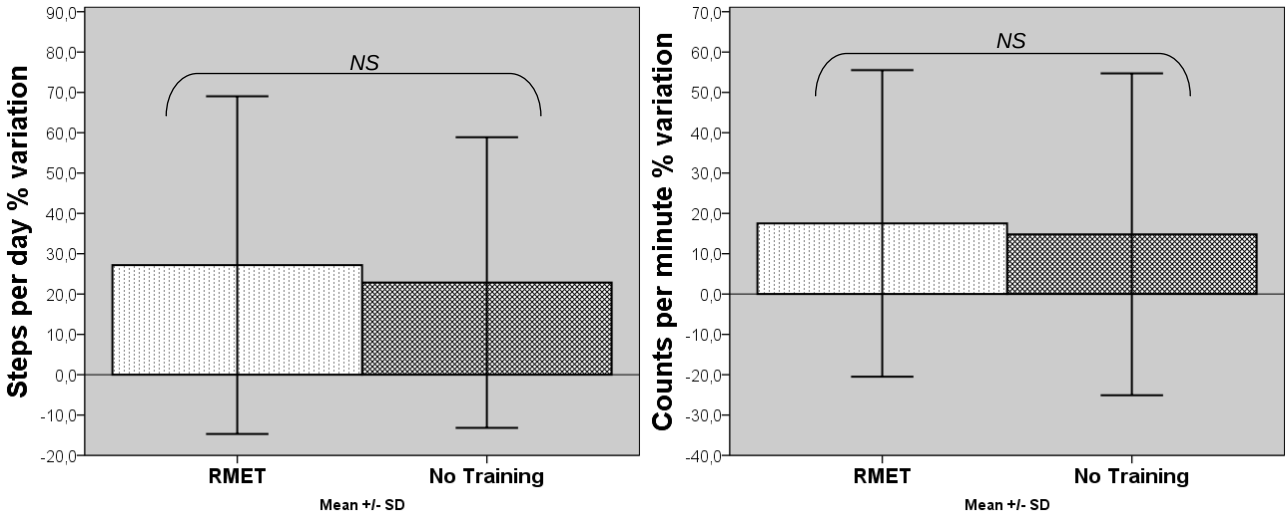

Figure 6 – Mean values (± SD) and statistical differences for groups comparison, in Steps per day and counts per minute % variations between baseline and post-protocol assessments; *NS* – *p* ≥ 0,05.

Abbreviations: SD, standard deviation; RMET, respiratory muscle endurance training; NT, no training; NS, not significant.

Table 3 shows the application of cut points previously described for healthy subjects [27]; it can be noted that both groups reduced their time in *Sedentary* level (RMET: *p* value = 0,836 : NT: *p* value = 0,789) despite it wasn't statistically significant. On *Light* DPA level, both groups increased their minutes per day. In fact, NT group reached significance for a 99% confidence interval (*p* value = 0,008), while baseline and post protocol differences for RMET group almost touch significance (*p* value = 0,056).

Passing to more physically active levels, in *Lifestyle* DPA was observed similar increases for both groups (RMET: *p* value = 0,121; NT: *p* value = 0,087). Here again, and despite the non significant results, were observed significance approximated values.

TABLE 3	Daily physical activity measurements			
	RMET Group (n = 16)		NT Group (n = 13)	
	Baseline	Post-Protocol	Baseline	Post-Protocol
Activity counts (per minute)	283,3 ± 107,01	303, 9 ± 74,53	254,3 ± 118,18	273,3 ± 111,88
Steps per day	5951,0 ± 2423,44	6970 ± 2336,08 *	5467,0 ± 2164,19	6432,7 ± 2641,96 *
Sedentary time (minutes/day)	458,4 ± 135,99	452,9 ± 82,81	497,31 ± 132,61	490,5 ± 160,26
Light PA time (minutes/day)	205,7 ± 58,23	233,6 ± 64,40 #	200,4 ± 55,23	251,1 ± 101,08 §
Lifestyle PA time (minutes/day)	65,8 ± 29,64	80,8 ± 30,48	64,1 ± 42,16	77,0 ± 47,21 #
Moderate to Vigorous PA time (minutes/day)	21,1 ± 18,82	22,5 ± 14,74	17,7 ± 12,24	17,9 ± 12,59

Note: Data are presented as mean ± SD; * - $p < 0,05$; § - $p < 0,01$; # - $p < 0,10$; when compared with baseline values;

Counts cut points for activity levels, retrieved from [27]: *Sedentary* – 0 to 99 counts; *Light* – 100 to 759 counts; *Lifestyle* – 760 to 1951 counts; *Moderate* – 1952 to 5724 counts; Vigorous – 5725 to 9498 counts.

Abbreviations: SD, standard deviation; RMET, respiratory muscle endurance training; NT, no training; PA, physical activity.

Finally, regarding *Moderate to Vigorous* DPA level, a slightly clinical non-significant improvement was observed for RMET (p value = 0,352) while NT group relatively maintained its values (p value = 0,927).

About the training effect (see figure 7), in none of the four physical activity levels: *Sedentary* (RMET % variation: 2,7 ± 19,80; NT % variation: -1,0 ± 19,51), *Light* DPA (RMET % variation: 16,6 ± 24,71; NT % variation: 22,8 ± 23,49), *Lifestyle* DPA (RMET % variation: 36,3 ± 59,23; NT % variation: 38,9 ± 81,91) and *Moderate to Vigorous* DPA (RMET % variation: 50,8 ± 83,61; NT % variation: 39,0 ± 122,84) were observed statistically significant result (p = 0,614, p = 0,496, p = 0,984, p = 0,423; respectively).

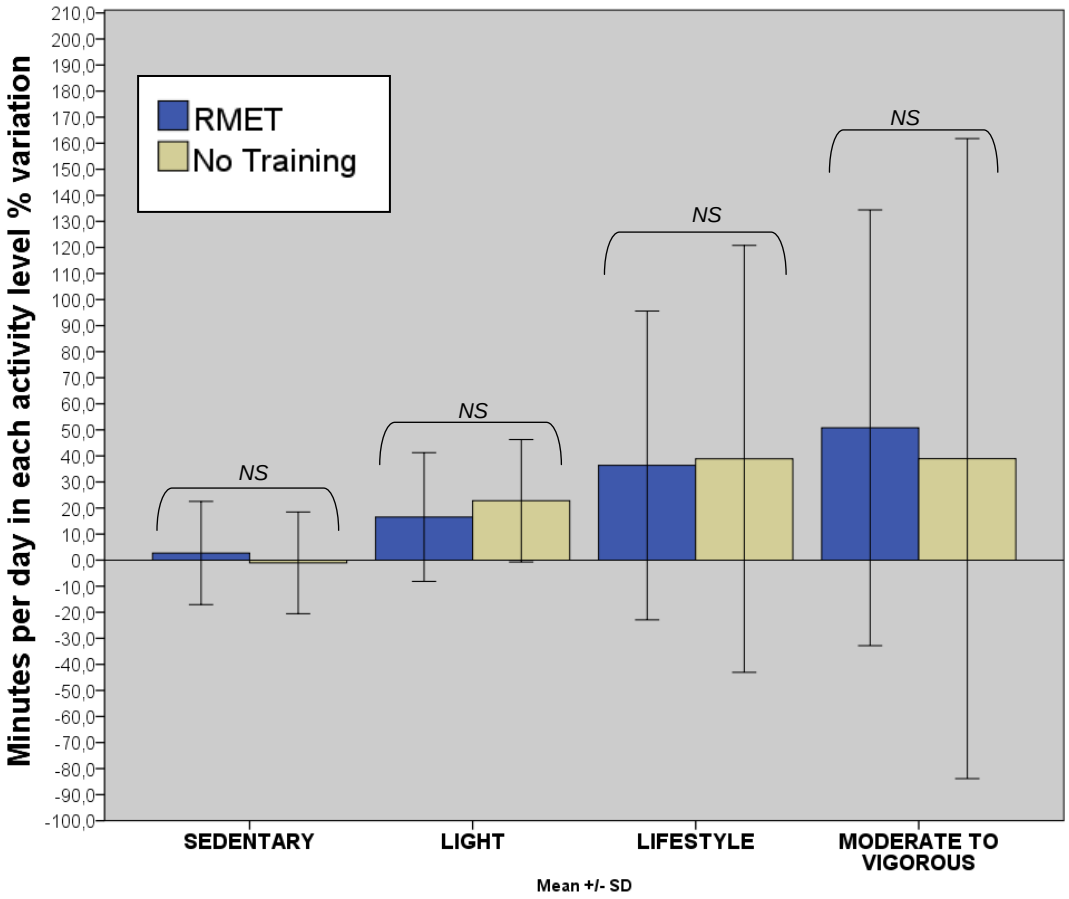

Figure 7 – Mean values (± SD) and statistical differences for groups comparison, in each four DPA levels % variations between baseline and post-protocol assessments; *NS* – $p \geq 0,05$.

Abbreviations: SD, standard deviation; RMET, respiratory muscle endurance training; NS, not significant; DPA, daily physical activity.

Correlations

Finally, on correlations between respiratory maximal pressures (Pimax and Pemax) and MVV (% variation), 6MWT (% variation), Steps per minute (% variation) and *Counts per minute* (% variation), it wasn't found any type of positive or negative correlations between this variables (see table 4).

TABLE 4 **Correlations between respiratory muscles % variation and MVV % variation, 6MWT % variation, *Steps per day* % variation and *Counts per minute* % variation**

		MVV % variation	6MWT % variation	*Steps per day* % variation	*Counts per minute* % variation
RMET group	Pimax % variation	0,429 (0,213)	0,063 (-0,475)	0,500 (0,182)	0,530 (0,170)
	Pemax % variation	0,989 (0,004)	0,224 (0,322)	0,744 (-0,089)	0,178 (-0,354)
NT group	Pimax % variation	0,555 (-0,181)	0,670 (-0,131)	0,400 (0,255)	0,464 (0,223)
	Pemax % variation	0,368 (-0,272)	0,393 (0,259)	0,304 (-0,309)	0,308 (-0,307)

Note: Data for each correlation are presented as *p* value (r).

Abbreviations: MVV, maximal voluntary ventilation; 6MWT, 6-minute walk test; Pimax, maximal inspiratory pressure; Pemax, maximal expiratory pressure; RMET, respiratory muscle endurance training; NT, no training.

DISCUSSION

According to the results of our study, respiratory muscles presented significant improvements on respiratory muscle strength as a main training effect. Comparison between groups failed to reach significance, despite that Pimax increment almost reach statistical significance. Moreover, inspiratory muscles revealed a greater response than expiratory which translate into significance for 99% interval confidence.

Nowadays, we think still don't exist a good definition to what can be called as a "endurance" or "strength" trainings on respiratory muscles. Some authors have used specific respiratory trainings in order to speculate for endurance improvements, like normocapnic hyperpnea [32, 34, 35]. With this type of training, it was found some statistical significance differences on constant load cycling endurance [34], sustainable pressure [32, 34], Pimax [32, 35], 6MWT [32], maximal oxygen consumption [32] and on Health Related Quality of Life (HRQoL) [34]. In our study, we used a combination of inspiratory and expiratory threshold training and we adopted the term "respiratory muscle endurance training" (RMET) due to the usage of low loads (e.g.: 30% for Pimax and for Pemax) and multiple repetitions (patients' resting ventilatory frequency). In fact, due to expiratory threshold device limitation of pressure, we also tried an adjustment by compensating the lack of resistance with a bigger amount of time for each training cycle. In order to evaluate some potential "endurance" alterations, we used MVV. However, and despite it's previously described good correlation with respiratory muscles [36], we couldn't find any responsiveness to RMET.

As we have said previously, we used simultaneously two threshold devices, each one for the two ventilatory phases. Regarding the fact that a great scientific "investment" have been made on inspiratory muscle training (IMT), we also used EMT for the reason that this specific musculature is often recruited when subjects are in exertion conditions; so we intended to add this training to the protocol in the way that it could have a similar demand as inspiratory training. Despite this, few studies have been made particularly attention to EMT.

Weiner and colleagues tried to isolate EMT with a 60% of Pemax. They found significant differences on expiratory strength and endurance between experimental and control group; 6MWT improved significantly only within the trained group [13]. In another study about EMT, improvements of expiratory strength, 6MWT, dyspnoea and HRQoL were also found [14].

About IMT, the main conclusions of a recent meta-analysis state that "*inspiratory muscles training present some evidence about their benefits in respiratory muscle strength and endurance, resulting in reduction of dyspnoea, improvements in physical working capacity and health related Quality of Life (QoL); this type of training also shows more effectiveness on COPD patients with more advanced inspiratory muscle weakness (Pimax bellow 60 cm/H_2O) and as a part of a pulmonary rehabilitation program*" [12]. Also, IMT alone have showed significant structural adaptations in COPD patients. *Ramírez-Sarmiento* and colleagues, found a significant increase on type I fibers proportion (by about 38%) and type II fibers size (by about 21%) in external intercostals muscles, by a 5 weeks with 60% of Pimax load, when compared with a control group [37]. Despite this, on IMT has been observed a variety of protocols, where some have used low loads (30% of Pimax) like our protocol [30, 31, 38-40], 40% of load [33], 50% of load [37, 41-43], 60% of load [44-48], 70% of load [49], high-intensity load (as tolerated) [29, 50, 51], incremental load along the training protocol with a predefined limit [52, 53].

Only one study had addressed a real similar training protocol like ours. *Weiner* and colleagues, applied a 3 months IMT plus EMT training protocol, based on 60% of Pimax and Pemax. In this research, it was compared IMT alone, EMT alone and IMT + EMT. The authors found a statistically significance within groups for Pemax in EMT alone and IMT + EMT; also found the same kind of difference in Pimax for IMT alone and IMT + EMT. Relevant improvements were also found for 6MWT and perception of dyspnoea in IMT group and IMT + EMT [48]. Despite its more prolonged time and superior training load, we presented similar results than the previously referred study, regarding Pimax and Pemax, 6MWT distance and perception of dyspnoea.

In our study, we also observed those decrease on perception of breathlessness and an increase on physical working capacity (6MWT distance). However it fails to reach significance on between group comparisons. Relatively to physical activity, no differences were seen regarding our respiratory endurance training application.

In COPD, physical activity is frequently impaired [3]. Inactivity may be one of the cornerstones on diseases progression. Along with deconditioning and muscle atrophy, all lead to a decrease in functional capacity. In fact, physical inactivity is thought to be a major therapeutic target in COPD [54]. According to some findings, 6MWT is a good predictor for inactivity during daily life in this population [3, 25]. In other hand, dyspnoea seems to be the main exercise limitation factor related to lung hyperinflation and mechanical restriction, which causes inefficient tidal volumes and minimal inspiratory reserve volumes, during exertion [6]; also dynamic hyperinflation correlate well with the amount of physical activity produced by COPD patients [25]. In spite of this and for the fact that we effectively could change dyspnoea and 6MWT positively, this might take us to the idea that respiratory muscle training can't produce enough effects to assure a significant clinical improvement on daily voluntary physical activity of COPD patients. We also didn't observe any correlations between respiratory muscle strength (which presented better responsiveness to our training than an endurance test like MVV), 6MWT and DPA. Interestingly, in our study, also we observed some improvements on DPA by NT group. This takes us to the idea that behavioral factors might play an extremely important role. Probably, a better understanding of all environmental factors (emotional and social) and a history of education for physical activity practice, might influence the individual perspective of COPD patients on how they would accept a new starting stimulus to exercise or an improvement on their physical activity daily practice; the amount of exercise prior to the disease's diagnosis could also be one the keys. Relating to this, the increase on DPA by the NT group may be also due to a more sensitiveness from health care professionals and governmental politics who promote the regular practice of physical exercise.

In other hand, through our study we also could speculate that respiratory muscles, in terms of DPA, might function as one more limiting factor, but not as stimulator when an improvement on their specific performance is observed.

The appearance of more research about respiratory muscle training impact on physical activity in COPD patients will help to clarify this issue.

Looking to the limitation of this research, studies with bigger and more homogeneous samples would produce better results and that a more restrict sample selection, by severity or , will lead to a more distinguish results.

Finally, for the fact that we have used an expiratory threshold device we did not evaluate cough and secretions production. Also, no adverse effects were registered during all research protocol.

CONCLUSIONS

The present study demonstrates that respiratory muscle endurance training based on combination of IMT and EMT at low loads, have the capacity to produce positive modifications on dyspnoea and physical working capacity which are related with physical activity impairment. However, and for the first time, we observed that our type of training protocol doesn't show capacity to improve DPA levels; here, respiratory musculature might only play a role of exercise limiter and not of stimulator. Also, we showed that MVV doesn't respond positively to the protocol applied, which resulted in a better responsiveness of strength parameters. Finally, we think that an expiratory component on respiratory muscle training might still play an important role. However, much more research is needed in order to understand the role respiratory muscle training and relation with physical inactivity in COPD.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

ACKNOWLEDGMENTS

This study had support from Teprel, S.A. and Philips Respironics, S.A. by the partial (50%) provision of training devices.

We would like to thank all patients for their availability and magnificent collaborative spirit.

REFERENCES

1. *Global Strategy for the Diagnosis, Management and Prevention of COPD*. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013.
2. WHO *The Global Burden of Disease: 2004 update*. 2008.
3. Pitta, F., T. Troosters, M.A. Spruit, V.S. Probst, M. Decramer, and R. Gosselink, *Characteristics of physical activities in daily life in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2005. **171**(9): p. 972-7.
4. Waschki, B., A. Kirsten, O. Holz, K.C. Muller, T. Meyer, H. Watz, and H. Magnussen, *Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study.* Chest, 2011. **140**(2): p. 331-42.
5. Garcia-Aymerich, J., P. Lange, M. Benet, P. Schnohr, and J.M. Anto, *Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study.* Thorax, 2006. **61**(9): p. 772-8.
6. Decramer, M., *Response of the respiratory muscles to rehabilitation in COPD*, in *J Appl Physiol*. 2009: United States. p. 971-6.
7. De Troyer, A. and T.A. Wilson, *Effect of acute inflation on the mechanics of the inspiratory muscles*, in *J Appl Physiol*. 2009: United States. p. 315-23.
8. Gea, J., A. Agusti, and J. Roca, *Pathophysiology of muscle dysfunction in COPD*, in *J Appl Physiol*. 2013: United States. p. 1222-34.
9. Hopkinson, N.S., M.J. Dayer, J. Moxham, and M.I. Polkey, *Abdominal muscle fatigue following exercise in chronic obstructive pulmonary disease*, in *Respir Res*. 2010: England. p. 15.
10. *Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society.* Am J Respir Crit Care Med, 1999. **159**(4 Pt 2): p. S1-40.
11. Ries, A.L., G.S. Bauldoff, B.W. Carlin, R. Casaburi, C.F. Emery, D.A. Mahler, B. Make, C.L. Rochester, R. Zuwallack, and C. Herrerias, *Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines*, in *Chest*. 2007: United States. p. 4S-42S.
12. Gosselink, R., J. De Vos, S.P. van den Heuvel, J. Segers, M. Decramer, and G. Kwakkel, *Impact of inspiratory muscle training in patients with COPD: what is the evidence?* Eur Respir J, 2011. **37**(2): p. 416-25.
13. Weiner, P., R. Magadle, M. Beckerman, M. Weiner, and N. Berar-Yanay, *Specific expiratory muscle training in COPD.* Chest, 2003. **124**(2): p. 468-73.
14. Mota, S., R. Guell, E. Barreiro, I. Solanes, A. Ramirez-Sarmiento, M. Orozco-Levi, P. Casan, J. Gea, and J. Sanchis, *Clinical outcomes of expiratory muscle training in severe COPD patients.* Respir Med, 2007. **101**(3): p. 516-24.

15. Miller, M.R., J. Hankinson, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, R. Crapo, P. Enright, C.P. van der Grinten, P. Gustafsson, R. Jensen, D.C. Johnson, N. MacIntyre, R. McKay, D. Navajas, O.F. Pedersen, R. Pellegrino, G. Viegi, and J. Wanger, *Standardisation of spirometry*, in *Eur Respir J*. 2005: Denmark. p. 319-38.
16. Wanger, J., J.L. Clausen, A. Coates, O.F. Pedersen, V. Brusasco, F. Burgos, R. Casaburi, R. Crapo, P. Enright, C.P. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D. Johnson, N. Macintyre, R. McKay, M.R. Miller, D. Navajas, R. Pellegrino, and G. Viegi, *Standardisation of the measurement of lung volumes*, in *Eur Respir J*. 2005: Denmark. p. 511-22.
17. Macintyre, N., R.O. Crapo, G. Viegi, D.C. Johnson, C.P. van der Grinten, V. Brusasco, F. Burgos, R. Casaburi, A. Coates, P. Enright, P. Gustafsson, J. Hankinson, R. Jensen, R. McKay, M.R. Miller, D. Navajas, O.F. Pedersen, R. Pellegrino, and J. Wanger, *Standardisation of the single-breath determination of carbon monoxide uptake in the lung*, in *Eur Respir J*. 2005: Denmark. p. 720-35.
18. Pellegrino, R., G. Viegi, V. Brusasco, R.O. Crapo, F. Burgos, R. Casaburi, A. Coates, C.P. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D.C. Johnson, N. MacIntyre, R. McKay, M.R. Miller, D. Navajas, O.F. Pedersen, and J. Wanger, *Interpretative strategies for lung function tests*, in *Eur Respir J*. 2005: Denmark. p. 948-68.
19. Black, L.F. and R.E. Hyatt, *Maximal respiratory pressures: normal values and relationship to age and sex.* Am Rev Respir Dis, 1969. **99**(5): p. 696-702.
20. Karvonen, J., S. Saarelainen, and M.M. Nieminen, *Measurement of respiratory muscle forces based on maximal inspiratory and expiratory pressures.* Respiration, 1994. **61**(1): p. 28-31.
21. Hautmann, H., S. Hefele, K. Schotten, and R.M. Huber, *Maximal inspiratory mouth pressures (PIMAX) in healthy subjects--what is the lower limit of normal?*, in *Respir Med*. 2000: England. p. 689-93.
22. Clausen, J.L., *Maximal inspiratory and expiratory pressures*, in *Pulmonary Function Testing: Guidelines and Controversies*, J.L. Clausen and L.P. Zarins, Editors. 1982, Academic Press Inc.: New York City. p. 187-191.
23. Bestall, J.C., E.A. Paul, R. Garrod, R. Garnham, P.W. Jones, and J.A. Wedzicha, *Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease.* Thorax, 1999. **54**(7): p. 581-6.
24. *ATS statement: guidelines for the six-minute walk test.* Am J Respir Crit Care Med, 2002. **166**(1): p. 111-7.
25. Garcia-Rio, F., V. Lores, O. Mediano, B. Rojo, A. Hernanz, E. Lopez-Collazo, and R. Alvarez-Sala, *Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation.* Am J Respir Crit Care Med, 2009. **180**(6): p. 506-12.

26. Matthews, C.E., B.E. Ainsworth, R.W. Thompson, and D.R. Bassett, Jr., *Sources of variance in daily physical activity levels as measured by an accelerometer.* Med Sci Sports Exerc, 2002. **34**(8): p. 1376-81.
27. Freedson, P.S., E. Melanson, and J. Sirard, *Calibration of the Computer Science and Applications, Inc. accelerometer.* Med Sci Sports Exerc, 1998. **30**(5): p. 777-81.
28. Hill, K., S.C. Jenkins, D.R. Hillman, and P.R. Eastwood, *Dyspnoea in COPD: can inspiratory muscle training help?* Aust J Physiother, 2004. **50**(3): p. 169-80.
29. Hill, K., S.C. Jenkins, D.L. Philippe, N. Cecins, K.L. Shepherd, D.J. Green, D.R. Hillman, and P.R. Eastwood, *High-intensity inspiratory muscle training in COPD.* Eur Respir J, 2006. **27**(6): p. 1119-28.
30. Lisboa, C., C. Villafranca, A. Leiva, E. Cruz, J. Pertuze, and G. Borzone, *Inspiratory muscle training in chronic airflow limitation: effect on exercise performance.* Eur Respir J, 1997. **10**(3): p. 537-42.
31. Villafranca, C., G. Borzone, A. Leiva, and C. Lisboa, *Effect of inspiratory muscle training with an intermediate load on inspiratory power output in COPD.* Eur Respir J, 1998. **11**(1): p. 28-33.
32. Scherer, T.A., C.M. Spengler, D. Owassapian, E. Imhof, and U. Boutellier, *Respiratory muscle endurance training in chronic obstructive pulmonary disease: impact on exercise capacity, dyspnea, and quality of life.* Am J Respir Crit Care Med, 2000. **162**(5): p. 1709-14.
33. Seron, P., P. Riedemann, S. Munoz, A. Doussoulin, P. Villarroel, and X. Cea, *[Effect of inspiratory muscle training on muscle strength and quality of life in patients with chronic airflow limitation: a randomized controlled trial].* Arch Bronconeumol, 2005. **41**(11): p. 601-6.
34. Koppers, R.J., P.J. Vos, C.R. Boot, and H.T. Folgering, *Exercise performance improves in patients with COPD due to respiratory muscle endurance training.* Chest, 2006. **129**(4): p. 886-92.
35. Mador, M.J., O. Deniz, A. Aggarwal, M. Shaffer, T.J. Kufel, and C.M. Spengler, *Effect of respiratory muscle endurance training in patients with COPD undergoing pulmonary rehabilitation.* Chest, 2005. **128**(3): p. 1216-24.
36. Pitta, F., M.Y. Takaki, N.H. Oliveira, T.J. Sant'anna, A.D. Fontana, D. Kovelis, C.A. Camillo, V.S. Probst, and A.F. Brunetto, *Relationship between pulmonary function and physical activity in daily life in patients with COPD.* Respir Med, 2008. **102**(8): p. 1203-7.
37. Ramirez-Sarmiento, A., M. Orozco-Levi, R. Guell, E. Barreiro, N. Hernandez, S. Mota, M. Sangenis, J.M. Broquetas, P. Casan, and J. Gea, *Inspiratory muscle training in patients with chronic obstructive pulmonary disease: structural adaptation and physiologic outcomes.* Am J Respir Crit Care Med, 2002. **166**(11): p. 1491-7.
38. Beckerman, M., R. Magadle, M. Weiner, and P. Weiner, *The effects of 1 year of specific inspiratory muscle training in patients with COPD.* Chest, 2005. **128**(5): p. 3177-82.

39. Kim, M.J., J.L. Larson, M.K. Covey, C.A. Vitalo, C.G. Alex, and M. Patel, *Inspiratory muscle training in patients with chronic obstructive pulmonary disease.* Nurs Res, 1993. **42**(6): p. 356-62.
40. Sanchez Riera, H., T. Montemayor Rubio, F. Ortega Ruiz, P. Cejudo Ramos, D. Del Castillo Otero, T. Elias Hernandez, and J. Castillo Gomez, *Inspiratory muscle training in patients with COPD: effect on dyspnea, exercise performance, and quality of life.* Chest, 2001. **120**(3): p. 748-56.
41. Hsiao, S.F., Y.T. Wu, H.D. Wu, and T.G. Wang, *Comparison of effectiveness of pressure threshold and targeted resistance devices for inspiratory muscle training in patients with chronic obstructive pulmonary disease.* J Formos Med Assoc, 2003. **102**(4): p. 240-5.
42. Patessio, A., C. Rampulla, C. Fracchia, F. Ioli, U. Majani, A. De Marchi, and C.F. Donner, *Relationship between the perception of breathlessness and inspiratory resistive loading: report on a clinical trial.* Eur Respir J Suppl, 1989. **7**: p. 587s-591s.
43. Preusser, B.A., M.L. Winningham, and T.L. Clanton, *High- vs low-intensity inspiratory muscle interval training in patients with COPD.* Chest, 1994. **106**(1): p. 110-7.
44. Heijdra, Y.F., P.N. Dekhuijzen, C.L. van Herwaarden, and H.T. Folgering, *Nocturnal saturation improves by target-flow inspiratory muscle training in patients with COPD.* Am J Respir Crit Care Med, 1996. **153**(1): p. 260-5.
45. Larson, J.L., M.K. Covey, S.E. Wirtz, J.K. Berry, C.G. Alex, W.E. Langbein, and L. Edwards, *Cycle ergometer and inspiratory muscle training in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1999. **160**(2): p. 500-7.
46. Magadle, R., A.K. McConnell, M. Beckerman, and P. Weiner, *Inspiratory muscle training in pulmonary rehabilitation program in COPD patients.* Respir Med, 2007. **101**(7): p. 1500-5.
47. Weiner, P., Y. Azgad, and R. Ganam, *Inspiratory muscle training combined with general exercise reconditioning in patients with COPD.* Chest, 1992. **102**(5): p. 1351-6.
48. Weiner, P., R. Magadle, M. Beckerman, M. Weiner, and N. Berar-Yanay, *Comparison of specific expiratory, inspiratory, and combined muscle training programs in COPD.* Chest, 2003. **124**(4): p. 1357-64.
49. Dekhuijzen, P.N., H.T. Folgering, and C.L. van Herwaarden, *Target-flow inspiratory muscle training during pulmonary rehabilitation in patients with COPD.* Chest, 1991. **99**(1): p. 128-33.
50. Belman, M.J. and R. Shadmehr, *Targeted resistive ventilatory muscle training in chronic obstructive pulmonary disease.* J Appl Physiol, 1988. **65**(6): p. 2726-35.
51. Madariaga, V.B., J.B. Iturri, A.G. Manterola, J.C. Buey, N.T. Sebastian, and V.S. Pena, *[Comparison of 2 methods for inspiratory muscle training in patients with chronic obstructive pulmonary disease].* Arch Bronconeumol, 2007. **43**(8): p. 431-8.

52. Berry, M.J., N.E. Adair, K.S. Sevensky, A. Quinby, and H.M. Lever, *Inspiratory muscle training and whole-body reconditioning in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1996. **153**(6 Pt 1): p. 1812-6.
53. Covey, M.K., J.L. Larson, S.E. Wirtz, J.K. Berry, N.J. Pogue, C.G. Alex, and M. Patel, *High-intensity inspiratory muscle training in patients with chronic obstructive pulmonary disease and severely reduced function.* J Cardiopulm Rehabil, 2001. **21**(4): p. 231-40.
54. Cooper, C.B., *Airflow obstruction and exercise.* Respir Med, 2009. **103**(3): p. 325-34.

MAIN CONCLUSIONS

According to the findings of our study, we think that must be highlighted the following conclusions:

1. Six-week respiratory endurance inspiratory and expiratory muscle training can produce positive effects in dyspnoea and physical working capacity, in COPD patients.

2. Six-week respiratory muscle endurance training might not have any positive effects on alteration of DPA levels, in COPD patients.

3. Respiratory muscle strength improvements do not have any type of correlations with other functional parameters like DPA, 6MWT and MVV.