ACUTE EFFECT OF NONINVASIVE VENTILATORY SUPPORT ON MAXIMUM EXERCISE CAPACITY IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): A PILOT STUDY

Ana-Maria Moga, B.Sc. (PT)

School of Physical and Occupational Therapy, Faculty of Medicine

McGill University, Montreal, Quebec, Canada

April 2011

A thesis submitted to McGill University

in partial fulfillment of the requirements of the degree of Master of Science

This thesis is dedicated to my parents, Georgeta and Ioan Moga,

for teaching me the reward of perseverance and devotion

TABLE OF CONTENT

ABSTRACT

Background: Non-invasive ventilation (NIVS) has been used as an adjunct to exercise. However, the extent to which NIVS improves exercise tolerance is highly variable.To date, no studies have examined the effect of NIVS on maximal exercise capacity when applied during a single exercise test.

Objective: To evaluate the acute effect of BiPAP (Vision, Respironics), compared to no assist, on maximum exercise capacity in individuals with COPD.

Methods: A randomized crossover design was used. Ten stable COPD patients (FEV_1 53 ± % pred) performed three symptom-limited incremental exercise tests on a cycle ergometer while breathing through a mouthpiece, with either: i) without pressure support PS (ØPS), ii) PS of 0 cm H_2O (PS0; IPAP & EPAP 4 cm H_2O), or iii) 10 cm H_2O (PS10; IPAP 14 & EPAP 4 cm H_2O) of assist on separate days. Exercise workload (WL_{max}), dyspnea and leg effort (Borg), end-expiratory lung volume (EELV), breathing pattern, O_2 uptake (VO_2) and CO_2 production (VCO_2) were measured during exercise.

Results: There was no difference in WL_{max} between PS10 (33±16) and PS0 (30.5±13). However, WL_{max} was lower with PS0 and PS10 than ØPS. Dyspnea at peak exercise was similar without PS, PS0 and PS10; at isoload it was lower without PS compared to PS10 and PS0 ($p<0.01$). Leg effort at peak exercise was higher without PS than PS10 and PS0 ($p<0.05$), whereas it was not different at isoload. Tidal volume (VT) and minute ventilation (VE) were highest with PS10 and lowest without PS both at peak exercise ($p<0.001$) and isoload ($p<0.001$). EELV was similar at peak exercise with all three conditions. VO_2 and VCO_2 were greater with PS10 and PS0 than without PS (both $p<0.001$), both at peak exercise and isoload.

Conclusion: Use of BiPAP during incremental exercise increases VT and V_E at the expense of increasing the VO_2, VCO_2 and dyspnea, which in turns reduces WL_{max} in COPD patients.

ABRÉGÉ*:*

Contexte : La ventilation non invasive (VNI) a été utilisée pendant un test d'exercice. Toutefois, la mesure dans laquelle la VNI améliore la tolérance à l'exercice est très variable. À ce jour, aucune étude n'a examiné l'effet de la VNI sur la capacité d'effort maximale lorsqu'il est appliqué au cours d'un test d'exercice dynamique aérobie maximal.

Objectif: Evaluer l'effet aigu de BiPAP (Respironics), comparativement à l'absence d'aide, sur la capacité maximale d'exercice chez les individus atteints de la maladie pulmonaire obstructive chronique (MPOC).

Méthodes: Une étude croisée randomisée a été utilisée. Dix patients souffrant de MPCO stable ($VEMS_1$ 53 ± % pred.) ont effectué trois preuves d'effort supplémentaire sur une bicyclette ergométrique tout en respirant à travers une bout buccal, soit) sans le soutien de la pression(ØPS), ii) avec un soutien de 0cm H_2O (PS0; IPAP & EPAP 4 cm H_2O) ou iii), avec un soutien de 10cm H_2O (PS10; IPAP 14 & EPAP 4 cm H2O). La fin des tests a été déterminée par les symptômes des patients, et chacun des tests a été effectué pendant un jour différent**.** Pendant l'exercice, nous avons mesuré la charge de travail(WL_{max}), la dyspnée et l'effort de la jambe (Borg), le volume pulmonaire en fin d'expiration (EELV), rythme respiratoire, la consommation d'O2 (VO_2) et la production de CO_2 (VCO_2).

Résultats: Il n'y avait aucune différence dans la charge de travail maximale du pic entre PS 10(33 ±16) et PS0 (30,5 ±13). Toutefois, la charge de travail maximum du pic était plus faible avec PS0 et PS10 de ØPS. La dyspnée pendant le pic de l'effort a été similaire à ØPS, PS0 et PS10. À isoload, elle était inférieure à ØPS par rapport à PS10 et PS0 ($p<0,01$). L'effort de la jambe à l'exercice de pointe était plus élevé à ØPS de PS10 et PS0 ($p<0,05$), alors qu'il n'était pas différent au isoload. Le volume courant (VT) et la ventilation minute (V_E) étaient les plus élevés avec PS10 et les plus bas à ØPS, à la fois à l'exercice de pointe ($p <0,001$) et isoload ($p <0,001$). EELV était similaire à l'exercice de pointe avec les trois

conditions. VO_2 et VCO_2 ont été plus grande avec PS10 et PS0 de ØPS (les deux $p<0,001$), à la fois à l'exercice de pointe et isoload.

Conclusion: L'utilisation du BiPAP pendant l'exercice augmente VT et V_E, ce qui cause une augmentation du VO_2, VCO_2, et la dyspnée, qui à son tour réduit WL à l'exercice maximal chez les patients MPOC.

ACKNOWLEDGEMENTS

I would like to acknowledge the support and contribution of several people without whom, this thesis would not have been possible. I would like to thank my supervisor Dr. Jadranka Spahija. Your continuous scientific inquisitiveness have been inspirational for fostering my physiological and research knowledge, creativeness and personal growth. Your attention to detail taught me to be diligent in my research and writing. Your mentorship provided me the opportunity to develop strong critical thinking, analytical skills, and overall, to become more knowledgeable person. You made my Masters Journey one of the richest and most memorable learning experiences in my life.

I would also like to thank the valuable and expert participation of the members of my supervisory committee. Dr. Didier Saey for his kindness in providing diligence attentiveness in training me on the magnetic stimulation, data analysis, and for the excellent editorial input, and Dr. Sara Ahmed for her professional input in the advancement of my thesis, all are very much appreciated.

At the same time I am also very grateful to Michel de Marchie M.D. for his readiness and enthusiasm in providing clinical supervision during the exercise tests.

I wish to thank McGill University, specifically the School of Physical and Occupational Therapy, for giving me the opportunity to pursue my Masters degree. I thank them for their support and for broadening my view of the rehabilitation world. I especially want to thank Dr. Eva Kehayia and Dr. Isabelle Gélinas, Maria Ruocco, Irena Mileva, Liliane Cardinal and my fellows for their support and for enriching my academic journey.

My gratitude, again, goes to the tireless and enthusiastic research subjects who gave so generously of their time and energy to participate in my long and demanding study. Thank you all!

At the same time, I would like to acknowledge my gratitude to all the staff from the Pneumology Department of Sacre Coeur Hospital for having their door always open for me. I am especially thankful to Fernand Pellant, the head of pulmonary function laboratory at HSCM, for coordinating and performing the Pulmonary Function Tests. My sincere gratitude also goes to Ms. Sadia Daheb for helping out with the assessment.

I am particularly indebted to Guy Jennings, for providing the Biopac software technical assistance with genuine concern and interest. A sincere heartfelt thank you!

I wish to thank the members of the Respiratory Research Axe from Sacre Coeur Hospital for their support in my endeavors, especially my fellow students, for their friendship, advice and encouragement: Barbara Trutshnigg, Mélanie Welman, Grégory Moullec, Myriam De Lorimier, Karine Truflandier, Rima Wardini, Emilie Chan-Thim, Amanda Rizk, Maryann Joseph, Khadije Jizi, and Myrella Bergeron-Prévost.

To Dan Moldoveanu, my friend, I especially appreciate the generous friendship, support, time and advice provided over these years, not to mention the considerate review of my first part of this thesis. Your friendship made this journey much enjoyable.Thanks buddy!

I would like to send my gratitude and my deepest appreciation to my family. Special thanks go to my parents, Georgeta Moga MD. and Prof. Ioan Moga PhD, for teaching me the value of education and confidence, the reward of perseverance and devotion, and for instilling in me a love of reading, learning, and the curiosity to explore new fields of knowledge. To my awesome siblings: Ligia, Florin and Arina Moga for being my best friends and for believing in me from the beginning and encouraging me never to give up, thanks a million!

Last and certainly not least, I would also like to thank my spouse Cosmin Jimborean who has been by my side since the beginning of my new life and

studies in Canada. I thank him for allowing me the opportunity to explore new knowledge and sacrificing his time to make this graduate experience happen. I thank him for making a peaceful environment, to carry on my academic work successfully. He has been a constant source of support – emotional, moral and, of course, financial – throughout this years and this thesis would certainly not have existed without him. He has seen my struggles and triumphs throughout this process and his support has been unwavering. I thank him for his love.

LIST OF ABBREVIATIONS:

Abbreviation	Meaning
COPD	Chronic obstructive pulmonary disease
NIVS	Non invasive ventilatory support
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
FRC	Functional residual capacity
EELV	End-expiratory lung volume;
IC	Inspiratory capacity
VT	Tidal volume
V_E	Minute ventilation
RR	Respiratory rate
Ti	Inspiratory time
TE	Expiratory time
PEEPi	Intrinsic positive end-expiratory pressure
WOB	Work of breathing
CO	Cardiac output
BiPAP	Bi-level positive airway pressure
CPAP	Continuous positive airways pressure
PS	Pressure support
PAV	Proportional assisted ventilation
Pmo	Mouth pressure
HRQOL	Health related quality of life
TWq	Twitch tension
MVC	Maximal voluntary contraction
VO_2	Oxygen consumption
VCO_2	Carbon dioxide production
SaO_2	Oxygen saturation
WLmax	Maximum exercise capacity

INDEX OF TABLES

INDEX OF FIGURES

PREFACE

Thesis Format:

The thesis is organized using a manuscript-based format and contains an original scientific paper which will be submitted for publication in journal in the near future. This thesis format has been chosen with the approval of the supervisory committee and Graduate Department of Rehabilitation Science and in accordance with the Guidelines for Thesis Preparation of the Faculty of Graduate Studies of McGill University (April 2011). We must admit that duplications are inevitable in this thesis.

Chapter 1 is an introduction of the thesis, providing a brief introduction to the subject of COPD and non-invasive ventilator support and presents the rationale for the research study.

Chapter 2 consists of a literature review and encompasses 3 major topics relevant to the research performed. The first section consists of a general presentation of chronic obstructive pulmonary disease (COPD) and includes a definition, classification, risk factors, pathophysiology and clinical manifestation. The second section addresses the factors limiting exercise in patients with COPD. The final section consists of a review of the literature concerning the non-pharmacological adjunct therapies to exercise used in COPD

Chapter 3 is a connecting text, which provides an overview of the topic, an integrative link between the literature review and the objectives of the research study

Chapter 4 consists of the measurements and psychometric properties of the measurements performed during the research study.

Chapter 5 constitutes a research paper investigating the acute effect of non-invasive ventilatory support on exercise capacity.

Chapter 5 is a general discussion containing the final conclusions and summary of the research paper, contribution to knowledge, future studies, and a

comprehensive reference list as stipulated by the Guidelines for Thesis Preparation of McGill University.

Contribution of Authors:

The following manuscripts are included in the thesis:

1. Mechanism of Non-Pharmacologic Adjunct Therapies Used During Exercise in COPD (i.e., presented as the review of the literature in Chapter II, section 2 and section 3) - submitted to Respiratory Medicine August 2011.
   Moga A.M., de Marchie, M., Saey, D. Spahija, J.,

2. Acute effect of Noninvasive Ventilatory Support on Maximum Exercise Capacity in Patients with Chronic Obstructive Pulmonary Disease (i.e., presented as manuscript in Chapter V) – ready for submission to COPD Journal- September 2011.
   Moga A.M., de Marchie, M., Saey, D, Spahija, J.,

All the work contributing to this thesis, including research protocol, literature review, ethics approval, screening medical charts to identifying potential subjects, experimentation, data collection, developed of a database and analysis, and writing of the research paper was performed by the candidate. The work was carried out in the laboratory and under the guidance of Dr. J. Spahija, and thus she figure as coauthor on all papers. Dr. M de Marchie provided technical assistance in the form of patient supervision during the exercise testing carried out in the study. Dr. Sara Ahmed provided theoretical input. Dr. Didier Saey provided training and theoretical input for the assessment of muscle strength via magnetic stimulation, data analysis solutions for the muscle strength and reviewed the papers. All coauthors also participated in the review of the thesis.

CHAPTER I

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a pulmonary disorder that is characterized by progressive irreversible airflow limitation. It is causedpredominantly by cigarette smoking and in addition to being a major cause of morbidity and mortality worldwide, it represents a substantial economic and social burden [1-3] .

Individuals with COPD commonly exhibit a limited ability to perform exercise [4-6] due to a heightened sense of breathlessness [7] and/or leg fatigue secondary to a reduced ventilatory capacity [7-8], and peripheral skeletal muscle dysfunction [9], respectively. The sedentary lifestyle and reduced functional capacity [10] observed in patients with COPD, has been associated with a decreased quality of life, increased use of health services, and reduced survival [11-13].

Although pulmonary rehabilitation programs have been shown to improve exercise tolerance and health related quality of life in patients with COPD, some individuals are unable to obtain such benefits because of their inability to exercise at a high enough exercise-intensity [4, 14-18].

Non-invasive ventilatory support (NIVS) [19] has been used as an adjunct therapy during acute exercise and pulmonary rehabilitation to help improve exercise capacity in such individuals [20-21]. However, the extent to which NIVS improves exercise tolerance is highly variable amongst individuals. It could be anticipated that individuals who demonstrate the greatest increases in exercise capacity when NIVS is applied during a single exercise test may obtain the greatest benefit from its use during pulmonary rehabilitation. To date, however, no studies have examined the effect of NIVS on maximal exercise capacity applied during a single exercise session.

The purpose of the current thesis was to evaluate the acute effect of NIVS on maximum exercise capacity in patients with COPD. The secondary objective was to explore the effect of NIVS on breathing pattern and operational lung volumes.

CHAPTER II

REVIEW OF THE LITERATURE

1. CHRONIC OBSTRUCTIVE PULMONARY DISEASE

1.1 Definition and Risk Factors

Chronic obstructive pulmonary disease (COPD) is a pulmonary disorder [4] characterized by a progressive irreversible airflow limitation that occurs as a result of alveolar wall destruction, bronchiolar narrowing [22] and airway inflammation in response to inhalation of noxious particles or gases [4].

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) chronic obstructive pulmonary disease is a preventable and treatable pulmonary disorder [4]. Numerous genetic, occupational, and environmental factors [23-25] have been associated with COPD, although cigarette smoking remains the primary cause of disease development [26] and its associated mortality [4, 27]. Additionally, Alpha 1-antitrypsin deficiency, which is a genetic disease, also causes an early-onset of COPD (emphysema) secondary to a deficiency in the elastase inhibitor resulting in overall breakdown in the lung elastic fibers [28].

Although COPD primarily affects lung function, extra-pulmonary manifestations are also frequently evident [4, 29]. Broadly speaking, the systemic manifestations include cachexia and loss of fat-free mass, cardiovascular disease, osteoporosis and peripheral muscle dysfunction, with underlying muscular abnormalities [30-31]. The mechanism of these effects is believed to be related to enhanced systemic inflammation and oxidative stress [32].

1.2 COPD Prevalence, Mortality, and Economic Burden

COPD is a major and increasing global health problem with important consequences with respect to mortality, morbidity, quality of life and health-care

costs worldwide. The prevalence of COPD is approximately 10% in the general population, and it is the fourth leading cause of mortality worldwide [2, 33-35].

According to the Canadian Lung Association [36], one and a half million Canadians are living with COPD, whereas an estimated 1.6 million Canadians could have the disease, but remain undiagnosed [37].

Moreover, WHO projects the disease to rank fifth as a worldwide chronic disability by 2020 [38]. Due to the high prevalence of COPD and its potential for severe disability, the economic burden (direct cost $646 - $736 million per annum) associated with this disease has been shown to have a significant impact on Canada's healthcare system cost [4].

1.3 Diagnosis and Classification of Disease Severity

COPD encompasses a heterogeneous group of pulmonary conditions that share airway obstruction as a prominent feature [4]. The most common forms are chronic bronchitis and emphysema; the relative contribution of which may vary widely among patients having the same degree of airflow limitation [4, 20].

Chronic bronchitis is defined clinically as the presence of cough and sputum production occurring on most days for at least three months, for two consecutive years [4, 39-40]. Chronic inflammation of the peripheral airways results in airway narrowing and remodeling, which increases airflow resistance (Figure 1) and produces flow obstruction [4, 41-43].

In contrast, emphysema is characterized by alveolar wall destruction which leads to permanent abnormal enlargement of the respiratory airspaces, distal to the terminal bronchioles [26, 44], (Figure 2). Damage of the lung parenchyma and its vasculature, results in a loss of lung elastic recoil, which in turn leads to small airway closure and irreversible decreases in maximum expiratory airflow [39, 41, 45-46]. The loss of lung elastic recoil refers to the inability of the lung to deflate after it has been inflated, and is expressed by plotting lung volume as a function of

transpulmonary pressure (i.e., pressure differential between the inside and the outside of the pleura) (Figure3).

The first symptom to develop in patients with emphysema tends to be dyspnea, which is typically elicited during activities of daily living or during previously tolerated physical activities [47]. In contrast, in chronic bronchitis, persistent cough and sputum production often precede the development of dyspnea [1, 4, 45, 47].

As previously mentioned, the main physiological abnormality associated with COPD is a decrease in the maximum expiratory flow rate. The forced expiratory volume in 1 second (FEV_1) and the ratio of the FEV_1 to the forced vital capacity (FVC) are measures that are used to assess the level of existing expiratory flow limitation, and thus COPD disease severity. A post-bronchodilator FEV_1/FVC ratio less than 70% of predicted is typically used in the diagnosis of COPD [4].

The GOLD spirometric classification of COPD disease severity [4] presently includes four stages ranging from mild to very severe. Table 1 illustrates severity classifications for COPD diagnosis based on FEV_1 and FEV_1/FVC. Studies have found that the FEV_1 correlates poorly with symptom severity, exercise capacity, health-related quality of life (HRQoL) and survival [48-50].

1.4 Pathophysiology and Clinical Manifestation in COPD

1.4.1 Changes in static lung volumes and breathing pattern in COPD

In general, the balance between the elastic recoil of the lung and the chest wall determines the resting volumes of the thorax [51-52]. Expiratory flow limitation, caused by airway inflammation and loss of lung elastic recoil [53], contributes to air trapping within the lungs. The increased volume of air remaining in the lungs at the end of a spontaneous expiration (i.e. end-expiratory lung volume (EELV) or functional residual capacity (FRC) is referred to as static pulmonary hyperinflation [54-57]. As a result of such air trapping, compared to healthy individuals, patients with COPD have altered static lung volumes and capacities [54-60].

The increased FRC leads to an upward shift in the operational lung volumes, decreasing the inspiratory reserve volume and the inspiratory capacity (IC) [61]. The IC, known as the maximum volume of air that can be inhaled after a normal tidal exhalation, has been shown to be decreased in COPD patients compared to healthy individuals [61-62].

During inspiration in healthy individuals, the inspiratory muscles contract to expand the chest cavity and then during expiration, the inspiratory muscles relax, and the lung and chest wall elastic recoil deflates the lungs. Although hyperinflation during tidal breathing is a compensatory mechanism to facilitate expiratory airflow for a period of time, it alters breathing mechanics and respiratory muscle function in COPD patients [63].

The breathing pattern is regulated within the limits set by the respiratory pump capacity in order to generate inspiratory and expiratory flows [64-65]. The respiratory cycle consists of inspiration and expiration, and can be characterised schematically by a spirogram, which consists of the tidal volume (VT) and inspiratory (T_I) and expiratory time (T_E). Several studies have found that, different from healthy individuals, breathing pattern is altered in COPD patients with changes presented in depth, rate and timing of breathing [66-67]. Such changes have been shown to be related to the severity of the disease [66-69]. Loveridge et al. [67] found that patients with a moderate COPD severity have higher than normal V_T values, whereas patients with more severe obstruction presented lower V_T levels [67]. Other studies have found that patients with severe COPD and chronic hypercapnia tend to have smaller V_T both at rest [66] and during exercise [68], compared to those who maintain a normal partial pressure of carbon dioxide (P_{CO2}).

Minute ventilation (V_E) is accomplished by two components: tidal volume and respiratory rate (RR) (i.e., $V_E = V_T * RR$). Patients with COPD tend to exhibit a normal or higher than normal resting minute ventilation [66-67, 70-71]. Hyperinflation decreases inspiratory muscles length, therefore, a greater tension is needed to generate sufficient change in thoracic pressure for tidal breathing [63,

72-73]. However, the ability of the inspiratory muscles to generate pressure is reduced in such individuals [74-75]. Therefore, in order to maintain a given V_E, COPD patients need to increase respiratory muscle activation [76], which, in turn, increases the work of breathing and O_2 cost of breathing [77].

1.4.2 Pulmonary gas exchange abnormalities in COPD

In addition to the expiratory flow limitation and static hyperinflation occurring at rest, some individuals with COPD also have significant gas exchange limitations as compared to healthy individuals [4].

The volume of gas that diffuses through the alveolar-capillary membrane each minute for a pressure difference of 1 mmHg represents the diffusion capacity of the lung for carbon monoxide (D_LCO) [77-82]. The impaired diffusion capacity is indicative of a reduced gas exchange across the alveolar-capillary membrane. Due to the destruction of the alveolar walls and the pulmonary capillary bed, patients with COPD may present a D_LCO of less than 55% of the predicted value, compared to health-age matched individuals [83-84]. O'Donnell and Webb [85] showed that individuals with a reduced D_LCO experience more severe dyspnea and disability, than those with a preserved D_LCO.

Ventilation to perfusion (V/Q) mismatching, also contributes to an increased physiologic dead space in COPD [80, 86-87]. Therefore, to achieve a given alveolar ventilation compared to healthy individuals, COPD patients need to increase V_E relative to their metabolic rate at all work loads, even at rest [55, 88-90].

Ventilation to perfusion mismatching accounts for the reduction in arterial blood gas, when the mismatch is severe, and is identified due to a reduction in arterial PO_2, (i.e., hypoxia) [91-96]. The extent of abnormal V/Q ratio can vary accordingly to the disease type (chronic bronchitis vs. emphysema) and severity [97], with the more severe diseased patients having greater hypoxemia, with arterial PO_2 values between of 55-60 mmHg [39, 96, 98-99].

1.4.3 Skeletal muscle dysfunction in COPD

Peripheral muscle dysfunction is a major systemic consequence of COPD and is an important factor leading to exercise limitation [100-102] and impaired quality of life. The following sections will review the structural and functional peripheral muscle changes that have been reported to occur in such patients. Table 2 and Table 3 provide an outline of skeletal muscle abnormalities in patients with COPD.

The etiology of the skeletal muscle dysfunction is complex and encompasses several mechanisms [103-104]. First, deconditioning [105-106], leads to progressive deterioration in peripheral muscle function, due to a net loss of muscle mass and decreased muscle capacity to generate force. Second, chronic hypoxia results in muscle wasting [107-108], decreased oxidative enzymes activity, and an increased glycolytic enzyme activity [108-110]. Third, systemic inflammation [111-112] can also alter skeletal muscle structure and function [113]; this theory is supported by the observation that many pro-inflammatory cytokines have been found to influence skeletal muscle growth and contractile performance [111, 114-116].

Finally, other mechanisms that have been considered to contribute to the skeletal muscle dysfunction in COPD patients include malnutrition [117-119], corticosteroid usage [120-121], smoking [122-123], oxidative stress [124] and reduced plasma leptin levels [125-126]. It is beyond the scope of this thesis to provide a detailed overview of all the mechanisms underlying the pathogenesis of skeletal muscle dysfunctions. The reader is instead referred to several excellent reviews on the topic [104, 113, 127-131].

1.4.3.1 Skeletal muscle wasting

Strength and endurance are the two basic characteristics of muscle performance. Strength is defined as the capacity of the muscle to produce a maximum contractile force, whereas endurance is defined as the ability of the muscle to maintain a certain force (muscle contraction) over time [104]. Several studies in patients with

COPD have shown that loss of either one of these characteristics leads to muscle weakness [9, 132] and diminished muscle performance [132-134]

Similar to healthy individuals, in patients with COPD muscle strength depends largely on muscle mass or fat-free mass. The reduction in muscle strength and endurance is structurally characterized by loss of fat-free mass and/or decline in cross-sectional muscle area (i.e., muscle atrophy) [9, 127, 135-139].

Although the decrease in lower limb strength varies among patients with moderate to severe COPD [132, 134, 140], Hamilton et al. [141] have shown that on average quadriceps muscle strength is reduced by 20-30% when compared with age-matched control subjects. Furthermore, it was postulated that, since the decrease in muscle strength was shown to be a significant determinant of exercise capacity, the latter could be related to the influence of muscle strength on the perception of leg effort during exercise, which is the principal limiting symptom in 40-45% of COPD patients [102, 141].

The loss of quadriceps muscles strength has been found to be significantly correlated with FEV_1 ($r=0.55$, $p<0.0005$) [132], suggesting that the peripheral muscle wasting increases with the COPD severity. Quadriceps weakness has also been shown to be correlated with a reduced 6-min walking distance [134]and reduced peak oxygen consumption [141], independent of lung function. Moreover, muscle cross-sectional area and strength have both been found to be strong predictors of mortality in COPD patients with the more advanced disease [12].

1.4.3.2 Structural muscle changes

The histological skeletal muscle abnormalities in patients with COPD are characterized by a reduction in the proportion of slow-twitch type I fatigue-resistant fibers [9, 142] combined with an increase in the proportion of, less efficient, type II fibers [9, 132, 143-144] Table 2 and Table 3.

In addition to the fiber–type proportion switch, several investigators [145-146] have reported that different from age-matched healthy controls, COPD patients

have a decreased capillarization with preserved or reduced capillary to fiber ratio in the vastus lateralis muscle [9, 145-146]. Saey et al. [147] found that COPD patients who developed quadriceps contractile fatigue during cycle exercise presented a lower capillary/fiber ratio in the vastus lateralis compared with those who did not develop fatigue, suggesting the reduced capillarization could contribute to the decreased exercise tolerance in certain COPD patients.

Studies have demonstrated that the shift in fibre type toward more glycolytic fibersis accompanied by a decrease in the oxidative metabolism in the peripheral muscles [148-150] in patients with COPD, compared to age-matched healthy subjects. Gosker et al. [151] attributed the decreased quadriceps oxidative capacity in part to a reduction in mithocondrial density [151]. Decrease in oxidative enzyme markers in the locomotor skeletal muscles [152] with a concomitant increase in glycolytic enzymes was also observed in patients with COPD [142, 153]. Several authors have suggested that the reduced type I oxidative fibers in the peripheral muscle are likely to contribute to the early lactate release during exercise in these patients [132, 152]. These intrinsic muscle alterations have been associated with a reduced peripheral muscle strength and endurance, as well as with an increased contractile fatigability [132, 134, 154-156].

Table 1GOLD Spirometric Classification of COPD Severity Based on Post-Bronchodilator FEV1.	
Severity Based on Post-Bronchodilator FEV_1	
Stage I: Mild	**$FEV_1/FVC < 0.70$** **$FEV_1 \geq 80\%$ predicted**
Stage II: Moderate	**$FEV_1/FVC < 0.70$** **$50\% \leq FEV_1 < 80\%$ predicted**
Stage III: Severe	**$FEV_1/FVC < 0.70$** **$30\% \leq FEV_1 < 50\%$ predicted**
Stage IV: Very Severe	**$FEV_1/FVC < 0.70$** **$FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure**

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; respiratory failure: arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level. From GOLD guidelines [4].

Table 2 Skeletal muscles changes	
Clinical	Reduced strength Increased fatigability Reduced endurance Reduced mid-thigh CSA
Functional	Increased muscle weakness Increased fatigability
Morphologic	Muscle fibres atrophy Reduced muscle mass
Cellular	Reduced proportion of slow-twitch type I fibers Increased proportion of fast-twitch type II fibers Reduced fibers CSA Reduced capillary contacts to fiber CSA Increased apoptosis Increased fatiguable myosin Heavy Chain
Metabolic	Reduced oxidative enzyme capacity Increased glycolytic enzyme activity Increased intracellular acidosis Increased lactic acid Reduced phosphocreatine depletion PCr/Pi ratio

From: Warburton and Mathur the pathophysiological changes of the skeletal muscle in patients with COPD [157].

Table 3Muscle fiber types and properties			
Fiber types	**Type I**	**Type II A**	**Type II B**
Twitch and fatigue characteristics	Slow	Fast resistant	Fast fatigue
Twitch and enzymatic characteristics	Slow oxidative	Fast oxidative-glycolytic	Fast glycolytic
Muscle fibers properties			
Resistance to fatigue	High	High	Low
Oxidative enzymes	High	High	Low
Phosphorylase (glycolytic)	Low	High	High
Adenosine triphosphate	Low	High	High
Twitch velocity	Low	High	High
Twitch tension	Low	High	High

From: KimurJ. - Electrodiagnosis in diseases of nerve and muscle [158]

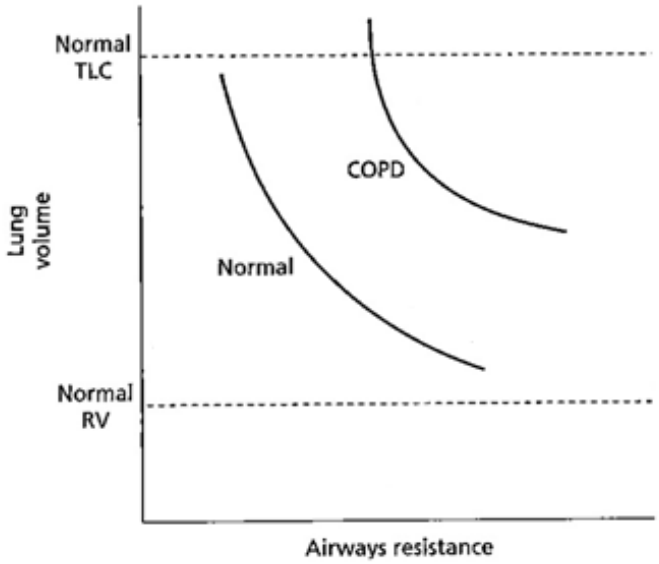


Figure 1 Airway resistance versus lung volumes

Lung volume is shown as a function of airway resistance in a normal individual and in a COPD patient. In both individuals airway resistance increases as lung volume becomes smaller. At any given volume lung volume, airway resistance is considerably larger in COPD patients. From [39].

Figure 2 Thin lung section from a patient with advanced emphysema.
From: Shapiro and Ingenito[28]

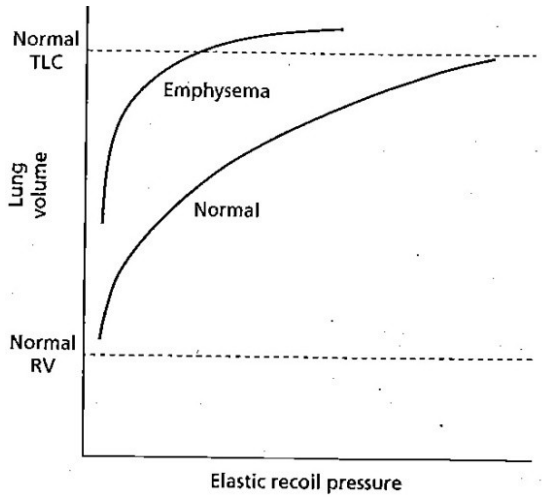


Figure 3 Lung volume as a function of transpulmonary pressure in a normal subject and a COPD patient.

At a given lung volume, lung elastic recoil pressure is reduced with emphysema. TLC- total lung capacity; RV –residual volume. From [159]

3. EXERCISE TOLERANCE AND FACTORS CONTRIBUTING TO EXERCISE LIMITATION IN COPD

2.1 Exercise intolerance

Individuals with COPD commonly exhibit a limited ability to perform exercise [4-6] as a result of a heightened sense of breathlessness [7] resulting from ventilatory capacity limitation secondary to lung hyperinflation [7-8] and/or leg fatigue, secondary to peripheral skeletal muscle dysfunction [9]. In order to avoid the unpleasant sensation of dyspnea that is triggered by exercise, individuals with COPD are inclined to lead a sedentary lifestyle [160]. The consequence of such inactivity is progressive deconditioning [105], diminished cardiorespiratory [161-162] and peripheral muscle function [112], as well as a reduced functional capacity [10] (Figure 4). The sedentary lifestyle and muscle weakness observed in patients with COPD has been associated with lower maximum exercise capacity, an increased use of health services, decreased quality of life and reduced survival [11-13].

COPD patients can exhibit a wide range of exercise capacities [48-50, 163] understanding each patient's source of limitation is very important for appropriate patient management. The physiological factors that can contribute to exercise limitation in patients with COPD will be reviewed in the following sections, along with certain adjunct therapies that may be used to improve exercise performance in such individuals.

2.2 Ventilatory limitation during exercise

Alterations occurring in the mechanical properties of the lungs in COPD result in an increased work of breathing [164-165] and impaired gas exchange [4]. Expiratory flow limitation, caused by airway inflammation and loss of lung elastic recoil [53], leads to air trapping within the lungs which increases the end-expiratory lung volume (i.e. static pulmonary hyperinflation) [54-56]. During

exercise, minute ventilation is increased predominantly by increasing the respiratory rate, whereas tidal volume, which approaches the limits of total lung capacity at end-inspiration, increases marginally before reaching a plateau. [7] The increased RR results in less time being available for exhalation, which further dynamically increases the end-expiratory lung volume (i.e. dynamic hyperinflation) [7, 56, 166-167] Figure 5. Because the respiratory system is less compliant at higher lung volumes, static and dynamic hyperinflation contribute to an increase in the inspiratory elastic work of breathing. This is further compounded by the fact that patients with COPD must generate an increased inspiratory threshold pressure before airflow occurs i.e. intrinsic positive end-expiratory pressure (PEEPi) [168]. The augmented mechanical work and neural output that occurs in patients with COPD contributes significantly to the development of exertional dyspnea [7, 55], a common exercise-limiting symptom in such individuals [102].

2.3 Peripheral muscle dysfunction in exercise intolerance

In addition to the clear evidence of dynamic hyperinflation and altered pulmonary mechanics contributing to exercise intolerance in COPD, skeletal muscle dysfunction also appears to play an important role in limiting exercise in such individuals [4, 102, 104].

Several studies have showed that skeletal muscle abnormalities characteristic to COPD (see section 1.4.3) have been associated with reduced peripheral muscle strength and endurance, as well as an increased contractile fatigability [104, 132, 134, 169]. Contractile muscle fatigue has been defined as a reversible reduced capacity of the skeletal muscle to generate force in response to a given neural input [170-171]. Evidence for the occurrence of quadriceps contractile fatigue during exercise in patients with COPD comes from several studies that have assessed quadriceps muscle strength via magnetic stimulation [100, 154, 172-174].

The skeletal muscle dysfunction observed in patients with COPD (see section 1.4.3), it is obvious that perceived exertional leg discomfort can contribute to

exercise intolerance in many patients with COPD [175]. Although the exact proportion varies among studies, leg fatigue has been found to be declared as the primary symptom limiting exercise at peak cycling exercise in approximately one third of patients with COPD [102, 176]. Some studies have also reported a moderately correlation between perceived exertional leg discomfort, measured using the Borg scale, and the magnitude of contractile muscle fatigue of patients with COPD [176-177]. This suggests that the occurrence of contractile fatigue could be reflected in the symptoms perceived by patients after exercise [178].

Studies have shown quadriceps strength to be correlated with maximum exercise capacity, independent of pulmonary function [100, 134, 141]. Saey et al. [100] demonstrated that even after an improvement in FEV_1 following bronchodilator medication, quadriceps contractile fatigue was still evident following endurance cycling in a subgroup of patients who previously reported leg fatigue as being the factor limiting maximum exercise. These findings suggest that the presence of leg fatigue modulates the exercise response to bronchodilation.

Although muscle fatigue is a complex phenomenon, changes in muscle energy metabolism maybe involved [100] . Several studies have found that, compared with aged-matched healthy individuals, COPD patients have lower lactate thresholds (i.e., the VO_2 at which blood lactic acid begins to increase) [105, 179]. Secondary to the lower lactate thresholds, an excessive accumulation of metabolic by-products during exercise [18, 180] further impairs contractility and increases the risk to fatigue in patients with COPD [175]. The increased CO_2 production also increases ventilatory demand and induces ventilatory limitation at lower than normal exercise workloads [181], thus causing early exercise termination in such patients [4, 102].

2.4 Cardiovascular responses during exercise

Cardiac output (CO), which is the body's energy supply and the product of stroke volume and heart rate (HR) is regulated principally by the demand for oxygen by

the cells of the body[182]. According to the Fick principle for O_2transport, the exercise–induced increase in VO_2 is achieved by an increased CO and an increased oxygen extraction at the level of the working respiratory and peripheral skeletal muscles. During both submaximal and maximal exercise in healthy individuals, CO increases nearly linearly with VO_2, suggesting that oxygen consumption is linearly related to the energy supply [183-185]. Although COPD patients likewise present an almost linear CO and VO_2 relationship, during sub-maximal exercise [186-188] HR has been reported to be higher than normal at any given VO_2 [189] implying that stroke volume (SV) is lower than normal [190]. In the absence of coexisting left heart disease, evidence suggests that the decreased SV occurs secondary to reduced right ventricular ejection fraction at rest and which, on average, fails to increase with exercise among patients with COPD [191-193]. As with CO, blood flow to the exercising peripheral muscles at a given submaximal exercise work rate is similar in patients with COPD and healthy individuals [150, 180]. In contrast individuals with COPD reach lower peak exercise work rates and exhibit a reduced peak VO_2 (30-50% lower than healthy) and peak CO (35 to 60% lower than healthy) with a normal or reduced HR, as well as a lower peak leg blood flow compared to healthy individuals [139, 150, 186-188, 194-197].

Dynamic hyperinflation appears to have a significant impact on cardiovascular function during exercise in patients with COPD [190]. Recently Vassaux et al. [198] showed a strong association (r=0.87) between inspiratory-to-total lung capacity ratio (IC/TLC represents an index of hyperinflation) at rest and exercise and oxygen pulse (i.e., VO_2/HR, a surrogate marker of cardiac function), demonstrating that the most hyperinflated patients, IC/TLC $\leq$ 0.25% - an indicator of severe static hyperinflation, had a lower peak exercise O_2 pulse at a similar work load than patients having less hyperinflation, IC/TLC>0.25% [198]. In an attempt to maintain the required ventilation during exercise when the ability to increase oxygen supply is limited, individuals with severe hyperinflation are forced to generate a larger intra thoracic pressure [191, 199]. This in turn, limits venous return, right and left ventricular blood volumes, and consequently, cardiac output

[191, 200-201]. In addition, loss of pulmonary vascular capacity with emphysema results in an increased pulmonary vascular resistance which may ultimately impair left ventricle (LV) filling. Barr et al. [201] reported that the severity of airflow obstruction (FEV_1/FVC) and the degree of emphysema on chest CT scans was inversely correlated with reductions in left ventricular end-diastolic volume, stroke volume and cardiac output. Although there was a stronger association in more severe patients, hemodynamic changes also occurred with mild emphysema and airflow obstruction. Watzet al. [202] reported that the IC/TLC was more strongly correlated with cardiac chamber size than measurements of airway obstruction or diffusion capacity, and that COPD patients with IC/TLC≤ 0.25% have not only an impaired LV filling, but also a reduced functional capacity as indicated by a lower 6-min walk distance.

2.5 Redistribution of cardiac output

Several studies [195, 203-205] have suggested that when the energy demands of the respiratory muscles are increased, such as during exercise, a competition for blood flow develops between the respiratory and peripheral muscles, which ultimately favours a redistribution of blood flow from the locomotor to the respiratory muscles. Evidence for this phenomenon, known as the "respiratory steal" or "blood stealing effect" [203], comes from Simon et al. [206] who found that about 45% of the patients with COPD participating in their study demonstrated a leg blood flow plateau during whole body incremental cycling exercise despite increasing exercise work load. They additionally found that the patients who exhibited such a leg blood flow plateau also revealed a greater work of breathing at sub-maximal exercise, indicating high O_2 demands of the respiratory muscles [206]. In this context, it has been suggested that reduction in blood flow to the working peripheral muscles may induce leg fatigue thereby limiting the duration and the intensity of exercise in patients with COPD as demonstrated by other studies [181, 207].

2.6 Hypoxemia during exercise

As a result of ventilation-perfusion mismatch and hypoventilation [208], gas exchange may become impaired in certain individuals with COPD (i.e. emphysema) [209] which can lead to hypoxemia [210] at rest and/or during exercise [211-212]. Studies have shown that in patients with severe COPD, even routine daily activities such as walking, stair-climbing, washing, or eating can induce hypoxemia [213-214]. Hypoxemia stimulates ventilatory drive, increasing minute ventilation, lowering$PaCO_2$, and in turn causing vasodilatation of the vascular bed, tachycardia, and an increased cardiac output [211, 215]. Chronic hypoxemia can additionally lead to pulmonary hypertension and cor pulmonale (right heart failure), thereby reducing cardiac output and impairing oxygen delivery [216]. Adding these factors to the effects of dynamic hyperinflation, it becomes evident that the hypoxemic patient with COPD is especially susceptible to muscle fatigue, lactic acidosis, and reduce exercise capacity [211, 216].

2.7 Locus of symptom limitation during exercise

The relative contribution of the previously described exercise-limiting factors varies considerably from patient to patient. Because of the diverse pathogenesis of the disease and unique patient characteristics (e.g. individual susceptibility to muscle fatigue) the locus of symptom limitation (i.e. the reason for stopping exercise) is not uniform among COPD individuals [217]. Compared to individuals with mild disease, patients with moderate-to-severe COPD have been reported to perceive dyspnea more intensely than leg fatigue [102].

Current knowledge indicates that the causes and mechanisms of exercise limitation in patients with COPD are complex and involve respiratory mechanical abnormalities, pulmonary gas exchange disturbances, as well as cardiac, respiratory and peripheral muscle impairments. The mechanisms of exercise limitation are heterogeneous within the COPD population, emphasizing the importance of comprehensive exercise assessment [217]. This information could assist in

identifying appropriate therapeutic strategies that could be used to help decrease ventilatory demand and improve exercise capacity.

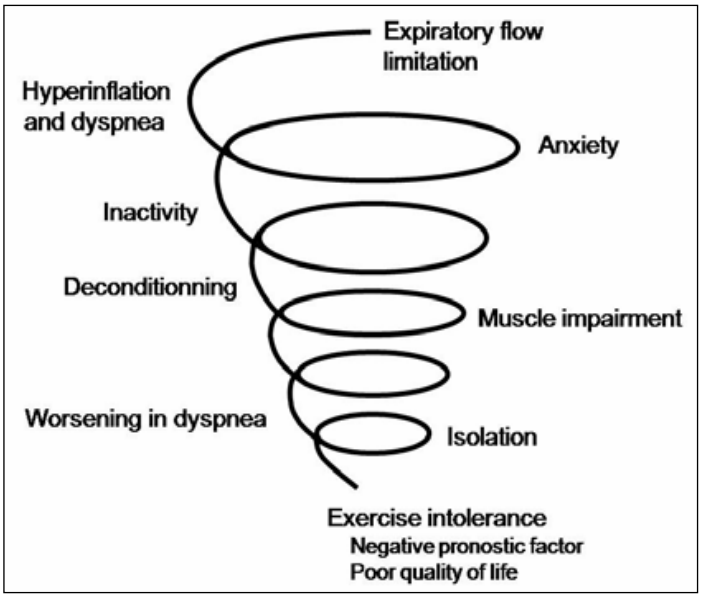


Figure 4 The deleterious effect of the decrease in daily life activities on muscle function and exercise capacity in COPD patients. From: Saey et al. [218]

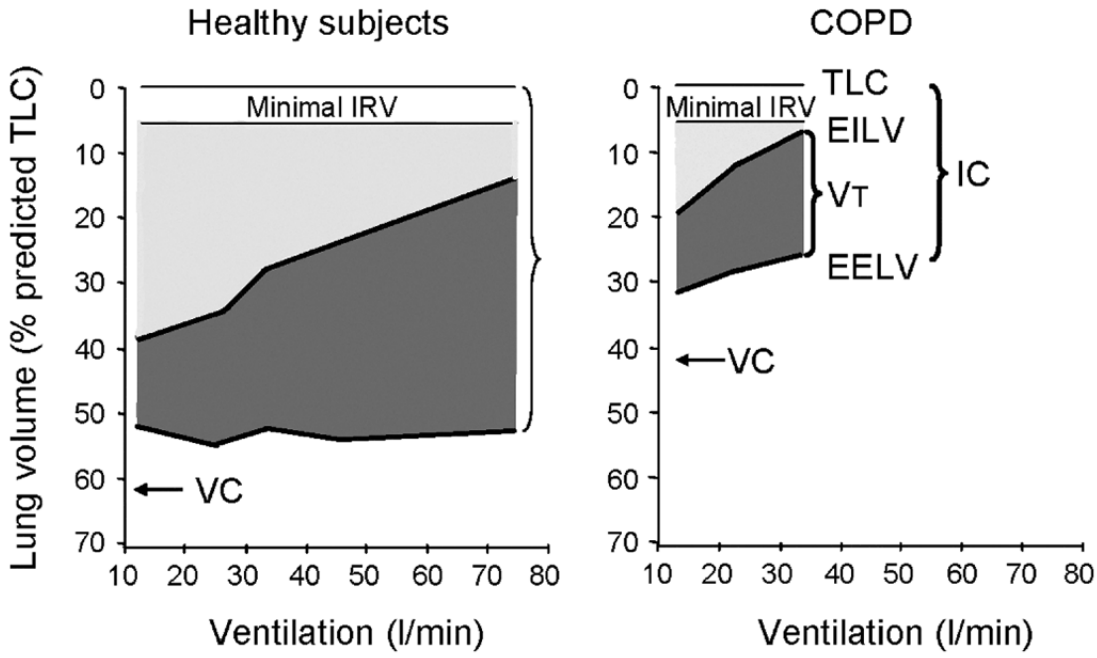


Figure 5 Changes in operational lung volumes as ventilation increases during exercise in patients with COPD and healthy subjects.

As can be seen, the expansion of tidal volume (VT) during exercise in COPD is significantly affected from both an increase in EELV and the minimal IRV. From O'Donnell et al. [55]

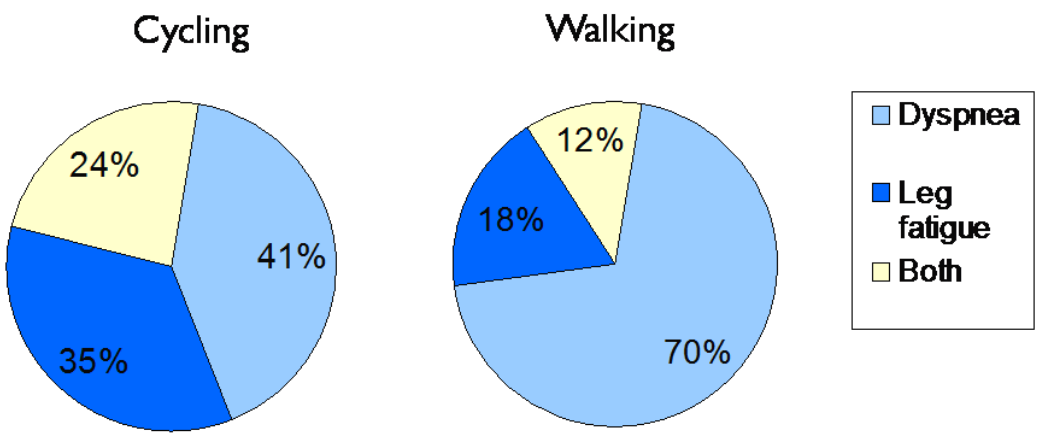


Figure 6 The key limiting symptom experienced by COPD patients after cycling and walking. From [176]

3. NON-PHARMACOLOGIC ADJUNCT THERAPIES USED DURING EXERCISE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In order to avoid the unpleasant sensation of dyspnea that is triggered by exercise, individuals with COPD are inclined to lead a sedentary lifestyle [160]. The consequence of such inactivity is progressive deconditioning [105], diminished cardio respiratory and peripheral muscle strength [112] as well as a reduced functional capacity [10]. With disease progression and decline of functional abilities, COPD patients often experience depression and anxiety, which can contribute to progressive withdrawal from usual activities and lead to social isolation [219].

3.1 Pulmonary Rehabilitation

In an effort to help reduce symptoms, improve exercise capacity and health-related quality of life (HRQoL), individuals with COPD are often referred to pulmonary rehabilitation programs [14, 17, 20, 220]. Although such programs typically use a multidisciplinary approach, combining education and exercise to optimize physical and social performance and autonomy, exercise training has been shown to be the essential component for improving exercise capacity and HRQoL [14-17, 20, 221-222].

The physiological benefits associated with pulmonary rehabilitation include a reduction of exercise lactic acidosis, minute ventilation and heart rate for a given work rate [18], enhanced activity of mitochondrial enzymes and capillary density in the trained muscles [106, 223] as well as enhanced anabolic processes in the peripheral muscles [224]. There is also some evidence that whole body aerobic exercise training may improve respiratory muscle function in patients with COPD, as demonstrated by an increase in the maximum inspiratory muscles pressure [225-227].

Although studies suggest that most patients with COPD can benefit from pulmonary rehabilitation [15, 18, 223, 228-230], some individuals with severe lung

disease (Table 1), may be unable to obtain a true physiological training effect because of their inability to exercise at a high enough exercise-intensity (i.e., 80% of the maximum work load) [18, 228].

These findings have spurred research, in the last decades, to identify therapeutic approaches such as supplemental oxygen [231-232], low density gases (Heliox) [233-234], or non-invasive ventilatory support (NIVS) [19-21], in order to help COPD patients increase their ability to exercise at higher intensities so as to enhance the physiological benefits of exercise and ultimately improve HRQoL.

The effect and potential physiological mechanisms underlying the use of supplemental oxygen, heliox and NIVS as non-pharmacologic adjunct therapies to exercise is the subject of the following sections.

3.2 Supplemental oxygen during exercise in patients with COPD

3.2.1. Short-term effects of supplemental O_2 on exercise capacity

A recent Cochrane systematic review [235] which evaluated the efficacy of hyperoxia during a single bout of exercise testing in COPD patients, concluded that supplemental oxygen increases exercise endurance (distance, time, number of steps) as well as maximum exercise capacity (exercise work rate). Included in this review were studies in which supplemental O_2 was administered during exercise to patients with COPD who were hypoxemic at rest and/or who desaturated with exercise [195, 231, 236-239] as well as individuals with COPD who did not meet the criteria for requiring supplemental O_2 during exercise [232, 240-241], indicating the positive effect of this therapeutic approach in a heterogeneous COPD population.

Two studies [232, 242] included in the Cochrane systematic review, are of particular interest. Fujimoto et al. [242] showed that patients with moderate to severe COPD accompanied by mild hypoxemia at rest (PaO_2> 60 mm Hg) had larger improvements in exercise capacity compared to patients with a mild COPD, independent of their level of oxygen saturation, suggesting that supplemental O_2

during exercise might have greater effects in patients who have more advanced disease. Exercise tolerance was also improved in a group of normoxemic COPD patients breathing supplemental oxygen [232]. Moreover, this last study found that only a modest increase in the fraction of inspired O_2 (i.e., FiO_2 of 0.3) was required for a direct increase in exercise endurance, whereas higher O_2 levels (i.e., FiO_2 of 0.5) did not further improved exercise tolerance [232].

3.2.2. Underlying mechanism of supplemental O_2

The way by which supplemental O_2 improves exercise tolerance appears to be multifactorial and involves several integrated mechanisms including changes in ventilatory drive, reduced ventilatory demand, alteration in central effort perception, and improved respiratory and peripheral muscle function [238, 240, 243-246]. The following sections briefly review these mechanisms.

3.2.2.1 Ventilatory response during exercise

Administration of supplemental O_2 in patients with COPD has been shown to reduce minute ventilation, respiratory rate [232] and ventilatory drive [237, 247] for a given exercise workload. The lower V_E which occurs secondary to a slower respiratory rate, has been reported to promote a reduction in dynamic hyperinflation [232, 237], thus placing the diaphragm on a more optimal contractile portion of its length-tension curve. Due to an improvement in the diaphragm's ability to sustain dynamic work, administration of supplemental O_2 to patients with COPD [248] has been reported to increase exercise endurance and to delay the onset of respiratory-muscle fatigue [238]. Interestingly, the association between increased endurance time with supplemental O_2 and the delayed onset of the diaphragmatic fatigue has also been found in several studies that examined healthy individuals breathing against inspiratory resistance [249-250].

While some authors have postulated that the decreased V_E that occurs with supplemental O_2 is related to slower ventilatory kinetics [247], others have

attributed the decreased V_E to delayed lactate accumulation, secondary to an increased peripheral muscle O_2 delivery [240, 251]. Evidence for the latter comes from a strong correlation between the decrease in V_E and fall in lactate accumulation (r=0.88, p=0.001) [240].

3.2.2.2. Cardiac responses and blood flow distribution

The evidence regarding the effect of hyperoxia on cardiac output during exercise in COPD patients is somewhat limited. However, several studies haves shown that the increase in maximum exercise capacity that occurs with supplemental oxygen is associated with an increased heart rate (HR) [246, 252] and/or stroke volume [252-253], thus CO [252].

It has been shown [241] that administration of supplemental O_2 during exercise to patients with COPD promoted a decreased ventilation which was followed by an increase in mean femoral O_2 delivery, indicating that a part of the blood flow may have been redistributed from the ventilatory to the peripheral muscles. However, as a recent study indicates, the increase in blood flow to the peripheral muscles during exercise is not necessarily the result of the blood flow redistribution mechanism [254] since an increase in the inspiratory muscles blood flow was also found with adjunct therapies that decrease the work of breathing, suggesting that other factors could contribute to this increase in peripheral blood flow [254]. Interestingly, Siqueira et al. [255] recently showed that the intra-muscular O_2 utilization is impaired in some COPD patient during constant work rate exercise, despite improved central O_2 delivery and blood oxygenation with supplemental O_2 administration.

3.2.3. Exercise training with supplemental O2

In contrast to evidence that administration of supplemental oxygen to hypoxic and normoxemic COPD patients during a single exercise bout decreases dyspnea and increases exercise capacity, the findings regarding the effectiveness of

supplemental oxygen used as an adjunct to exercise training over several weeks, are less consistent [231, 256-259]. Some studies [256-259] reported that training with supplemental O_2 had no effect on maximal exercise capacity, endurance exercise and HRQoL compared to breathing air [260] in both normoxic and hypoxemic patients with COPD. In contrast, other studies found that training with supplemental oxygen, compared to room air, enabled normoxic COPD patients to reach higher exercise training intensities and increase exercise endurance [231].

Exercise with supplemental O_2 can lead to dyspnea reduction, improved peripheral oxygenation and in exercise capacity. However, hypoxemic patients often cannot perform a sufficient intensity of exercise to gain such benefits. Breathing supplemental O_2 during exercise can improve blood saturation and increase the ability of patients with COPD to exercise.

3.3 Heliox breathing during exercise in patients with COPD

The complex configuration of the bronchial tree together with its branching angles and the airway internal diameter with its degree of roughness causes airflow to change from a laminar to a turbulent pattern, as air moves from the central to the conductive and peripheral airways [261-262]. Turbulent flow is further increased in patients with COPD consequent to airway inflammation and a loss of alveolar tethering, which causes narrowing of the airways. The resultant effect in such patients is an increased airway resistance and an increased work of breathing (WOB) at rest and even more prominent during exercise [8].

Breathing a low-density gas mixture such as normoxic heliox- which is a three times less dense gas mixture than air composed of 79% helium and 21% O_2, - decreases airway resistance by maintaining or re-establishing laminar flow within the tracheobronchial tree at higher flow rates [263-269].

3.3.1. Short-term effects of Heliox administration

The administration of heliox during exercise in individuals with airflow obstruction has been shown to reduce resistive work of breathing and increase maximum expiratory flow, thus promoting faster lung emptying [233, 270]. In addition, evidence shows that heliox breathing increases V_E during exercise [233, 254, 264, 271-273] and also improves exercise tolerance [233, 264, 271-273] while reducing dynamic hyperinflation and dyspnea at isotime [234, 254, 264, 271, 273]. This indicates that heliox is able to alleviate dyspnea and work of breathing by primarily reducing ventilator constraints [233-234, 264, 273]. Using esophageal and gastric balloon catheters, Vogiatzis et al. [254] recently demonstrated the positive effect of heliox on reducing the work of the inspiratory and expiratory muscles during exercise [254].

There is emerging evidence which suggests that heliox induced-respiratory muscle unloading and also improves distribution of the cardiac output to the peripheral muscles during bicycle exercise in COPD patients [195, 203, 254, 271]. Richardson et al. [195] showed that heliox administration promoted an increased VO_{2peak} and peak work load during whole body cycling exercise, with no change in arterial saturation, suggesting that the VO_2 increased secondary to enhanced peripheral O_2 availability and improved perfusion of the peripheral muscles.

Respiratory muscle unloading via heliox administration has also been associated with an improved O_2 delivery and extraction in the exercising locomotory muscles in moderate-to-severe COPD [233]. The increase in O_2 delivery to peripheral muscle has been assumed to result from a redistribution of blood flow from the respiratory to the leg muscles [195, 233]. Interestingly, a recent study found that heliox breathing during near-maximum exercise (i.e., 75% peak work load) improved both quadriceps and intercostals muscle oxygen delivery due to an increase in both arterial O_2 content and quadriceps and intercostals muscle blood flow in patients with moderate-to-severe COPD with static but not dynamic hyperinflation [254]. In contrast to the previous studies, these findings do not

support the “respiratory steal” phenomenon, instead it was concluded that the increase in muscle blood flow and perfusion was due to the reduction in the work power performed by the respiratory muscle.

In addition to the normoxic heliox, the effects of different oxygen concentrations (hyperoxia) in the heliox gas mixture have also been investigated in several recent studies [234, 264, 274]. In these studies, improvement in exercise performance was associated with an increased ventilatory capacity and a decreased dynamic hyperinflation [264] and dyspnea [234, 264]. These studies indicated that compared to either normoxic heliox or hyperoxia alone, administration of a combination of helium and hyperoxia can provide greater effect in reducing dynamic hyperinflation and work of breathing and improving exercise performance.

Heliox breathing unloads respiratory muscles and relieves both dyspnea and leg discomfort during exercise allowing COPD patients to increase time to exhaustion thereby the possibility of enhancing the physiological training effect [273], which in turn, could ultimately result in an improved activity of daily life and HRQOL [234, 254].

3.3.2 Effects of heliox during exercise training in COPD patients

A recent systematic review [266] investigating the effect of heliox on dyspnea and exercise performance during training found that heliox improved both exercise intensity and endurance in patients with moderate-to-severe COPD. These findings were associated with an improved ventilatory capacity, a decreased dynamic hyperinflation and reduced work of breathing [266]. Whether or not heliox has an effect on exertional dyspnea has not been identified yet.

Although there is evidence showing that administrating a gas of low density during a single session is a useful strategy for ameliorating the acute exertional symptoms and exercise capacity in a selective group of individuals with COPD, further studies are needed to identify whether or not these benefits are transferable when heliox is used as an adjunct to pulmonary rehabilitation.

3.4 Non-invasive ventilatory support during to exercise in COPD patients

Non-invasive ventilatory support (NIVS) is an innovative method used to provide ventilatory assist to breathingwith the goal of unloading the inspiratory muscles, thereby reducing the WOB and optimizing gas exchange in patients with cardiopulmonary disease [275-277]. NIVS has been used in a variety of clinical situations, including non-invasive management of patients with acute respiratory failurefollowing exacerbation of COPD and for patients suffering of sleep apnoea [278-280], just to name a few. In such settings, NIVS have been shown to substantially reduce diaphragm activity and inspiratory effort and to improve dyspnea and alveolar ventilation [281-284]. Moreover, it has been shown, in mechanically ventilated patients, that the time course for the reduction in both inspiratory effort and diaphragmatic electromyography activity is about 6-7 breaths [285].

For the last two decades, there has been increasing interest in the use of NIVS as an adjunct to exercise with the aim of enhancing exercise training intensity by unloading the inspiratory muscle in patients with COPD [211]. NIVS differs from traditional invasive mechanical ventilation, by the fact that it does not require the patient to be intubated (i.e., endotracheal or nasotracheal tube) for delivery of the positive pressure [286]. NIVS can be delivered through a variety of interfaces such as mouthpiece, nasal prongs, or facemask [21, 211, 287]. Studies investigating the effect of NIVS on exercise have used such ventilatory modes as continuous positive airway pressure (CPAP) [19, 288], bi-level positive airway pressure (BiPAP) [289-296], pressure support ventilation (PSV) [276, 297-300] and proportional assist ventilation (PAV) [301-305].

BiPAP has been the most commonly used mode of ventilation as an adjunct to exercise training during pulmonary rehabilitation programs [289-296]. BiPAP provides continuous positive pressure at two levels, one for inspiration (IPAP) and another for expiration (EPAP), where IPAP is a higher level of pressure and EPAP a lower level of pressure, both of which are above atmospheric pressure. The

difference between IPAP and EPAP is a reflection of the amount of pressure support provided to the patient. However, it should also be noted that when both IPAP and EPAP are set to the same level of pressure, the pressure delivered resembles the action of a CPAP mode. The airway management system in BiPAP ventilators is equipped with a solenoid valve system to permit separate adjustments of IPAP and EPAP. In addition, BiPAP has an intentional leak port which serves to eliminate exhaled gas.

CPAP and IPS have also been used during exercise in several studies. Different from BiPAP, CPAP delivers only one level of continuous constant positive airway pressure that elevates the baseline pressure (airway pressure which is constantly higher than atmospheric pressure) [19, 288]. While during BiPAP inspiratory and expiratory air pressure is delivered continuously, during PSV, which is a pressure-targeted mode, each breath is patient triggered and cycled. Similar to the EPAP delivered with BiPAP, a positive end-expiratory pressure (PEEP) can also be added to PSV.

Unlike BiPAP, CPAP and PSV, the pressure delivered to a patient with PAV is not constant and may vary each cycle [306]. PAV provides assist in proportion to the patient's spontaneous effort, according to the equation of motion (i.e., a mathematical model of the interaction between the ventilator and the patient). This requires that the pressure that is delivered within a breath is continuously readjusted in proportion to the pressure that is generated by the inspiratory muscles, determined using instantaneous measurements of inspiratory airflow and volume [301]. PAV is said to provide a better patient-ventilator synchrony [301, 307]. However, the need for continuous measurement of the patient's respiratory mechanics (i.e., resistance, elastance and iPEEP) and adjustment of ventilator settings greatly increases the complexity of this mode of ventilation. Different from PAV, BiPAP does not need continuous calibration of patient's respiratory mechanics. For a more in-depth review on the topic the reader is referred to more comprehensive reviews of the ventilator modes mentioned [21, 306].

3.4.1 Short-term effects of NIVS on exercise capacity

Studies evaluating the acute effect of NIVS during exercise using CPAP [19, 288, 308], BiPAP[290], PSV [276, 300, 309-310] and PAV [203, 302-303] during treadmill [300, 309] and cycling exercise [19, 276, 308] have been found to reduce dyspnea and increase endurance time in individuals with moderate-to-severe COPD [19, 203, 276, 302, 308-309]. However, the extent to which NIVS was reported to improve exercise performance varied greatly across studies. Although, the majority of studies demonstrated benefit with NIVS in the studies investigating the short–term effects, not all the evidence has supported the use of NIVS during exercise in patients with COPD. Two trials [295, 311] found that acute administration of NIVS during submaximal treadmill exercise resulted in a reduced walking distance in COPD patients. This difference in response to NIVS has been attributed to differences in patient selection or testing modalities. In line with this premise, Van'tHul et al. showed that patients with the weakest inspiratory muscles exhibited the greatest increases in bicycle exercise endurance with NIVS, suggesting these individuals may obtain a greater benefit from this adjunct therapy during exercise [299].

3.4.1.1 Ventilatory response to NIVS during exercise

In general, patients with COPD become increasingly dynamically hyperinflated during exercise due to the presence of expiratory flow limitation and a reduced time available for expiration. Increases in minute ventilation are achieved primarily by increasing the RR, whereas VT, which approaches the limits of TLC at end-inspiration, can only increase marginally before reaching a plateau [7]. Several studies demonstrated that NIVS administration during exercise increases V_E as a result of increases in both V_T and RR [276, 302] or only in V_T [19], whereas others have reported no change in V_E for a given workload [203, 299, 308, 312]. There is evidence, however, that NIVS promotes a reduction in inspiratory work load, whether [276] or not [308] V_T and EILV are increased [275, 313]. The inconsistent

effect of NIVS on breathing pattern observed among studies could be explained in part by the heterogeneous nature of the COPD patients participating in the studies, as well as by the fact that different modes of mechanical ventilation and different levels of ventilatory unloading were provided across studies.

The development of dynamic hyperinflation, which leads to neuromechanical uncoupling of the diaphragm (i.e., considerable mismatch between inspiratory effort and ventilatory output), contributes to the increased dyspnea as experienced by COPD patients [7]. Under conditions of impaired length-tension relationship [74], COPD patients need to increase diaphragm activation in order to maintain the same pressure generated across the diaphragm (i.e., transdiaphragmatic pressure) [314]. This increased activation will consequently augment the respiratory effort sensation, energy demand, as well as the inspiratory muscle fatigability [315-316].O'Donnell et al. [19] investigated the effect of NIVS on operational lung volumes during rest and exercise in patients with stable COPD and found that CPAP had no significant effect on EELV during exercise in COPD patients. Likewise, Spahija et al. [313] found that PSV had no effect on EELV, whereas EILV was significantly increased due to a larger VT. Although NIVS had no direct effect on EELV, using esophageal and gastric balloons the authors [313] found that PSV significantly reduced diaphragm muscle activation thereby inspiratory effort and dyspnea leading to a higher exercise capacity in COPD patients. Significant relationship between decrease in dyspnea and reduction in diaphragm activation has been reported by other studies [276, 308-309].

3.4.1.2 Effect of NIVS on cardiac performance and blood flow distribution during exercise

In patients with more severe COPD, up to 50% of the whole body oxygen uptake during exercise goes to the respiratory muscles due to an increased work of breathing [317], enhancing the likelihood of the occurrence of the respiratory steal phenomenon [195, 203]. There are several lines of evidence suggesting that reducing the work of breathing via NIVS during exercise may decrease ventilatory

muscle blood flow requirements, which allow a fraction of the limited CO to be redirected to locomotor muscles, thereby improving peripheral muscle perfusion, and in turn exercise capacity [203, 318].

Unloading the respiratory muscles during high-intensity exercise (70-80%W_{max}) using NIVS has been shown to improve peripheral muscle oxygenation [291, 319] and to reduce blood lactate levels [302, 310], which in turn not only reduces the occurrence of leg fatigue but also improves endurance time in patients with COPD [291, 319-320]. Reduction in lactic acidosis may reduce the stimulus to breathe, further would decrease VO_2 requirements so that V_E would not have to be increased as much, potentially delaying dynamic hyperinflation and dyspnea [302, 310].

The effects of NIVS on the cardiac performance are complex with most resulting from a NIVS associated rise in mean intra-thoracic pressure and a fall in transmural pressure [277, 321-323]. In a study evaluating the effect of PSV+PEEP, Oliviera et al. [319] showed that NIVS promoted an increase in stroke volume, heart rate, CO and ultimately exercise endurance in one subgroup of COPD patients; however, in another subgroup NIVS resulted in a decreased stroke volume and heart rate, thereby reduced CO with no improvement in exercise endurance. The study found that patients in the latter subgroup tended to be more hyperinflated, suggesting that NIVS may have a deleterious effect on hemodynamics and exercise tolerance in COPD patients who exhibit greater static hyperinflation.

3.4.2 Effects of NIVS administrated during pulmonary rehabilitation programs

A recent systematic review of the literature [324] investigating the effect of NIVS as an adjunct to exercise training programme in patients with COPD concluded that NIVS administration during exercise training promoted an increased exercise training duration, which in turn resulted in greater physiological training effects. To date, however, the findings from the studies assessing the effect of NIVS on

exercise performance during exercise training programs [294-295, 298, 304-305, 325] have been inconsistent. Several studies have demonstrated that the use of NIVS as an adjunct to exercise training has enhanced training intensity [294, 298, 304] and lead to increased maximum exercise capacity [304], peak oxygen consumption [294], and exercise tolerance [298]. Other studies [295, 325], in contrast, reported no increase in exercise intensity throughout the training period. Moreover, several authors have also shown that NIVS resulted in significant improvements in post-training peak oxygen consumption [325] and walking endurance [295], whereas others [305] showed no effect on post-training exercise performance.

Although considerable research has been devoted to the effect of adjunct therapies for pulmonary rehabilitation programs**,** rather less attention has been paid to the patients that are most likely to benefit from them. The studies that have evaluated the use of NIVS for exercise training differ with regards to: 1) the underlying pathophysiological abnormalities of the COPD patients studied, 2) the exercise protocols and training intensities used, and 3) the ventilators and assist modes used [21]. To identify the characteristics of individuals who benefit from this adjunct therapy the first step would be to identify the COPD patients who respond to the acute effect of NIVS during exercise. A further study would serve to identify the patients' characteristics or the predictors associated with NIVS improvements.

The findings of the studies that evaluated NIVS mirror somewhat those obtained with heliox and supplemental oxygen. Acute trials have shown improvement in physiologic parameters and exercise endurance. However, the benefit from long term application of NIVS during exercise training has not been clearly established yet [211]. NIVS applied during exercise may decrease dyspnea and improve exercise among patients with COPD, but current evidence is inconsistent. Although this approach is sometime considered as difficult, impractical and time consuming, one has to remember that different from the other adjunct therapies, NIVS could make a very difficult-to-train patient (i.e., very severe patients) trainable [292, 295].

3.5 Conclusion

Reducing dyspnea and peripheral muscle fatigue in patients with COPD is a key mechanism for improving exercise tolerance and activity. In the current review, three physiologically based interventions able to improve exercise tolerance have been discussed. Although the administration of supplemental O_2, heliox and non-invasive ventilatory support during exercise has been shown to unload the inspiratory muscles, reduce breathlessness, and enhance exercise endurance in patients with moderate-to-severe COPD, current available data demonstrates significant variability in their effectiveness across patients. It is proposed that these techniques should be targeted towards individuals who show the most promising response. Whether the symptoms limiting exercise contribute to such variability is unknown, raising the question whether patients who are limited by dyspnea obtain greater benefits from these adjunct therapies during exercise than those who are limited by leg fatigue. The examination of the acute effect of NIVS on exercise may provide insight into why some patients experience a greater benefit than others from these adjunct therapies and may help guide in identifying the most appropriate candidates for these forms of therapy.

CHAPTER III

RATIONALE AND OBJECTIVES FOR THE MANUSCRIPT -

Individuals with COPD commonly exhibit a limited ability to perform exercise due to a heightened sense of breathlessness and/or leg fatigue that occurs as a consequence of reduced ventilatory capacity and peripheral skeletal muscle dysfunction [4]. Although pulmonary rehabilitation (PR) programs have been shown to improve exercise tolerance and HRQoL in patients with COPD, some individuals are unable to obtain such benefits because of their inability to exercise at a high enough exercise-intensity. Noninvasive ventilation has been used as an adjunct during pulmonary rehabilitation to help improve exercise capacity in such individuals. However, the extent to which NIVS improves exercise tolerance is highly variable. It is anticipated that individuals who demonstrate the greatest increases in exercise capacity when NIVS is applied during a single incremental exercise test obtain the greatest benefit from its use during pulmonary rehabilitation program. To date, no studies have examined the effect of NIVS on maximal exercise capacity when applied during a single exercise test.

The purpose of the current thesis was to evaluate the acute effect of BiPAP on maximum exercise capacity in patients with COPD. To achieve this purpose, a study was conducted evaluating whether non-invasive ventilatory support, compared to no assist, increases maximum exercise capacity in individuals with COPD. Secondary objective was to explore the effect of NIVS on breathing pattern and operational lung volumes.

CHAPTER IV

MEASUREMENTS AND PSYCHOMETRIC PROPERTIES

The present chapter reviews the procedures and psychometric properties of the measurement techniques for the main and exploratory objectives.

Maximal exercise test

The gold standard in exercise testing is the symptom-limited incremental exercise test with gas exchange measurements or cardio pulmonary exercise testing (CPET) [326], which consists, in general, of 3minutes of rest followed by 3 minutes of unloaded pedaling followed by the incremental phase (i.e., progressive increase in work load) of exercise every minute (5to 25 W/minute) until the patient reaches volitional exhaustion [327]. CPET has been used to determine maximal exercise capacityor aerobic capacity (VO_2) and to identify the system that limits exercise performance in individuals with COPD [327]. Maximum exercise capacity evaluation identifies disease status and functional capabilities in COPD patients [326, 328-329].

Maximum aerobic capacity is difficult to obtain in COPD patients because such patients usually terminate exercise before a true VO_{2max} is reached due to the disease limiting factors, such as respiratory, cardiovascular and peripheral limitation (see section 2). Therefore, the peak aerobic capacity or work load is recorded instead.

Individuals with COPD commonly exhibit a limited ability to perform exercise [5-6, 228]. Compared to healthy individuals, patients with COPD demonstrate lower maximum exercise capacities and lower levels of peak oxygen consumption (VO_{2peak}) [139, 150, 195], with the lowest levels observed in patients with more severe COPD [150, 195, 330]. Although moderate correlations between VO_{2peak} and force expiratory volume in first second (FEV_1) have been reported in patients

with mild (r=0.69), moderate (r=0.65), and severe (r=0.87) COPD [331], others have foundFEV_1 to be a poor predictor of exercise capacity [48-50].

Patients with COPD typically experience dyspnea during exercise; however, the locus of symptom limitation (i.e., the reason for stopping exercise) is not uniform across patients [217]. Whereas the majority patients with COPD stop exercise because of dyspnea, others are limited by leg fatigue or a combination of dyspnea and leg fatigue [95, 102]. Compared to individuals with mild COPD, those with moderate-to-severe disease tend to perceive dyspnea more intensely than leg fatigue [102]. However, patients with COPD also exhibit skeletal muscle abnormalities, which can contribute to exercise intolerance [175]. Although the exact proportion varies among studies, leg fatigue has been reported as the primary symptom limiting exercise during cycling in approximately one third of the patients with COPD [102, 176], whereas dyspnea predominates during walking [95] (Figure 6). Some studies have also reported a moderate correlation between leg discomfort during exercise and the magnitude of contractile muscle fatigue of patients with COPD [176-177].

Maximum exercise capacity attained by a subject will be assessed by a symptom-limited incremental bicycle exercise test. Several studies [327, 332-335] examined the reliability of the symptom-limited incremental exercise in individuals with COPD and found a good reproducibility(r>90) for WL(Watts), V_E(L/min), VO_2 (L/min), VCO_2 (L/min), and heart rate at peak exercise in a test-retest procedure test.

Dyspnea

Dyspnea or breathlessness is defined as the perception of respiratory discomfort [8, 55, 89, 336]. Breathlessness is a persistent and progressive symptom that the COPD patient can experience at rest, during daily activities or lower levels of exercises [4-5, 102], as well as during high levels of exercise when ventilation and respiratory drive are increased [5, 337]. In COPD, dyspnea intensity during

exercise is higher at any given ventilation, or work rate than in healthy individuals [5]. Furthermore, dyspnea intensity during exercise has been shown to correlate strongly with measures of dynamic lung hyperinflation and effort-displacement ratio i.e. ratio relating inspiratory effort (Pes expressed as fraction of the maximum Pes at isovolume: Pes/PImax) to the ventilatory output [5, 7].

Dyspnea is a subjective measure, which could be described as having both quantitative (i.e., intensity of breathlessness) and qualitative dimensions [5, 8, 338]. Although there are various scales used to measure the magnitude of breathlessness sensation, the most commonly used scales during exercise are the visual analogue and the Borg scales. It is beyond the scope of the present thesis to discuss in detail the scales used to evaluate the level of dyspnea, but the reader is directed to excellent papers on this topic [5, 8, 338].

The modified Borg scale (Appendix *A2*) [339] will be used to assess dyspnea during exercise in patients with COPD. Participants are asked to rate their perception of dyspnea by selecting the number of the scale that best describes the intensity of the sensation felt. The scale is presented in a vertical format with scores and descriptors ranging from 0 = "nothing at all" to 10 = "extremely severe", reflecting the perceived magnitude of exertional dyspnea [339]. Although the modified Borg scale has been used to measure dyspnea during exercise, the scale has also been used in the assessment of the perceived sensation of peripheral muscles effort.

The validity and reliability of the modified Borg scale have been supported in many studies evaluating patients with COPD. Validity of the Borg Scale has been documented by a high degree of correlation with V_E (r =.98) [334, 340-342] and VO_2 (r=.95) [340, 342-343] during incremental exercise in patients with COPD [334, 340, 342, 344]. Moreover, a similar linear relationship has also been established relating Borg scores with W_L [342]. A very good reproducibility (r=0.96) for rating the respiratory sensations at peak exercise has also been shown in COPD patients when repeated within 1-10 days [334] and weekly over a 6 week period [342, 344].

Inspiratory capacity

Inspiratory capacity (IC) is the maximal volume of air than can be inhaled after a spontaneous expiration to EELV. The rate and magnitude of dynamic lung hyperinflation during exercise is generally measured by serial inspiratory capacity measurements. Since total lung capacity (TLC) does not change during activity, the change in IC reflects the change in dynamic EELV, or the extent of DH [8]. This has been found to be reliable method for tracking the acute changes in the lung volumes [345-346]. Inspiratory capacity is an important predictor of maximal exercise capacity [347]. IC measurements will be used to derive the end-expiratory lung volume (EELV=TLC-IC) at rest and during exercise.

Quadriceps muscle strength assessment

The traditional method of assessing quadriceps strength is through maximal voluntary contraction [170]. However, assessments which rely on the patient making a maximal voluntary effort have the disadvantage that the patient may fail to make a truly maximal effort [348]. To overcome this limitation non-volitional assessment of skeletal muscle strength using magnetic or electrical stimulation has been developed [100, 154, 172]. Nevertheless, a good correlation between maximum voluntary contraction (MVC) and quadriceps twitch tension (r=0.61) was found in COPD patients [100].

Magnetic stimulation is a sensitive technique for the assessment of skeletal muscle strength, independent of subject motivation, by measurement of twitch tension through nerve stimulation. It has been shown that this form of stimulation is more reliable and less painful than traditional electrical stimulation, making it more acceptable to patients [172]. A twitch contraction can be obtained in a rested muscle (unpotentiated twitch) or can be preceded by a maximum voluntary contraction (potentiated twitch) [178]. Kufel et al. work on quadriceps fatigue [349] demonstrated that the fall in the potentiated twitch was greater than in the unpotentiated twitch after MVC, indicating that the former is more sensitive and

reproducible to detecting early muscle contractile fatigue. Because of all of these genuine reasons, this thesis project will employ supramaximal magnetic stimulation of the femoral nerve.

With the individual seated in a recumbent chair (with the backseat fixed at approximately 45^{o}), the dominant leg will be stabilized at a 90° knee flexion. The ankle will be attached to a strain gauge (TSD121C, Biopac System, INC., CA, USA) through a non-elastic ankle strap to measure the isometric knee extension tension. The strain gauge will be adjusted perpendicularly to the ankle. The strain gauge signal will be amplified (DA100C, Biopac System, INC.,CA, USA) then transformed by an analogue transducer (Biopac System, INC,CA, USA) and stored on the computer for a later analysis (Acknowledge 4.1 software, Biopac).

Maximum voluntary contraction was recorded during a 3-second isometric manoeuvre. MVC manoeuvres were separated by 1 minute intervals and reported values were the means of the three strongest contractions. Verbal encouragement was provided throughout these manoeuvres. Non-volitional strength of the quadriceps was measured using a 42 mm figure-of-eight coil, which was powered by double magnetic stimulators (MagstimBiStim²; Magstim Co Ltd., Whitland, Dyfed, Wales, UK). The coil was placed over the femoral nerve at the position leading to the strongest muscle contraction. Potentiated quadriceps twitch force (Twq) was measured three seconds after the MVC manoeuvre at 100% stimulator output intensity. A series of TWq measurements were performed until three reproducible values were obtained. Reported values for the TWq corresponded to the mean of the three highest values. To ensure supra-maximality [100], a quadriceps twitch force/power output relationship was obtained, thereby confirming that a plateau in quadriceps twitch force was obtained in each subject (39). As shown by other investigators [100, 177], a fall in TWq ≥15% is beyond the technical variation of the measurement and considered to indicate quadriceps contractile fatigue. An excellent reliability of TWq measurements ($r=0.92$, $p=0.0001$) has been demonstrated when used in patients with COPD [100].

CHAPTER V

ACUTE EFFECT OF NONINVASIVE VENTILATORY SUPPORT ON MAXIMUM EXERCISE CAPACITY IN PATIENTS WITH COPD

Moga A.M.,B.Sc.,PT[1,2], De Marchie M. MD[3],Saey D.Ph.D[4], Spahija J. Ph.D[1,2.]

1. School of Physical and Occupational Therapy, McGill University, Montreal, Quebec, Canada;
2. Respiratory Health Research Center, Sacré-Coeur Hospital, Montreal, Quebec, Canada;
3. Department of Adult Critical Care, Sir Mortimer B. Davis Jewish General
4. Centre de Recherche, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Québec, Canada;

Manuscript prepared for the submission to COPD Journal

Running title: Effect of BiPAP on Exercise Capacity in COPD

Communication addressed to: Jadranka Spahija PhD
Hôpital du Sacré-Coeur de Montréal
Axe de recherche en santé respiratoire
5400 boul. Gouin Ouest,
Montréal, Quebec, H4J 1C5
CANADA
Telephone: (514) 338-2222 ext.3654
jadranka.spahija@mcgill.ca

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide and results in substantial economic and social hardship [1-2]. COPD is principally defined by a progressive irreversible airflow limitation. However, it is also accompanied by such systemic manifestations as peripheral muscle dysfunction, cardiovascular disease, cachexia and osteoporosis. Patients with COPD typically have a limited ability to perform exercise [4-6] due to a heightened sense of dyspnea [7] and/or leg fatigue secondary to reduced ventilatory capacity [7-8] and skeletal muscle dysfunction[9]. As a consequence of the decreased exercise capacity, individuals with COPD become progressively deconditioned [105], with further manifestations of diminished respiratory [161-162] and peripheral muscle strength [112] as well as reduced functional capacity [10].

Exercise training is an effective strategy in the management of COPD [14, 17, 20, 220]. There is evidence that training at a moderate to high exercise-intensity produces significant improvements in exercise tolerance, muscle strength and health related quality of life [14-18, 223, 229-230]. However, some individuals with COPD are unable to obtain such benefits due to the occurrence of dyspnea at low exercise intensities [4, 18]. Noninvasive ventilatory support (NIVS) has been used as an adjunct to pulmonary rehabilitation [19-21] to help COPD patients exercise at higher intensities, thereby enhancing the physiological benefits of exercise.

Recent studies have suggested that the short-term use of NIVS during exercise in individuals with COPD can unload the inspiratory muscles, reduce dyspnea and increase endurance time [19, 203, 276, 302, 308-309]. However, the extent to which NIVS improves exercise has been found to vary greatly across studies. Hyperinflation reduces the length of the inspiratory muscles and consequently decreases their ability to generate pressure [74]. Under these conditions, central

respiratory drive and respiratory muscle activation must be increased in order to generate a given pressure [350-351]. The augmented mechanical respiratory muscle work and neural output that occurs in such patients contributes significantly to the development of exertional dyspnea [102]. Moreover, patients with the weakest inspiratory muscles have been found to exhibit the greatest increases in exercise endurance with NIVS, suggesting these individuals may obtain a greater benefit from this adjunct therapy during exercise [299].

To date, the findings from the studies assessing the effect of NIVS as an adjunct to pulmonary rehabilitation have been inconsistent [294-295, 298, 325]. Some studies have demonstrated that using NIVS to enhance exercise training intensity [294, 298, 304], results in an increased peak work load [304], peak oxygen consumption [294]and exercise tolerance [298], whereas others have reported no increase in exercise intensity throughout the training period and no effect on exercise performance [295, 305, 325].

We anticipate that individuals, who demonstrate the greatest increases in their exercise capacity acutely, when NIVS is applied during a single incremental exercise test, are likely those individuals who obtain the greatest benefits from its use during the pulmonary rehabilitation. The reasoning behind this assumption is based on the work load - time to exhaustion relationship [352], which demonstrates that the tolerable duration of high intensity constant load cycling decreases hyperbolically as a function of work load [352]. This relationship indicates that when exercise is performed at a high workload, available intramuscular energy stores may be utilized rapidly, whereas, when exercise is performed at lower work rates, they may be sustained for a longer duration [352]. The variability seen in the effect of NIVS on training intensity and exercise endurance may be due to the fact that some patients exercise at a lower percentage of their maximum exercise capacity.

To the best of our knowledge, no previous study has investigated the acute effect of pressure support (PS) on incremental maximum exercise capacity.

The objectives of the present study are therefore to: (1) evaluate the extent to which non-invasive ventilatory support, compared to no assist, increases maximum exercise capacity in individuals with COPD; (2) to evaluate the effect of NIVS on operational lung volumes, symptoms, quadriceps strength, metabolic parameters, symptoms, breathing pattern at rest and during exercise.

We hypothesize that PS of 10 cmH_2O (PS10) will significantly increase maximum exercise capacity in individuals with COPD. We also hypothesize that NIVS will improve the physiological parameters at rest and during exercise.

METHODS

Study participants

Ten patients (7 women / 3 men) with stable moderate-to-severe COPD were recruited from the pulmonary outpatients clinics of a tertiary hospital (Sacré-Cœur Hospital and Jewish Rehabilitation Hospital, Montreal, QC, Canada). All patients were between 47- 80 years of age and had a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <0.7. Stability was operationally defined as unchanged respiratory symptoms, no change in medications used, and no exacerbation in the previous 4 weeks. Subjects with known cardiovascular, musculoskeletal or locomotor disease, alpha1-antitrypsin deficiency, neurologic or psychiatric illness, as well as those requiring supplemental oxygen were excluded from the study. The study was approved by the hospital's ethics committee and all participants gave their written informed consent.

Procedure

The study had a cross-over randomized design and comprised three separate experimental visits (Figure 7). Patients were asked to abstain from smoking on the

days of the study and to avoid eating for at least 3 hours prior to undergoing testing. Patients were also instructed to take their usual medication throughout the study.

During the first visit, subjects underwent anthropometric measurements, pulmonary function tests, a resting 12-lead electrocardiogram and completed a physical activity questionnaire. Pulmonary function tests (System 1085; Medical Graphics Corp, MN, USA) were performed according to American Thoracic Society standards [353]. Lung volumes and spirometry were determined using a whole-body plethysmograph (System 1085; Medical Graphics Corp, MN, USA). Maximum inspiratory and expiratory mouth pressures (PImax and PEmax) were measured at functional residual capacity (FRC) and total lung capacity (TLC), respectively (Medical Graphics Corp, MN, USA). Spirometry, lung volumes maximum pressures, and single-breath diffusion capacity for carbon monoxide (DLCO) were compared with reported norms [354]. Predicted values are based on norms by Knudson et al [354].

During this first visit, subjects also underwent a symptom limited-incremental exercise test on a bicycle ergometer (Lode, Groningen, The Netherlands) while breathing through a mouthpiece (VBite, Hans Rudolph) with nose clips on. The mouthpiece was connected to a respiratory circuit consisting of a pneumotachograph(model 4813; Hans Rudolph, Kansas City, MO, USA) connected to a pulmonary gas exchange analyzer (COSMED K4 b2, Rome, Italy) and a Hans Rudolph one way valve. Participants initially breathed at rest for 6 minutes while seated on a bicycle. This was followed by a 1-min unloaded warm-up period, after which the exercise work rate was increased by 5 watts every minute until a symptom limited end-point; during this time subjects were encouraged and asked to maintain a pedaling rate at 60 ± 8 revolutions per minute throughout exercise. Immediately after the exercise endpoint, patients performed 1 minute of unloaded cycling and then stop pedaling.

The effect of NIVS on maximum exercise capacity was determined during the second and third visits (completed at least 48 hours apart) with subjects repeating

the incremental exercise tests respecting the same procedure as in the first visit, however, this time they were assisted by a mechanical ventilator, which delivered bi-level positive airway pressure (BiPAP Vision, Respironics). Subjects received 0 cm H_2O of pressure support (PS0; sham) during one visit and 10 cm H_2O of PS (PS10; intervention) during the other. To avoid any ordering effect, PS0 and PS10 were delivered utilizing a randomized balanced order (sealed envelopes).

With BIPAP, the difference between the inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) that is delivered is a reflection of the amount of pressure support (PS) that is provided to the patient. Since 4 cm H_2O EPAP is the lowest level of assist that can be delivered with the BiPAP, for delivery of 10 cm H_2O of PS, the IPAP was set to 14 cm H_2O and the EPAP to 4 cm H_2O. In contrast, for the sham condition (PS0), the ventilator delivered 4 cm H_2O of both IPAP and EPAP.

During visits 2 and 3, subjects breathed through the same respiratory circuit as during visit 1, with the exception of an additional slide valve (Hans Rudolph) and the ventilator tubing containing a disposable exhalation valve (BiPAP). These extra components allowed the assist from the ventilator to be delivered to the subjects and the inspiratory capacity manoeuvres to be performed.

During all three visits, before the incremental exercise test, quadriceps muscle force [potentiated twitch force (Twq)] was quantified during maximal voluntary contraction (MVC) and magnetic stimulation of the femoral nerve. (Magstim BiStim²; Magstim Co. Ltd, Whitland, Dyfed, Wales, UK) Quadriceps force was measured again at 10 and 40 min after the exercise to quantify force loss induced by bicycle exercise. The study design is schematically depicted in Figure 7.

Measurements

Maximum exercise capacity

Peak exercise was operationally defined as the highest workload (WLmax) reached and maintained for at least 30 seconds [53]. Isoload was defined as the lowest

maximum exercise work load reached from any of the three exercise test conditions.

Breathing pattern and gas exchange

Breathing timing parameters, minute ventilation (V_E), tidal volume (VT), respiratory rate (RR),and mouth pressure (Pmo) were measured at rest and during exercise on a breath-by-breath basis using a pneumotachograph (Pneumotachograph, model 4813; Hans Rudolph, Kansas City, MO, USA) and a differential pressure transducer (Biopac Systems, Santa Barbara, CA, USA).The analog flow signal from the exercise system was digitized using a 16-bit A/D converter (MP 100A-CE, Biopac Systems, Santa Barbara, CA, USA) at 100 Hz and stored on a personal computer for offline analysis.

Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) (COSMED K4 b2, Rome, Italy), were measured at rest and during exercise on a breath-by-breath basis. Calibration of the COSMED K4 b2 system was performed, immediately before each test, by using a 3-liter syringe to calibrate the turbine, using a gas reference gas mixture (16% O2 and 5% CO2; balanced N2). The Hans Rudolph pneumotachograph was as well calibrated for linearity before each test using a 1-litre syringe.

Heart rate and oxygen saturation were measured continuously at rest and during exercise using a 3-lead ECG and a pulse oximeter (COSMED K4b2, Rome, Italy), respectively.

Operational Lung Volume

Changes in operational lung volumes were derived from measurements of inspiratory capacity performed by the participants at rest, every minute during the exercise, and peak exercise. End expiratory lung volume (EELV) was obtained by subtracting the inspiratory capacity (IC) volume from measures of TLC previously obtained during pulmonary function testing [55, 346].

Dyspnea and Leg Fatigue Symptoms

The perception of dyspnea and leg fatigue was assessed at every minute (i.e., last 15 seconds in the minute) during exercise using the modified 10-point Borg scale (*Appendix A2.0*) [339]. After completing the test, participants were also required to describe the main reason for stopping the exercise, thus identifying the locus of symptom limitation (e.g. discomfort with breathing or/and leg effort).

Quadriceps strength measurements

Potentiated quadriceps twitch force of the dominant leg was measured by supra-maximal magnetic stimulation of the femoral nerve 3 seconds following isometric maximal voluntary contraction of the quadriceps (MVC) as previously reported [147, 355] (Chapter IV). The MVC manoeuvres were separated by 30 seconds and the reported values correspond to the mean of the three strongest contractions. Verbal encouragement was provided during this manoeuvre.

Physical Activity Score

The level of physical activity in daily living was assessed by using the Voorips questionnaire [100] (*Appendix A 3.0*). This physical activity questionnaire was described by Baecke et al.[356], adapted further for elderly individuals [357] and used in patients with COPD [100, 355, 358]. The questionnaire attributes a score for household, sport, and other leisure time physical activities together resulting in a global physical activity score. A score of 9 to 16 indicates a moderate level of daily physical activity, whereas a score of less than nine points is considered to represent a sedentary lifestyle [100].

Off-Line ventilatory data analysis:

Breath by breath analysis was performed. For each individual, RR,V_E, Pmo and timing parameters of the breathing pattern including inspiratory time (Ti),

expiratory time (Te) and total breathing cycle time (Ttot), were determined from the flow tracing. Tidal volume was obtained by digital integration of flow.

Breath-by-breath data were ensemble averaged from last 15 breaths of each minute during exercise in every subject studied and group mean values were then calculated, using these means.

STATISTICAL ANALYSIS

The primary outcome measured was maximum exercise capacity (WL_{max}), assessed using a symptom-limited incremental bicycle test. The secondary objectives were operational lung volume, metabolic parameters, breathing pattern, symptoms and peripheral muscle strength at rest and during exercise.

Basic descriptive statistics were used to describe the characteristics of the sample. Patient's socio-demographic characteristics and scores on all measures were expressed as means values and standard deviations (SD) unless otherwise specified. Differences in exercise work load (i.e., primary objective) and physiological responses (i.e., secondary objectives) at peak exercise and at isoload between the three symptom-limited incremental exercise tests were examined with a one-way repeated measures analysis of variance (ANOVA). If a significant difference was found the analysis was followed up with the Student-Newman-Keuls test for post hoc comparisons.

The rationale behind ANOVA has been chosen based on the scale type of the primary outcome (i.e., continuous), type of intervention (categorical dichotomous scale) as well as the number of times the outcome was measured, i.e., three repeated measurement points. Same principle has been applied for the selection of the statistical test for the second objectives.

The level of significance for all statistical tests was $\alpha = 0.05$.

RESULTS

Participant characteristics

Ten individuals with COPD, 3 males and 7 females, aged 68.30± 6.43 years, completed the study. Table 4 presents the main characteristics of the study participants. Participants had moderate to severe airflow obstruction, exhibited static hyperinflation (i.e., increased FRC above normal value) and a reduced DLCO. Using the Physical Activity Questionnaire, patients reported having generally maintained a moderate level of physical activity. In addition, respiratory muscle weakness was observed in 70%of the subjects as indicated by a lower than predicted PImax value. One patient was a current smoker and 9 were ex-smokers, having stopped smoking at least 2 years prior to the study.

Ventilator pressures

Mean inspiratory and expiratory mouth pressures (Pmo) during exercise without PS, as well as with PS0 and PS10 are shown in Figure 8. Without PS, mean Pmo was negative during inspiration, whereas it averaged +3 cm H_2O and +10cm H_2O during inspiration with PS0 and PS10, respectively. The expiratory Pmo was similar during PS0 and PS10, and was significantly higher than without assist.

Primary objective:
The effect of NIVS on maximum exercise (primary objective)

Responses to incremental exercise without PS, as well as with PS0 and PS10 are shown in Table 6. Typical of patients with COPD, our patients demonstrated a reduced maximum exercise capacity without ventilatory assist [50, 359].

The exercise workload achieved by each individual without the ventilator and during PS0 and PS10, as well as the group means are presented in Figure 11. Participants reached a significantly lower WL (p=0.001) when exercise was performed with both levels of assist compared to without PS (Table 5.3). The

decrease in exercise capacity with PS10 was 10.00 ± 8.2 W, with a 95% confidence interval of 5.84. Compared to exercise without assist, WL_{max} with PS10 was lower in 7 individuals (70%) whereas it was unaltered in 3 (30%) (Figure 11). Compared to PS0, 6 out of the 10 subjects had a higher peak exercise capacity with PS10. However, no statistical difference in the peak WL was found between PS0 and PS10 (Figure 11).

Secondary outcomes:

Breathing pattern during rest and exercise

Breathing pattern responses at rest and during exercise in the absence of PS, with PS0 and PS10 are shown in Table 5 and 6. Compared to exercise without PS, VT was increased with PS10 at rest and peak exercise, whereas PS0 was not different in either condition. At rest, the RR was similar when no PS was delivered and during PS0, whereas it was significantly higher with PS10 due to a lower T_I and T_E. In contrast, at peak exercise, the RR and other breath timing components were unaltered with the addition of the ventilator, whether or not assist was provided, compared to when no ventilator was used. As illustrated in Figure 9, the V_E was higher at rest and at peak exercise with PS10 compared to no assist or PS0, whereas at isoload, V_E was higher with both PS0 and PS10compared to no assist.

Operational lung volumes during rest and exercise

The operational lung volumes responses at rest and during exercise without PS, PS10, and with PS0 are shown in Figure 14/ Table 5 and 6. Resting EELV was marginally increased with PS10 compared to no assist (~170 ml). In contrast, no difference in the EELV was found between the 2 levels of assist. Whereas EELV increased by ~ 500 ml with exercise without any assist, there was no difference between no assist, PS0 or PS10.

Gas exchange parameter during rest and exercise

At rest, both VO_2 and VCO_2 were found to be significantly higher during the application of PS10 compared to no assist and PS0. Although the WL_{max} attained was lower during both PS0 and PS10 than the no assist session, both VO_2 and VCO_2 at peak exercise and at isoload were significantly higher during PS10 and PS0 compared to no assist (Table 5 and 6 / Figure 13).

Exertional symptoms

Despite differences in the peak exercise capacity, the Borg ratings of dyspnea at peak exercise were similar for PS0 and PS10. Compared to no ventilatory support, dyspnea was significantly higher at isoload with PS10 and PS0 ($p = 0.009$ and $p = 0.003$, respectively) Ratings of perceived leg discomfort at peak exercise were significantly reduced with PS10 compared to no assist ($p<0.05$), whereas there was no difference in the level of leg discomfort at isoload between the three conditions (Table 6 /Figure 12).

Maximum exercise capacity without PS was limited primarily by intolerable dyspnea in 8 patients, by leg discomfort in 1 subject, and by a combination of shortness of breath and leg discomfort in 1 patient. With PS10 and PS0, dyspnea was reported as the exercise limiting symptom (i.e., locus of limitation) by all 10 patients.

Quadriceps muscle fatigue

Compared to pre-exercise values, the mean value for quadriceps twitch tension was found to be decreased at 10 minutes post-exercise. Four patients demonstrated a ≥15% fall in quadriceps twitch tension at 10 minutes post the incremental cycle exercise without PS and were considered to be fatiguers.

In these patients, the fall of quadriceps twitch force persisted for up to 30 minutes post-exercise and subjective reasons for exercise cessation were discomfort in legs

and dyspnea (1 patient), dyspnea (2 patient), and leg fatigue (1 patient). In the remaining patients, there was no fall in quadriceps twitch tension and the reason for exercise cessation was dyspnea.

DISCUSSION:

This is the first study to evaluate the acute effect of NIVS (BiPAP) on maximum exercise capacity achieved during a progressive incremental cycling exercise test and on related physiological parameters, in patients with stable moderate-to-severe COPD. The main findings of the present study are that in such patients, 10 cm H_2O of PS delivered during exercise, using BIPAP via a mouthpiece, does not improve maximum exercise capacity compared to 0 cm H_2O of PS. In contrast, a reduced maximum exercise capacity was found between PS10 and exercise in the absence of ventilatory assist. Furthermore, NIVS did not alter EELV at isoload or peak exercise compared to exercise without assist.

In the current study we administered bi-level positive pressure (BiPAP Vision, Respironics) in form of sham, PS at 0 cm H_2O (IPAP & EPAP of 4 cm H_2O), and intervention, PS at 10 cm H_2O (IPAP 14 & EPAP 4 cm H_2O). This mode and these levels of assist were selected based on the fact that they have previously been used in studies as adjunct therapies for exercise training in patients with COPD [299-300]. Different from other ventilatory modes, BiPAP has a continuous flow and delivers two levels of pressure that can be adjusted independently; however, the EPAP on the BiPAP Vision cannot be reduced below 4 cm H_2O.

To the best of the authors' knowledge, this is the first study in which the effects of NIVS were evaluated not only by comparing the effects of two intensities of BiPAP on maximum exercise capacity achieved during a progressive incremental cycling exercise test, i.e., PS0 and PS10, but also by comparing these effects to maximum exercise capacity without PS. This was because: first, we wanted to avoid any placebo effect, and therefore we chose to integrate a sham condition (PS0), and second, to investigate if the application of PS of 0 cm H_2O, in

comparison to exercise without PS would alter exercise performance in the presence of a continuous EPAP of 4 cm H_2O. In the present study, although there was a trend towards higher WL_{max} with PS10, no significant difference was found between WL_{max} with PS0 and PS10 in moderate-to-severe COPD patients. In line with our findings, Dolmage and Goldstein [303] also found that compared to sham at 0 cm H_2O CPAP, the application of either 5 cm H_2O of CPAP or 6 cm H_2O of PAV did not significantly increase endurance time in a sample of 10 moderate-to-severe COPD. O'Donnell et al. [360] similarly noted that 4.8 cm H_2O of CPAP did not change endurance time compared to 1 cm H_2O of CPAP (i.e., sham) in patients with chronic heart failure. In contrast to our findings, Bianchi et al. [312] also found that endurance time was increased with 6 cm H_2O compared to 1 cm H_2O of CPAP in severe hypercapnic COPD patients. One possible explanation for the differences in our findings could be the small sample size of the present study.

Compared to the response observed when no ventilatory assist was provided, 80 % of the COPD patients in our study exhibited a lower WL_{max} with PS10, whereas WL_{max} was unaltered in remaining 20%. The decline in the maximum exercise capacity in the eight patients averaged 10 Watts. The decrease or no change in maximum exercise capacity observed with PS10 confirms in part the results of other studies. V'ant Hul et al. [299] reported that 67 % of the COPD patients participating in their study had either a decline in cycling exercise endurance or did not significantly improve exercise time with 10 cm H_2O of inspiratory pressure support compared to exercise without PS. Different from our findings, others have reported that the use of PS [300, 361], increased exercise performance in severe COPD patients. The disparity of findings steam from differences in the applied experimental protocols, as the findings of Keilty [300] and Polkey [361] were obtained during endurance treadmill exercise test, whereas we administered a progressive incremental cycling exercise test. In addition, the use of different ventilators and level of assist delivered during exercise may also explain the different findings obtained across studies.

The breathing pattern adopted during exercise by our patients with PS0 and PS10 is similar to that reported by other studies in COPD patients [276, 302] and healthy subjects [288, 307]. We observed significant increases in VE from a concomitant increases in VT with no change in RR both at isoload and peak exercise. In general, minute ventilation and breathing pattern are determined by the intensity and pattern of respiratory muscle contraction (i.e. respiratory muscle output) and the mechanical properties of the respiratory system [362]. Efforts to maintain adequate ventilation in pace with the metabolic demands during exercise force COPD patients to adopt strategies that ultimately increase respiratory muscle work [19]. In patients with COPD, dynamic hyperinflation is a consequence of the increased ventilatory demands of exercise [19, 308, 340]. Hyperinflation decreases inspiratory muscle length, which reduces the ability of such muscles to generate pressure [74]. Under these conditions, central respiratory drive and respiratory muscle activation are increased [314, 350-351], thereby increasing the work of breathing and ultimately the O_2 cost of breathing [350, 363]. The augmented mechanical work and neural output that occurs in patients with COPD contributes significantly to the development of exertional dyspnea [7, 55], a common exercise-limiting symptom in such individuals [102, 364].

NIVS has been proposed as an adjunct to exercise in order to unload the overburdened ventilatory muscles with the aim to help increase exercise capacity in patients with COPD. Administration of PSV during exercise in patients with COPD has been shown to decrease exercise-induced respiratory muscle activity, hence ventilatory muscle demand and dyspnea [276, 309, 313, 361, 365]. Such reduction in the work of ventilatory muscles was found to result in the improvements in dyspnea and exercise performance. In the current study, EELV increased from rest to exercise when no ventilator was used, and there was no further change with the addition of either PS0 or PS10. These findings are consistent with other studies that have used BiPAP, CPAP and PAV as modes of ventilation [89, 276, 288, 303, 308, 312-313, 366].

In our study, the ventilator was set to deliver BiPAP with a constant inspiratory pressure of 10 cm H_2O and EPAP of 4 cm H_2O. It has previously been suggested, that when ventilatory assist is provided with a constant inspiratory pressure, there is a poor relationship between the patient's effort and the response of the assisting device [303]. Ventilation may be better supported if the mode of ventilatory support is more closely matched with the effort made by the subject. Different from PS and CPAP, PAV is said to enhance the synchrony between patient effort and ventilatory support [301, 307], thus improving patient comfort, reducing dyspnea and increasing exercise tolerance [302-303]. However, the need for continuous measurement of the patient's respiratory mechanics (i.e., resistance, elastance, and iPEEP) and adjustment of ventilator settings greatly increases the complexity of this mode of mechanical ventilation.

In order to standardize the intervention provided, it was decided that in the current study, the level of IPAP and EPAP would not be individualized for each patient. Previous studies have suggested that setting EPAP above the level of PEEPi could contribute to a significant rise in EELV [305, 367]. We did not measure PEEPi in our subjects either at rest or during exercise, and considered that it would not be feasible to individually titrate inspiratory and expiratory positive pressure settings without the actual measures of respiratory mechanics. The minimum EPAP that can be set by default on the Vision BiPAP ventilator is 4 cm H_2O. It is quite possible that, with the increased ventilatory demands of exercise, an inadequate level of assist may have been provided in our study. The lack of tailoring both IPAP and EPAP may have caused less effective ventilatory muscle unloading, which could be one explanation why PS10 was not efficient in improving maximum exercise capacity in our patients. However, without the assistance of esophageal pressure recordings, the extent to which PS10 unloaded the ventilatory muscles or reduced diaphragm activation throughout the course of exercise remains unknown.

The application of 4 cm H_2O EPAP in our study may potentially have resulted in a

substantial load on the expiratory muscle leading to increased expiratory muscle recruitment. O'Donnell et al.[19] found that for a patient who was much less hyperinflated, application of 4-5 cmH_2O of CPAP was not effective in improving inspiratory muscle function, inspiratory sensation or exercise endurance. In a further report, O'Donnell et al. [288] suggested that in the absence of expiratory flow limitation, EPAP could place an added burden on either the expiratory or inspiratory muscles. Other studies have reported a marked increase in expiratory muscles activation with CPAP in asthmatic patients with induced bronchoconstriction [368] and COPD patients during exercise [276, 308]. It has been suggested that active expiration may be associated with a significant increase in O_2 consumption under loaded conditions [369].

The present study found that VO_2 and VCO_2 during exercise increased significantly with the application of NIVS, indicating the likelihood of respiratory muscle recruitment. These findings are partly in accordance with the findings of Maltais et al. [276], although the increased VCO_2 that resulted with PS in that study, was not accompanied by an increase inVO_2. Our findings suggest that an additional factor may have contributed to our results.

Bianchi et al. [312] found a reduction in $PETCO_2$ with NIVS during exercise. Unlike the Bianchi study, in which a Sanders non rebreathing valve (NRV) was used [312], we used the standard disposable exhalation valve incorporated in the BiPAP tubing system. It is possible that in the absence of a non-rebreathing valve, the patients in our study may have experienced some degree of CO_2 rebreathing while inspiring and expiring through the single circuit used on the BiPAP ventilators. It has been suggested that some exhalation valves may be more effective than others in allowing venting of expiratory gas towards the atmosphere [370]. Whereas the risk of CO_2 rebreathing with the BIPAP system is presumably low when the expiratory time is sufficiently long and /or when sufficient levels of PEEP are used [370], the high ventilatory requirements and reduced time available for expiration, as occurs during exercise, may have promoted an increased

CO_2rebreathing in our study. Additionally, the use of 4 cmH_2O of EPAP may not have been sufficient to enable elimination of the CO_2 that was produced during exercise. The CO_2 rebreathing may ultimately have contributed to greater stimulation of the respiratory centers, resulting in a more rapid increase in dyspnea sensation and earlier exercise termination. In our subjects, the averaged Borg dyspnea ratings during PS10 and PS0 were significantly higher than during exercise without PS at isoload.

Methodological considerations:

As with any study, this project has a number of limitations that must be considered when interpreting the results. Although the estimated sample size for the study was 16 individuals with COPD (*Appendix A4.0*), we decided to end the study based on the negative response observed from the NIVS test compared to the no ventilator test. Since the study's estimated sample size was not reached, the risk of a beta error cannot be excluded between PS0 and PS10.Therefore, the small sample size in our study may have precluded being able to observe an effect of PS10 compared to PS0; thus, we cannot exclude a possible type II error.

Next, the standard disposable exhalation valve incorporated in the BiPAP tubing system to prevent exercise induced CO_2rebreathing, used in this study, could have also contributed to the findings obtained. Despite the device, cycling during assist periods was associated with significantly greater VCO_2, than cycling without assist. This seems to indicate that our subjects may have experienced some degree of CO_2 rebreathing. Therefore, we cannot eliminate the possibility that the decreased exercise capacity with assist may have been caused by CO_2 re-breathing. Also, we cannot dismiss the possibility that the use of another non-rebreathing valve could have resulted in different findings.

One could assume that given that the first bicycle exercise test performed with no assist was not randomized, a potential bias such as a learning effect might have been introduced. We believe that no learning effect occurred, since the results obtained during the ventilator condition were detrimental. In addition, various

studies evaluating the variability in measurements obtained during clinical trial of maximum exercise reported no change in repeated measurements [332-333, 335, 371].

Finally, as only patients with COPD, free of cardiac, neurological and musculoskeletal disorders were included in our study, this sample may not be representative of all COPD patients, since many such patients have comorbidities. In addition, none of the subjects were receiving supplemental O_2, therefore the results of this study cannot be generalized to this subgroup of COPD patients. It is possible that the results of this study could have been altered had patients with more mild disease been recruited.

CONCLUSION

In conclusion, the current study demonstrates that administration of 10 cm H_2O of pressure support delivered using BiPAP (IPAP of 14 cm H_20 and EPAP of 4 cm H_20) with a disposable exhalation port has no effect on maximum exercise capacity in patients with COPD compared to sham PS0. Furthermore, we showed that PS10 decreased maximum exercise capacity, compared to exercise without ventilatory support. This latter finding may be related to a combination of the remaining 4 cm H_2O EPAP support and CO_2 rebreathing occurring with use of the standard disposable exhalation port used with the breathing circuit. Whether incorporating a CO_2 plateau valve can alter the findings remains to be elucidated. Hence, more randomised controlled studies, enrolling larger sample sizes are required to determine the effect of non invasive ventilatory support on maximum exercise in patients with chronic obstructive pulmonary disease.

ACKNOWLEDGMENT: The authors would like to thank V. Rose from the Jewish Rehabilitation Hospital as well as S. Daheb and the pneumology department at Hôpital du Sacré-Cœur de Montréal for their assistance with patient recruitment

and assessment. We thank S. Delisle for kindly providing the BiPAP ventilator. We also thank the patients for their participation in the study.

Conflict of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Author Contributions:

Ana-Maria Moga was responsible for conducting the literature review and writing the document. Dr. Jadranka Spahija provided guidance on the literature review and editing the paper.

Ana-Maria Moga was responsible for coordinating the overall activities of the trial including recruitment, scheduling of the tests, running of the trial, the evaluations, as well as analyzing the data and writing the manuscripts. Michel de Marchie M.D. participated in the clinical supervision during the exercise tests. Dr. Didier Saey provided training and theoretical input for the assessment of muscle strength via magnetic stimulation and reviewed the thesis. Dr. Jadranka Spahija supervised all aspects of the project, providing procedural guidance, assisted during the studies, as well as edited and reviewed the thesis.

Tables and figures:

Table 4 Characteristics of the 10 patients with COPD

Variables	Mean±SD
Anthropometric data	
Sex, male/female	3/7
Age, yr	68.30 ± 6.43
Height, cm	160.50 ± 8.37
Body mass, kg	64.87 ± 10.12
BMI, kg/m^2	25.16 ± 3.40
Physical activity score	14.36
Pulmonary function	
FEV_1, L (% pred)	1.19 ± 0.42 (53.30 ± 21.81)
FVC, L (%pred)	2.70 ± 0.94 (95.70 ± 24.45)
FEV1/FVC, %	45.80 ± 12.99
FRC, L (%pred)	3.96 ± 1.33 (139.1 ± 34.63)
TLC, L (% pred)	5.85 ± 1.53 (122.1 ± 20.43)
RV, L (%pred)	3.04 ± 1.31 (159.3 ± 54.26)
RV/TLC, % pred	50.90± 11.99
PI max, cmH_2O	70.06 ± 19.81
DLCO,mL/mmHg/min (%pred)	10.02 ± 3.91 (47.30±19.32)
SaO_2, %	94.78±2.29

Values are means ± SD. Definitions of abbreviations: BMI = body mass index; FEV_1 = forced expiratory volume in 1^{st} second; FVC = forced vital capacity; FRC = functional residual capacity, RV = residual volume; TLC = total lung capacity; PImax = maximum inspiratory pressure; PEmax = maximum expiratory pressure; D_{LCO} = diffusion capacity of the lung for carbon monoxide, SaO2- arterial oxygen saturation.

Table 5Physiological parameters at rest in 10 patients with COPD

Variables	Without PS	PS0	PS10	P ANOVA
VT, L	0.68±0.12	0.751±0.17	0.89±0.16**‡	< 0.001
RR br/min	16.65±3.86	17.09±3.84	22.44±4.69**‡	< 0.001
VE, L/min	11.22±2.73	12.51±2.83*	19.83±4.10*†	< 0.001
Ti, s	1.49±0.42	1.30±0.32	0.86±0.12**‡	< 0.001
TT, s	3.86±0.89	3.69±0.67	2.82±0.51** ǂ	< 0.001
VT/Ti, L/s	0.51±0.18	0.61±0.21	1.03±0.23**‡	< 0.001
VT/Te, L/s	0.31±0.07	0.33±0.07*	0.49±0.16*†	< 0.001
PIF, cm H_2O	0.74 ± 0.25	0.90±0.35	1.61±0.29 ** ǂ	< 0.001
PEF,cm H_2O	0.55±0.15	0.54±0.16*	0.88±0.33*†	< 0.001
IC, L	1.79±0.52	1.66 ±0.48	1.61±0.53*	0.045
SaO_2, %	95.53±3.38	95.95± 2.56	96.58±2.26	0.100
HR, bpm	72.62±26.70	72.78±27.70	77.98±30.06*†	0.023
VO_2, L/min	237.69±41.46	285.50±126.75	371.73±120.75**†	0.005
VCO_2, L/min	176.10±31.64	228.64± 92.76	313.16±109.66**‡	< 0.001
Dyspnea	0.4±0.10	0.3 ±0.63	0.7±1.36	0.319

Values are means ± SD. VT, tidal volume; RR, respiratory rate; VE, minute ventilation; Ti, inspiratory time; TT, total breath time; VT/Ti, mean inspiratory flow; VT/Te, mean expiratory flow ; PIF, peak inspiratory flow; PEF, peak expiratory flow; IC, inspiratory capacity; SaO_2 arterial oxygen saturation; HR, heart rate; VO_2, oxygen uptake; VCO_2, carbon dioxide output;
For post-hoc contrasts: *p< 0.05, relative to without PS; **p< 0.001, relative to without PS; † p< 0.05, relative to PS0; ǂ p< 0.001, relative to PS0.

Table 6 Physiological parameters at peak exercise in 10 patients with COPD

	Without PS	PS0	PS10	P. ANOVA
WL, Watts	43±19.5	30.5±13.0**	33±16.7**	< 0.001
VT, L	1.04±0.38	1.14±0.37	1.29±0.32**ǂ	< 0.001
RR br/min	30.46±10.39	30.03±9.34	30.10±6.61	0.913
VE L/min	29.13±6.16	32.41±8.17	37.74±8.51**ǂ	< 0.001
Ti, s	0.90±0.33	0.84±0.23	0.79±0.13	0.905
TT, s	2.16±0.62	2.15±0.53	2.08±0.40	0.512
VT/Ti L/s	1.18±0.22	1.37±0.26*	1.61±0.23**ǂ	< 0.001
VT/Te, L/s	0.86±0.25	0.91±0.29	1.04±0.31**†	< 0.001
PIF, cm H_2O	1.75±0.38	2.05±0.30*	2.31±0.25**†	< 0.001
PEF, cm H_2O	1.45±0.34	1.42±0.31*	1.68±0.34*†	0.002
IC, L	1.28±0.57	1.22±0.44	1.23±0.47	0.633
VO_2, mL/min	843±249.0	1396.6±577.1**	1379.9±582.5**	< 0.001
VCO_2,mL/min	689±269.0	1072.1±475.7**	1087.0±490.9**	< 0.001
SaO_2 %	93±2.96	93.3±3.31	93.6±2.2	0.463
HR, bpm	103.33±41.46	97.1±38.84	97.64±39.1	0.146
Dyspnea	7.35±2.1	7.5±1.9	7.15±1.8	0.75
Leg fatigue	5.10±2.8	3.50±1.5	3.40±2.4*	0.035

Values are means ± SD. VT, tidal volume; RR, respiratory rate; VE, minute ventilation; Ti, inspiratory time; TT, total breath time; VT/Te, mean expiratory flow; VT/Ti, mean inspiratory flow; PIF, peak inspiratory flow; PEF, peak expiratory flow; IC, inspiratory capacity; SaO2- arterial oxygen saturation; HR, heart rate; VO_2, oxygen uptake; VCO_2, carbon dioxide output;

For post-hoc contrasts: *p≤0.05, relative to no assist; **p< 0.001, relative to no assist; † p< 0.05, relative to PSV0; ǂ p< 0.001, relative to PSV0.

Table 7 Physiological parameters at isoload in 10 patients with COPD

	Without PS	PS0	PS10	P. ANOVA
VT, L	1.01±0.34	1.14±0.37*	1.29±0.32**ǂ	<0.001
VE L/min	24.00±5.46	31.66±8.01**	36.18±8.15**†	<0.001
RR br/min	26.51±12.15	28.87±7.31	28.83±7.05	0.279
Ti, s	1.07±0.40	0.85±0.22	0.80±0.13	0.273
TT, s	2.63±0.88	2.20±0.49*	2.18±0.44*	0.007
VT/Ti L/s	0.98±0.15	1.35±0.27**	1.61±0.22**†	<0.001
VT/Te, L/s	0.70±0.23	0.88±0.27**	0.99±0.30**†	<0.001
PIF, cm H_2O	1.39±0.23	2.01±0.35**	2.25±0.21**	<0.001
PEF,cm H_2O	1.14±0.28	1.37±0.29*	1.58±0.33**†	<0.001
IC, L	1.42± 0.59	1.24±0.41	1.25±0.46	0.06
VO_2,mL/mi	679.0±166.1	1392.3±575.3**	1318.7±562.6**	<0.001
VCO_2,mL/mi	548.3±212.5	1065.2±473.2**	1030.4±481.9**	<0.001
SaO_2 %	94.6±3.5	93.6±3.4	94.0±2.4	0.252
HR, bpm	92.9±36.6	96.6±38.9	110.9±24.9	0.285
Dyspnea	3.65±2.03	6.85±2.63*	6.05±2.36*	0.003
Leg fatigue	2.45±1.71	3.3±1.57	2.65±1.89	0.339

Values are means ± SD. VT, tidal volume; RR, respiratory rate; VE, minute ventilation; Ti, inspiratory time; TT, total breath time; VT/Te, mean expiratory flow; VT/Ti, mean inspiratory flow; PIF, peak inspiratory flow; PEF, peak expiratory flow; IC, inspiratory capacity; SaO2- arterial oxygen saturation; HR, heart rate; VO_2, oxygen uptake; VCO_2, carbon dioxide output;
For post-hoc contrasts: *p< 0.05, relative to no assist; **p< 0.001, relative to no assist; † p< 0.05, relative to PSV0; ǂ p< 0.001, relative to PSV0.

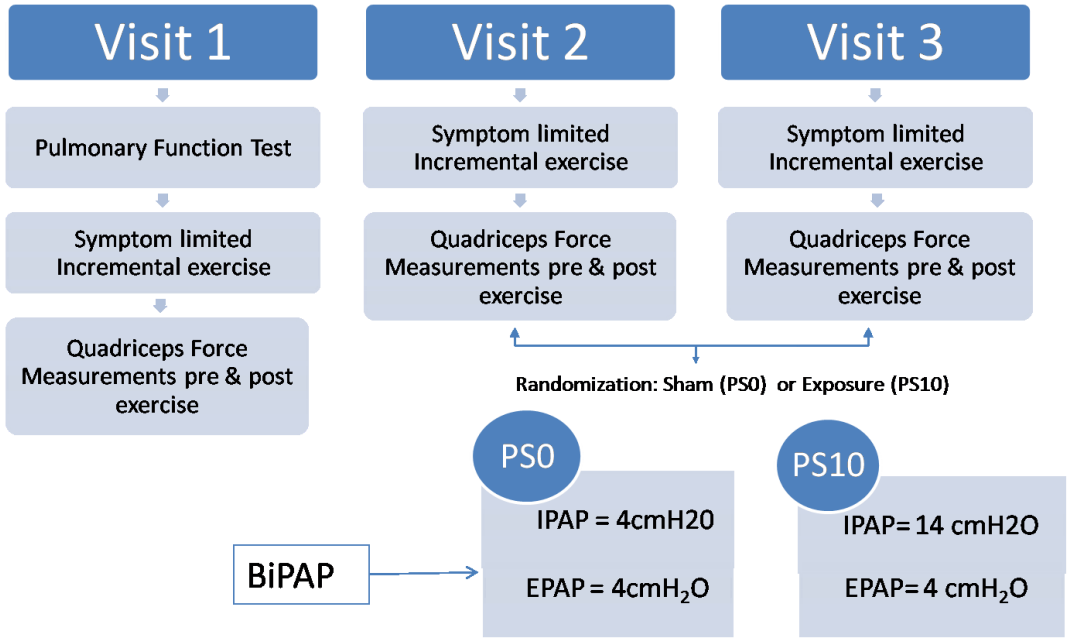


Figure 7 Schematic representation of the experimental protocol

Inspiratory pressure support PS of 0 cmH2O and PS 10 cmH2O were administrated in a random order. Measurement of quadriceps strength includes femoral nerve magnetic stimulation.

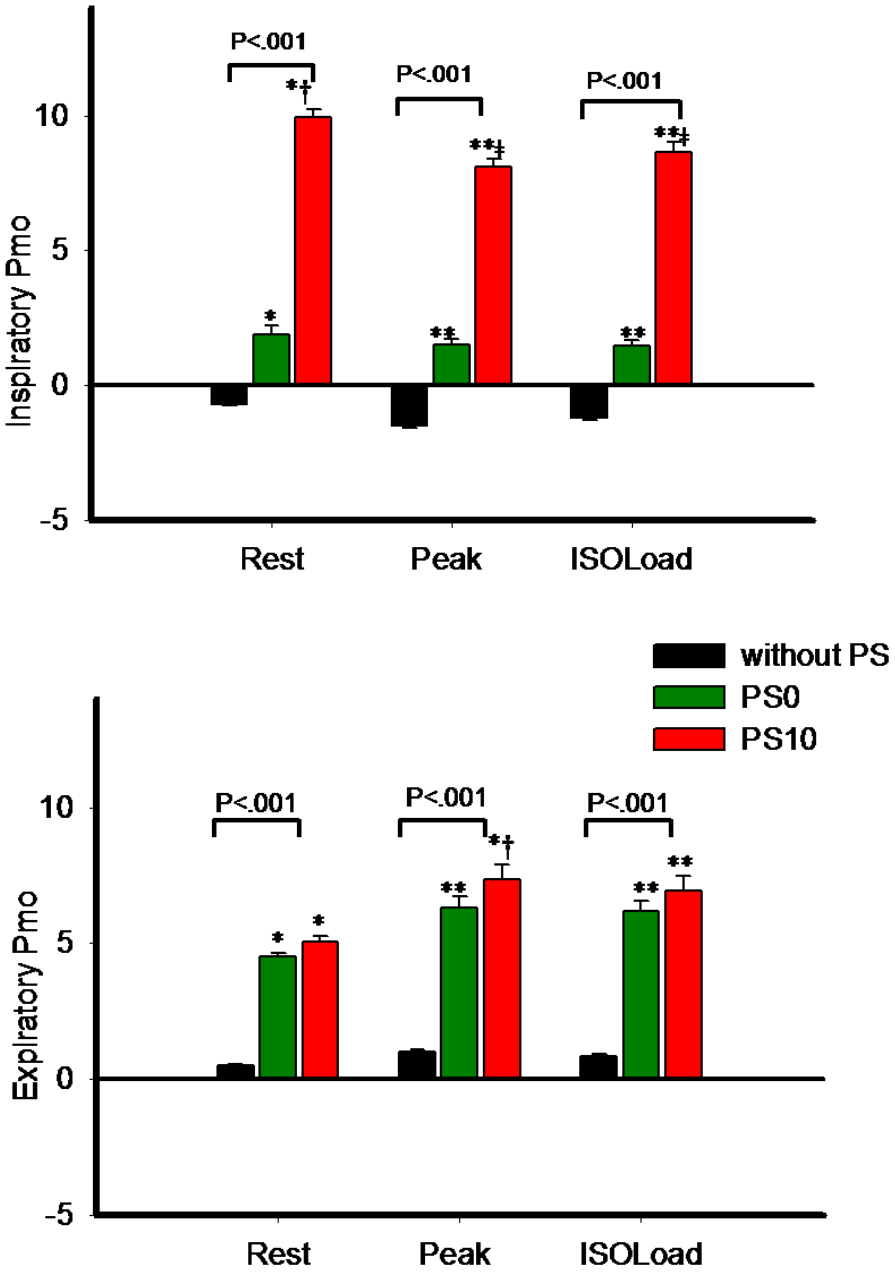


Figure 8 Mean inspiratory and expiratory mouth pressure at rest, peak exercise and isoload.

Plots are average values ±SE obtained in the 10 patients.

ANOVA was P<0.001 when comparison was performed among PS0, PS10 and without PS. For post-hoc contrasts: *p< 0.05, relative to without PS; **p< 0.001, relative to without PS; † p< 0.05, relative to PS0; ǂ p< 0.001, relative to PS0.

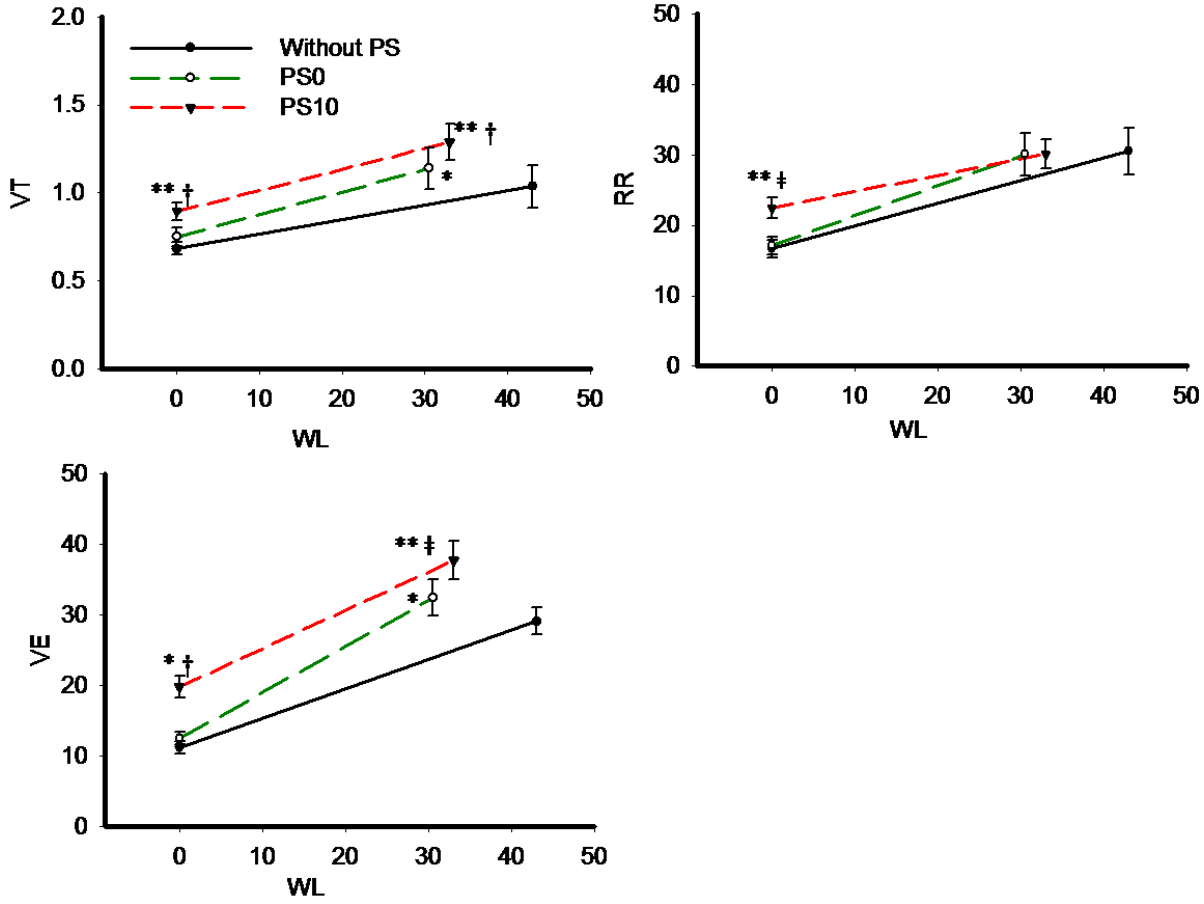


Figure 9 Change in tidal volume, respiratory rate, minute ventilation from rest to peak exercise without PS, with PS0 and PS10.

Graphs are means ± SE at rest, and peak exercise. For post-hoc contrasts: *p< 0.05, relative to without PS; **p< 0.001, relative to without PS; † p< 0.05, relative to PS0; ǂ p< 0.001, relative to PS0

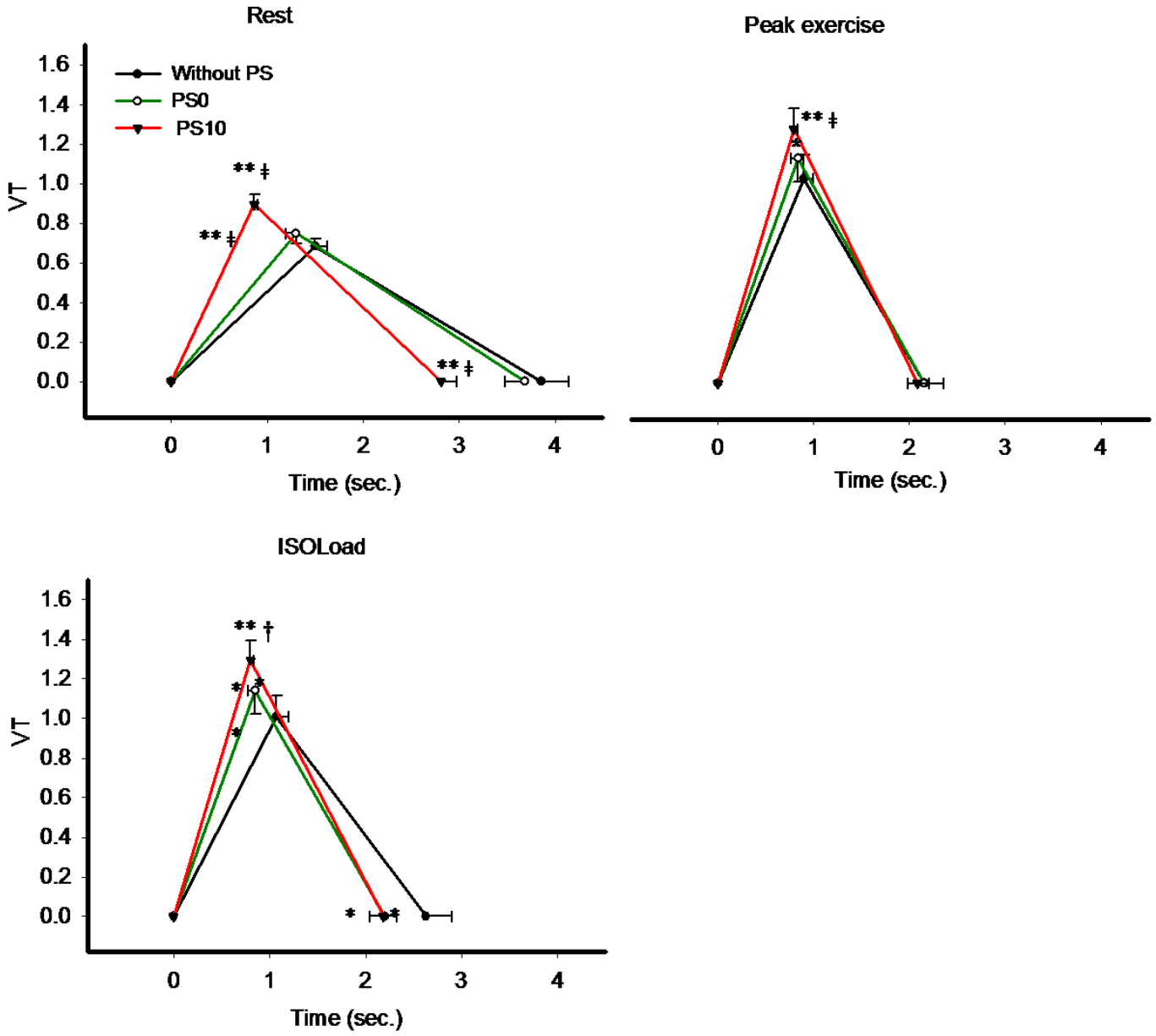


Figure 10Spirograms depicting the breathing pattern at rest, peak exercise and isoload while breathing without PS, with PS0 and with PS10.

For post-hoc contrasts: *p< 0.05, relative to without PS; **p< 0.001, relative to without PS; † p< 0.05, relative to PS0; ǂ p< 0.001, relative to PS.

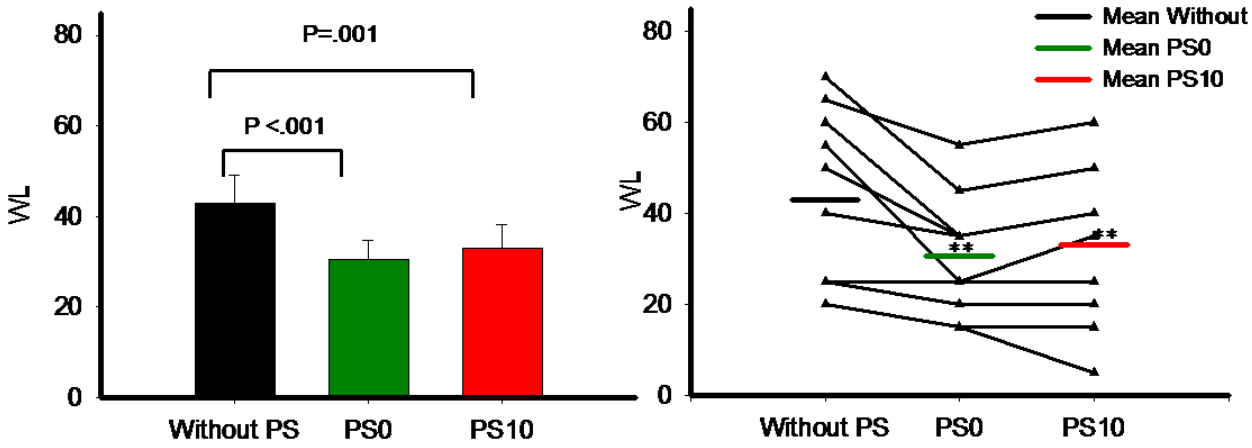


Figure 11 Maximum exercise capacity reached during the three experimental conditions. Group mean values of maximum workload reached during symptom-limited incremental bicycle exercise without PS (black bar), with PS0 (green bar) and with PS10 (red bar) are presented in the left panel. Individual values are shown in the right panel. For post-hoc contrasts: **p< 0.001, relative to without PS.

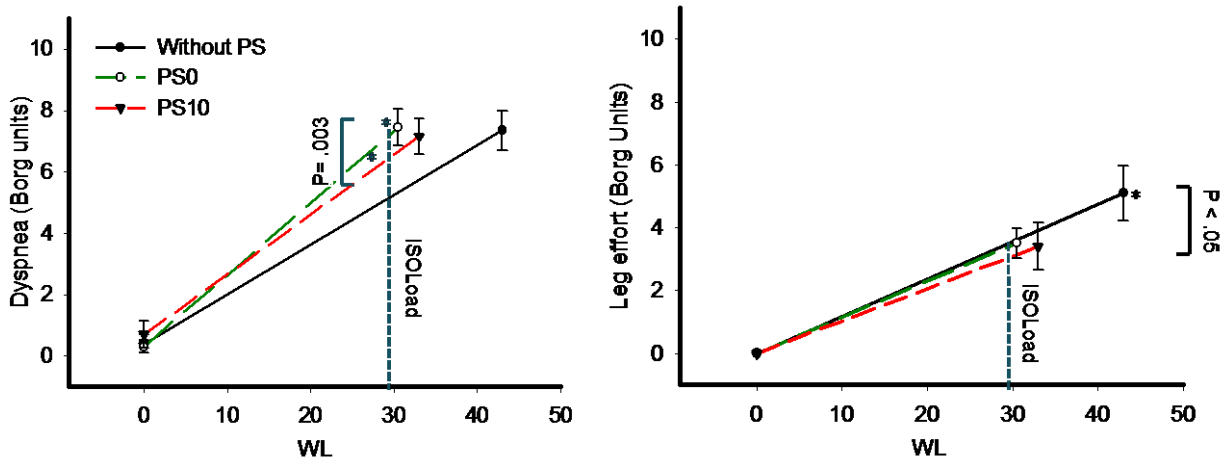


Figure 12 Dyspnea and leg fatigue Borg scores in ten COPD patients.

Comparisons were made within the three conditions at rest, isotime, and at peak exercise. *p< 0.05, relative to without PS;

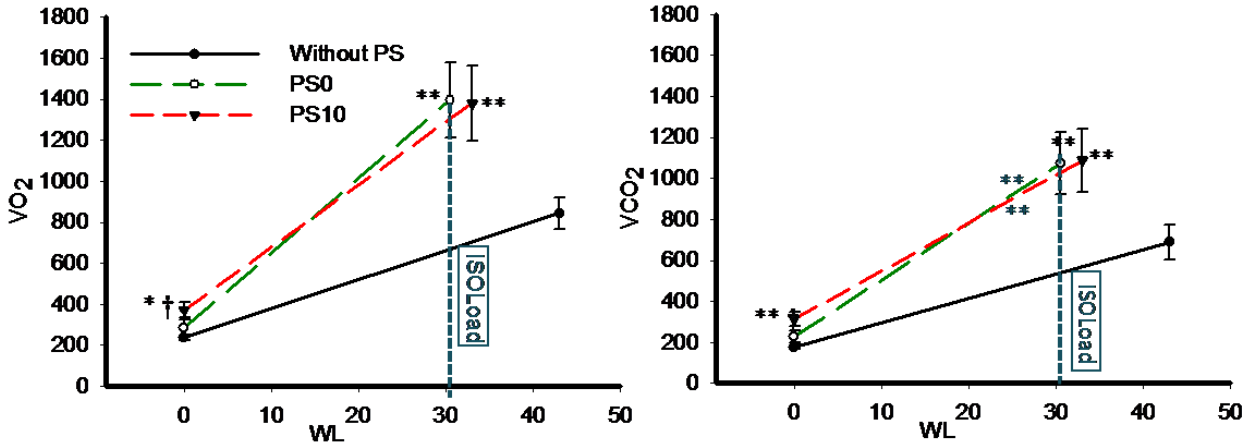


Figure 13 Metabolic parameters comparison at rest, peak exercise and isoload between the three experimental conditions of breathing without PS, with PS0 and with PS10.

Plots are average values ±SE obtained in the 10 patients. For post-hoc contrasts: *p< 0.05, relative to without PS; **p< 0.001, relative to without PS; † p< 0.05, relative to PS0.

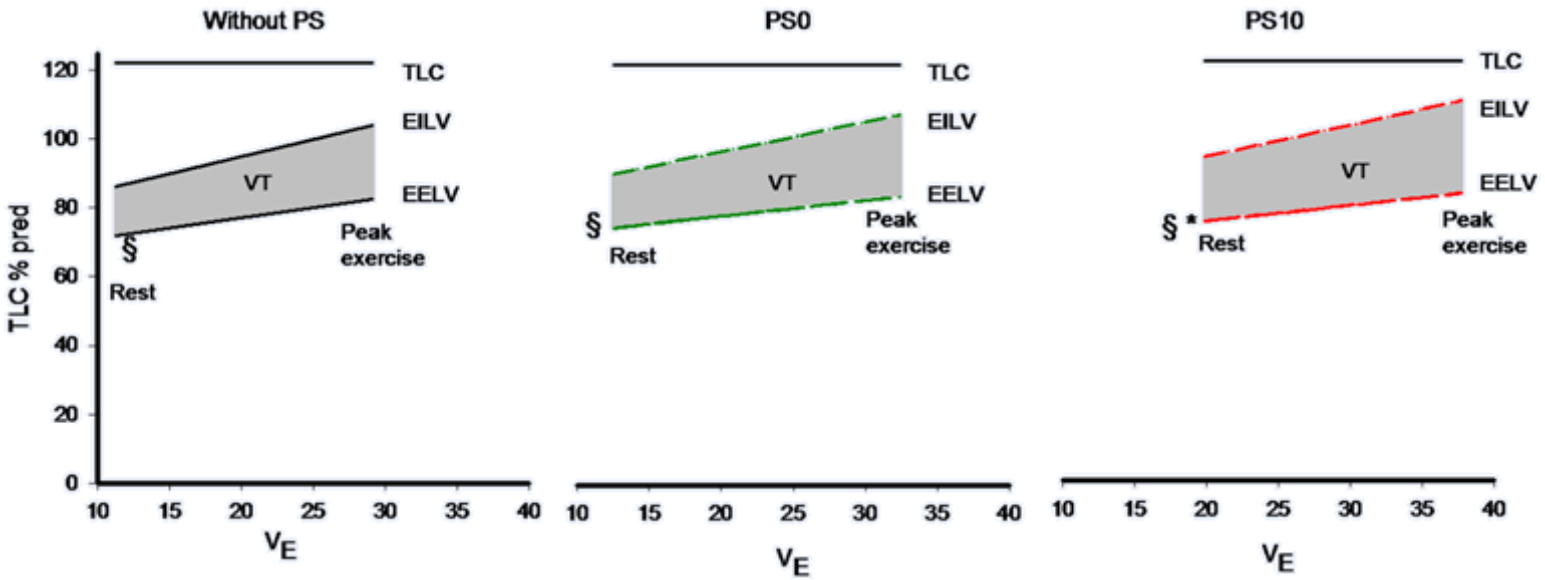


Figure 14 Changes in operational lung volumes from rest to peak exercise are shown as ventilation increases with exercise without PS, with PS0 and with PS10.

ANOVA between the three conditions: § $p < 0.05$,

For post-hoc contrasts: *$p< 0.05$, relative to without PS;

CHAPTER VI

CONCLUSION

Chronic obstructive pulmonary disease is a progressive disease that can significantly affect an individual's exercise capacity and their quality of life. Exercise, which can improve one's ability to perform physical activity, can be useful in preventing disability, reducing functional decline [372] and in turn improving quality of life [223]. Some individuals with COPD are unable to obtain such benefits because of their inability to exercise at a high enough exercise-intensity. Non-invasive ventilatory support has been used as an adjunct during exercise to help improve exercise capacity in such individuals. Although non-invasive ventilatory support has been promulgated by some studies as an effective adjunct to exercise endurance in individuals with COPD, its effect on maximum exercise capacity has as yet not been evaluated. Relevant literature was reviewed (Chapter II) and a case was made for the use of NIVS to change exercise capacity in COPD. The study presented in this thesis has contributed to the body of knowledge in this area, by addressing the objective of evaluating the acute effect of non-invasive ventilatory support on exercise capacity among individuals with COPD.

A cross-over study design was employed and ten subjects participated in the study. Results indicated that: 1) although there was a trend towards a higher WL_{max} with PS10 when compared to PS0, this difference has not reach significance; 2) maximum exercise capacity was lower in 80 % of the COPD patients and unaltered in remaining 20% with PS10, compared to PS0. This decrease in WL_{max} could be attributed to an increase CO_2 rebreathing. Although our breathing circuit incorporated a disposable exhalation port, it was probably not efficient enough to eliminate the exhaled gas from the circuit during exercise. Additionally, the 4 cmH_2O of EPAP that was used in our study may not have been sufficient to eliminate the amount of CO_2 that was produced during exercise. It would be

interesting to note if similar results are obtained if higher EPAP levels are administrated and a non-rebreathing CO_2 valve is incorporate in the breathing circuit. This work also identified that BiPAP has no effect on operational lung volumes during exercise.

In conclusion, the study reported in the preceding chapter has provided a distinct contribution to the advancement of knowledge with regards to the acute effect of non-invasive ventilatory support on maximum exercise capacity in COPD. Such work has promoted new understanding of the BiPAP effect on exercise capacity in individuals with moderate-to-severe COPD and the incidence of CO_2 rebreathing when such a ventilator is used.

APPENDICES

A 1.0 Literature review for acute effect of NIVS during exercise in COPD

Table Studies evaluating the acute effect of NIVS as an adjunct to exercise

Author	Sample size	Severity Age	Design	Level of assist (cmH_2O)	Exercise Apparatus intensity	Outcome	Author's conclusion
O'Donnell (1988)	6 (1♀)	67.2±8.5 severe	CPAP vs. air	CPAP range 4-5	Bicycle 50% VO_{2peak}	T_{LIM} Dyspnea	CPAP significant increase in T_{LIM} by 48% and dyspnea scores decreased at isotime.
O'Donnell (1988)	5 COPD and 5 healthy	59.8 1.21 39.6 Moderate to severe	CPAP vs. CPIP vs. CPEP.	1. CPAP= 4 -5 2. CPIP=4-5 CPEP=4-5 The magnitude and duration (40-60 s) in a given subject was similar for all 3 modes. Procedure:	Bicycle 40% Wmax	respiratory sensation(category scale +5 hard to -5 easy) breathing pattern Borg	In COPD, CPAP significant reduction in sense of breathing effort ($p < 0.05$) principally through its effect of unloading the inspiratory muscles, as well the CPIP $p<0.05$. Where CPEP results were inconsistent and insignificant. No significant change in breathing patterns HR or IC during CPAP, CPIP and CPEP. In healthy, CPAP increased the respiratory sensation ($P<0.01$) and V_T by 17% ($p<0.01$); CPIP significantly

Author	Sample size	Severity Age	Design	Level of assist (cmH_2O)	Exercise Apparatus intensity	Outcome	Author's conclusion
				1.control-CPAP 2.CPIP-control- CPEP			facilitated breathing effort ($p<0.01$). CPEP increased the sense of breathing effort ($p<0.005$). Similarly, there was no sign difference (at the $p<0.01$) in any of the ventilatory parameter during CPIP and CPEP in normal group
Petrof (1990)	8	NP 25±3	CPAP	CPAP 7.5-10	Bicycle	Rrespiratory muscle EMG Dyspnea TLim	-CPAP reduced inspiratory muscle effort, as indicated by the pressure-time integral of transdiaphragmatic ($P<00.01$) and esophageal pressure ($P<00.05$). In contrast, the pressure-time integral of gastric pressure, used as an index of abdominal muscle recruitment during expiration, increased ($P<0.01$). - CPAP improved dyspnea in 5 of the 8 patients. This was directly related to reductions in integral of Pes.dt ($P<0.01$) but inversely related to increases in integral of Pga.dt ($P<0.01$).
Keilty(1994)	8	0.73±0.2 NP 68±6	PSV vs. CPAP vs. O_2	(fltrigger=0.5 IPS =12-15	Treadmill comfortable	T_{LIM} Dyspnea	PSV significantly increased walking distance ($p=0.01$) by 62% (90m, range 14-533m) and a decrease in dyspnea,

Author	Sample size	Severity Age	Design	Level of assist (cmH_2O)	Exercise Apparatus intensity	Outcome	Author's conclusion
		severe (hypoxic at rest)	Sham	CPAP= 6 O_2 2L/min via Sham- air2l/min from a cylinder	speed		when compared with control walking. Also, SaO_2 improved by 3% » (1-9%). Neither CPAP (6 cmH_2O) nor O_2 (2L/min) significantly increase the exercise capacity.
Maltais (1995)	7	0.75±0.10 NP 53±5 Severe	PSV vs. spontaneous breathing	(trigger= -1) IPS=11±SE 1 applied for 3-4 min., preceded and followed by control periods of similar durations.	Bicycle ~50% W_{max}	Feasibility, Breathing pattern, inspiratory effort, dyspnea	PSV was well tolerate during ex in severe CAO. PSV » Significantly decreased TI and inspiratory effort and dyspnea while V_E , V_T/T_I and V_T/T_E increased ($p<0.05$). Significant decrease in pressure–time integral for the inspiratory muscle ($p < 0.0005$) and the diaphragm ($p<0.0005$).
Dolmage (1997)	10 3♀	NP 29±7 59±6 Moderate-severe	PAV vs. CPAP vs. CPAP+PAV	CPAP 5±2 PAV: VA : 6±3 FA : 3±1 (comfortable	Bicycle 60-70% W_{max}	T_{LIM} Dyspnea	- CPAP+PAV increased significantly T_{LIM} by 9 to 272% (from 0.32-19.90 min) No difference in dyspnea between sessions.

Author	Sample size	Severity Age	Design	Level of assist (cmH_2O)	Exercise Apparatus intensity	Outcome	Author's conclusion
				level) CPAP + PAV Sham: CPAP 0 PAV 0			
Bianchi (1998)	15 1♀	NP 32±10 64±8 Severe hypercapnic	PAV vs. CPAP vs. PSV.vs. Sham	PAV: VA : 8.6±3.6 FA: 3±1.3 (run - away method). EPAP~ 1 add to PAV. CPAP=6 PSV comfort level IPAP=12-16 EPAP=1 Sham:CPAP 1	Bicycle 80% W_{max}	T_{LIM} Dyspnea Leg fatigue	- in comparison with sham, PAV, PSV, and CPAP significantly increased T_{LIM} (from 7.2 ±4.4 to 12.2 ±5.6, 10±5.2, and 9.6 ±4. min respectively) and reduced dyspnea (at isotime)(from 6.5±1.5 to 4.2 ±1.9, 4.4±1.4, and 5.3±1.9). The greatest improvement was observed with PAV. At isotime, in comparison with sham, PAV and PSV, significant decrease leg fatigue.
Polkey (2000)	8	severe	PSV vs. Spbrt.		Treadmill	Plasma lactate levels	PSV prologues the time to exercise-induce lactataemia.

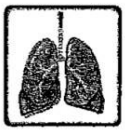
Author	Sample size	Severity Age	Design	Level of assist (cmH_2O)	Exercise Apparatus intensity	Outcome	Author's conclusion
							This technique may prove to be a useful adjunct in pulmonary rehabilitation.
Hernandez (2001)	8 1♀ 24.9±6.6 62.8±6.9 Severe	0.70±0.21	PAV vs. Sham	(fl trigger= -0.5) PAV: VA : 9.8±2.1 FA : 3.3±1.0 "run-away" method Control: CPAP1-2	Bicycle 80%VO_{2max}	T_{LIM} Dyspnea	Compared with control (323±245s) , PAV showed a significant increase in T_{LIM} (507±334s) (p=0.02) associated with improvements in dyspnea, breathing pattern and arterial blood gases.
Van'tHul (2004)	45 12♀ 39±13 67±7 Moderate-severe	1.06±0.39	PSV_5vs. PSV_{10} vs. no PSV(sham	(fl trigger= 3 $Lmin^{-1}$) PSV_5=5 PSV_{10} =10	Bicycle 75% W_{max}	T_{LIM}	Significant increase in T_{LIM} for PSV_{10} compared with no PSV(6.3±6.7 vs 4.2±2.6, p<0.01), and with PSV_5 (6.3±6.7 vs 4.4±2.9, p<0.01). But, the results varied. PImax correlated high with T_{LIM} PSV10.
Dreher	20	1.06±0.39	NPPV +	NPPV set to	6 MWT	Feasibility	NPPV+supp O_2 significantly decreased

Author	Sample size	Severity Age	Design	Level of assist (cmH_2O)	Exercise Apparatus intensity	Outcome	Author's conclusion
(2007)	8♀	27±7.5 65.1±8.7Severe CRF receiving NPPV for HMV	supp O_2 vs. Supp O_2 (pressure-limited assist/control mode)	maximally decrease elevated $PaCO_2$ supp O_2 2.1±0.9 I: 2.9± 0.44 E:0.4±0.1kPa RR 20±2 b/min	with a rollator	of NPPV during walking Walking distance Dyspnea Arterial blood oxygen level	dyspnea from 6 to 4 and walking distance significantly increased from 209 to 252m. NPPV+supp O_2 improves oxygenation, preventing hypoxia-induced complications. Walking only with Supp O_2 significantly decreases arterial O_2 tension. NPPV+supp O_2 feasible for palliative care.
Borghi-	16	NP	PAV vs.	PAV	Bicycle	Locomotor muscle	**PAV** resulted significant increase in T_{LIM} (p=0.01). Significant increase in VO_2,

Author	Sample size	Severity Age	Design	Level of assist (cmH_2O)	Exercise Apparatus intensity	Outcome	Author's conclusion
Silva (2008)		60 NP Moderate - severe	Sham	VA : 5.8±0.9 FA : 3.5±0.8 ("run-away " method) Sham-5 PSV& 2 PEEP	70-80% W_{max}	oxygenation Systemic O_2delivery to peripheral muscle. T_{LIM}	V_E, and decrease in dyspnea and leg fatigue at isotime and Tlim. PAV reduced significantly the blood lactate at Tlim. Using PAV during exercise can improve leg muscles oxygenation, $\Delta[O_2Hb]$ and TOI and local blood volume $\Delta[Hb_{tot}]$. These findings were not related to an increase in systemic O2 delivery to working muscle. These data might indicate that a fraction of available CO was redirected from ventilatory to peripheral muscle as a consequence of respiratory muscle unloading.

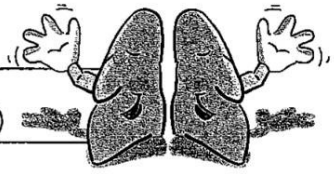
A 2.0 Modified Borg Scale

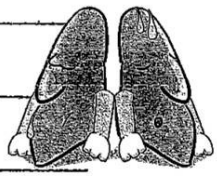
Échelle de Borg

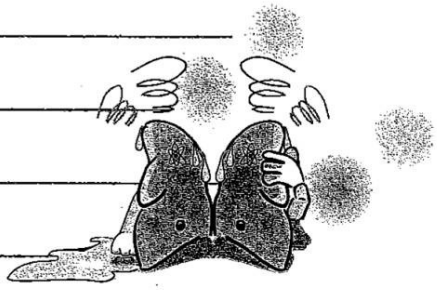


(Perception de l'essoufflement)

0	Rien du tout
0.5	Très très léger (à peine perceptible)
1	Très léger
2	Léger
3	Modéré
4	Un peu sévère
5	Sévère
6	
7	Trés sévère
8	
9	Extrêmement sévère
10	Maximal







A 3.0 A Physical Activity Questionnaire

HOUSEHOLD ACTIVITIES

1) Do you do the light household work? (dusting, washing dishes, repairing clothes, etc.)?

0. Never (<once a month) 0

1, Sometimes (only when partner or help is not available)

2. Mostly (sometimes assisted by partner or help)

3. Always (alone or together with partner)

2) Do you do the heavy housework? (washing floors and windows, carrying trash disposal bags, etc.)?

0. Never (<once a month) 0

1. Sometimes (only when partner or help is not available)

2. Mostly (sometimes assisted by partner or help)

3. Always (alone or together with partner)

3) For how many persons do you keep house? (including yourself; fill in "0' if you answered "never" in 01 and 02.) 0

4) How many rooms do you keep clean, including kitchen, bedroom, garage, cellar, bathroom, ceiling, etc.? (fill in "0" if you answered "never" in 01 and Q2.)

0. Never do housekeeping 0

1. 1—6 rooms

2. 7—9 rooms

3. 10 or more rooms

5) If any rooms, on how many floors? (fill in "0" if you answered Never in Q4.) 0

6) Do you prepare warm meals yourself, or do you assist in preparing?

0. Never 0

1. Sometimes (once or twice a week)

2. Mostly (3—5 times a week)

3. Always (more than 5 times a week)

7) How many flights of stairs do you walk up per day? (one flight of stairs is 10 steps.)

0. I never walk stairs 0

1. 1—5

2. 6—10

3. More than 10

8) If you go somewhere in your hometown, what kind of transportation do you use?

0. I never go out 0

1. Car

2. Public transportation

3. Bicycle

4. Walking

9) How often do you go out for shopping?

0. Never or less than once a week 0

1. Once a week

2. Twice to four times a week

3. Every day

10) If you go out for shopping, what kind of transportation do you use?

0. I never go out for shopping 0

1. Car

2. Public transportation

3. Bicycle

4. Walking

Household score = (01 + 02 + ... + 010)/10

SPORT ACTIVITIES

Do you play a sport?

Sport 1: name_____

Intensity (code) ……. …(1a)

Hours per week (code)……(1b)

Period of the year (code)……(1c)

Sport 2: name_____

Intensity (code) ……..(2a)

Hours per week (code)…….. .(2b)

Period of the year (code)…….(2c)

Sport-score: Σ(ia * ib * Ic)

LEISURE TIME ACTIVITIES

Do you have other physical active activities?

Activity 1: name_____

Intensity (code)…… (1a)

Hours per week (code)……...(1b)

Period of the year (code)……(1c)

Activity 2 till 6: as activity 1.

Leisure time activity score: Σ (ja*jb*jc)

QUESTIONNAIRE SCORE =Household score + Sport score + Leisure time activity score.

Codes:

Intensity code1[1]:

0: lying, unloaded	code 0.028
1: sitting, unloaded	code 0.146
2: sitting, movements hand or arm	code 0.297
3: sitting, body movements	code 0.703
4: standing, unloaded	code 0.174
5: standing, movements hand or arm	code 0.307
6: standing, body movements, walking	code 0.890
7: walking, movements arm or hands	code 1.368

8: walking, body movements, cycling, swimming code 1.890

Hours per week:

1. less than 1 hr.wk^{-1} code 0.5

2. [1,2> h.wk^{-1} code 1.5

3. (23> h.wk^{-1} code 2.5

4. [3,4> h. wk^{-1} code 3.5

5. [4,5> h . wk^{-1} code 4.5

6. [5,6> h. wk^{-1} code 5.5

7. [6,7> h . wk^{-1} code 6.5

8. [7,8> h . wk1^{-1} code 7.5

9. more than 8 h . wk^{-1} code 8.5

Months a year:

1: less than 1 month. yr^{-1} code 0.04

2: 1—3 months code 0.17

3:4—6 months code 0.42

4:7—9 months code 0.67

5: more than 9 months. yr^{-1} code 0.92

[1]Unitless intensity code, originally based on energy costs.

A 4.0 Sample size calculation

Sample size:

The study sample size was calculated based on the primary outcome. First, the standard deviation (SD) of WLmax from the linear relationship of VO_2 to workload [373]. Taking 20% from the highest WLmax value i.e., 66 we obtain a SD of 13.2. Then, the effect size value for WLmax was computed based on data from a study that found that the use of bronchodilators during exercise increased maximum exercise capacity by 8 Watts in COPD individuals [374]; Thus to detect a mean difference of 10W (1 level Work rate), with a power of 0.80, alpha of 0.05, and assuming a SD of 13.2, 16 individuals would need to be studied to give a probability of 0.808 of rejecting the null hypothesis.

REFERENCES:

1. Pauwels, R.A., et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary.* Am J Respir Crit Care Med, 2001. **163**(5): p. 1256-76.
2. Mathers C, L.D., *Projections of Global Mortality and Burden of Disease from 2002 to 2030.* PLoS Med, 2006. **3** (11).
3. Mannino, D.M. and A.S. Buist, *Global burden of COPD: risk factors, prevalence, and future trends.* Lancet, 2007. **370**(9589): p. 765-73.
4. Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management and Prevention of COPD*. 2009 [cited 2010 January 16]; http://www.goldcopd.org.
5. O'Donnell, D.E., et al., *Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms.* Am J Respir Crit Care Med, 1997. **155**(1): p. 109-15.
6. Gallagher, C.G., *Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease.* Clin Chest Med, 1994. **15**(2): p. 305-26.
7. O'Donnell, D.E., *Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease.* Proc Am Thorac Soc, 2006. **3**(2): p. 180-4.
8. O'Donnell, D.E., et al., *Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable.* Proc Am Thorac Soc, 2007. **4**(2): p. 145-68.
9. Whittom, F., et al., *Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease.* Med Sci Sports Exerc, 1998. **30**(10): p. 1467-74.
10. Pitta, F., et al., *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. Marquis, K., et al., *Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2002. **166**(6): p. 809-13.
12. Swallow, E.B., et al., *Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease.* Thorax, 2007. **62**(2): p. 115-20.
13. Yohannes, A.M., R.C. Baldwin, and M. Connolly, *Mortality predictors in disabling chronic obstructive pulmonary disease in old age.* Age Ageing, 2002. **31**(2): p. 137-40.
14. Troosters, T., et al., *Pulmonary rehabilitation in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2005. **172**(1): p. 19-38.
15. Lacasse, Y., et al., *Pulmonary rehabilitation for chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2006(4): p. CD003793.
16. Bernard, S., et al., *Aerobic and strength training in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1999. **159**(3): p. 896-901.
17. Ries, A.L., et al., *Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines.* Chest, 2007. **131**(5 Suppl): p. 4S-42S.

18. Casaburi, R., et al., *Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease.* Am Rev Respir Dis, 1991. **143**(1): p. 9-18.
19. O'Donnell, D.E., R. Sanii, and M. Younes, *Improvement in exercise endurance in patients with chronic airflow limitation using continuous positive airway pressure.* Am Rev Respir Dis, 1988. **138**(6): p. 1510-4.
20. Nici, L., et al., *American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation.* Am J Respir Crit Care Med, 2006. **173**(12): p. 1390-413.
21. Ambrosino, N. and S. Strambi, *New strategies to improve exercise tolerance in chronic obstructive pulmonary disease.* Eur Respir J, 2004. **24**(2): p. 313-22.
22. Saetta, M., R. Finkelstein, and M.G. Cosio, *Morphological and cellular basis for airflow limitation in smokers.* Eur Respir J, 1994. **7**(8): p. 1505-15.
23. Becklake, M.R., *Occupational exposures: evidence for a causal association with chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1989. **140**(3 Pt 2): p. S85-91.
24. Larson, R.K., et al., *Genetic and environmental determinants of chronic obstructive pulmonary disease.* Ann Intern Med, 1970. **72**(5): p. 627-32.
25. Sandford, A.J. and P.D. Pare, *Genetic risk factors for chronic obstructive pulmonary disease.* Clin Chest Med, 2000. **21**(4): p. 633-43.
26. Turato, G., R. Zuin, and M. Saetta, *Pathogenesis and pathology of COPD.* Respiration, 2001. **68**(2): p. 117-28.
27. US Department of Health, E.a.W., *The health consequences of smoking: Chronic Obstructive Pulmonary Disease*, P.H.S. US Department of Health and Human Services, Office on Smoking,, Editor. 1984, DHHS (PHS) 84-50205: Rockville.
28. Shapiro, S.D. and E.P. Ingenito, *The pathogenesis of chronic obstructive pulmonary disease: advances in the past 100 years.* Am J Respir Cell Mol Biol, 2005. **32**(5): p. 367-72.
29. Petty, T.L., *COPD in perspective.* Chest, 2002. **121**(5 Suppl): p. 116S-120S.
30. Friedlander, A.L., et al., *Phenotypes of chronic obstructive pulmonary disease.* COPD, 2007. **4**(4): p. 355-84.
31. Dourado, V.Z., et al., *Systemic manifestations in chronic obstructive pulmonary disease.* J Bras Pneumol, 2006. **32**(2): p. 161-71.
32. Fabbri, L.M. and K.F. Rabe, *From COPD to chronic systemic inflammatory syndrome?* Lancet, 2007. **370**(9589): p. 797-9.
33. Lopez, A.D., et al., *Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data.* Lancet, 2006. **367**(9524): p. 1747-57.
34. Xu, F., et al., *Prevalence of physician-diagnosed COPD and its association with smoking among urban and rural residents in regional mainland China.* Chest, 2005. **128**(4): p. 2818-23.
35. Menezes, A.M., et al., *Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study.* Lancet, 2005. **366**(9500): p. 1875-81.
36. The Lung Association, *Leger Marketing Research – consumer poll.* 2008
37. *Undiagnosed COPD patients were identified according to standardized disease predictors endorsed by Canadian physicians and the Lung Association known as*

the Lung Health Test. Available at http://www.lung.ca/diseases-maladies/copd-mpoc/breathworks-actionair/test.html 2007.
38. Murray, C.J. and A.D. Lopez, *Evidence-based health policy--lessons from the Global Burden of Disease Study.* Science, 1996. **274**(5288): p. 740-3.
39. Calverley, P.M. and P. Walker, *Chronic obstructive pulmonary disease.* Lancet, 2003. **362**(9389): p. 1053-61.
40. Macnee, W., *Pathogenesis of chronic obstructive pulmonary disease.* Clin Chest Med, 2007. **28**(3): p. 479-513, v.
41. MacNee, W., *Pathogenesis of chronic obstructive pulmonary disease.* Proc Am Thorac Soc, 2005. **2**(4): p. 258-66; discussion 290-1.
42. Groneberg, D.A. and K.F. Chung, *Models of chronic obstructive pulmonary disease.* Respir Res, 2004. **5**: p. 18.
43. Hogg, J.C., et al., *The nature of small-airway obstruction in chronic obstructive pulmonary disease.* N Engl J Med, 2004. **350**(26): p. 2645-53.
44. Snider, G.L., *The definition of emphysema. Report of a National Heart, Lung, and Blood Institute, Division of Lung Diseases workshop.* Am Rev Respir Dis, 1985. **132**(1): p. 182-5.
45. Barnes, P.J., *New concepts in chronic obstructive pulmonary disease.* Annu Rev Med, 2003. **54**: p. 113-29.
46. Rennard, S.I., *Chronic obstructive pulmonary disease: linking outcomes and pathobiology of disease modification.* Proc Am Thorac Soc, 2006. **3**(3): p. 276-80.
47. Kasper, D., ed. 16 ed. Harrison's Princiles of Internal Medicine. 2006, McGraw-Hill Companies,.
48. Carlson, D.J., A.L. Ries, and R.M. Kaplan, *Prediction of maximum exercise tolerance in patients with COPD.* Chest, 1991. **100**(2): p. 307-11.
49. Gilbert, R., J. Keighley, and J.H. Auchincloss, Jr., *Disability in Patients with Obstructive Pulmonary Disease.* Am Rev Respir Dis, 1964. **90**: p. 383-94.
50. Jones, N.L., G. Jones, and R.H. Edwards, *Exercise tolerance in chronic airway obstruction.* Am Rev Respir Dis, 1971. **103**(4): p. 477-91.
51. Pellegrino, R. and V. Brusasco, *On the causes of lung hyperinflation during bronchoconstriction.* Eur Respir J, 1997. **10**(2): p. 468-75.
52. Fishman, A.P., *Fishman's pulmonary diseases and disorders*. 1998, New York: McGraw-Hill, Health Professions Division.
53. Saetta, M., et al., *Structural aspects of airway inflammation in COPD.* Monaldi Arch Chest Dis, 1994. **49**(3 Suppl 1): p. 43-5.
54. Aliverti, A., et al., *Respiratory muscle dynamics and control during exercise with externally imposed expiratory flow limitation.* J Appl Physiol, 2002. **92**(5): p. 1953-63.
55. O'Donnell, D.E., S.M. Revill, and K.A. Webb, *Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2001. **164**(5): p. 770-7.
56. Pride, N.B. and P.T. Macklem, *Lung mechanics in disease*, in *Handbook of Physiology, Section 3: The respiratory system*, P.T. Macklem and J. Mead, Editors. 1986, Bethesda: American Physiological Society. p. 659-692 .
57. Leith, D.E. and R. Brown, *Human lung volumes and the mechanisms that set them.* Eur Respir J 1999. **13**(2): p. 468-472.

58. Belman, M.J., *Exercise in patients with chronic obstructive pulmonary disease.* Thorax, 1993. **48**(9): p. 936-46.
59. Gibson, G.J., *Pulmonary hyperinflation a clinical overview.* Eur Respir J, 1996. **9**(12): p. 2640-9.
60. Ferguson, G.T., *Why does the lung hyperinflate?* Proc Am Thorac Soc, 2006. **3**(2): p. 176-9.
61. Milic-Emili, J., *Inspiratory capacity and exercise tolerance in chronic obstructive pulmonary disease.* Can Respir J, 2000. **7**(3): p. 282-5.
62. Cooper, C.B., *The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function.* Am J Med, 2006. **119**(10 Suppl 1): p. 21-31.
63. Larson, J.L., M.K. Covey, and S. Corbridge, *Inspiratory muscle strength in chronic obstructive pulmonary disease.* AACN Clin Issues, 2002. **13**(2): p. 320-32.
64. Fry, D.L. and R.E. Hyatt, *Pulmonary mechanics. A unified analysis of the relationship between pressure, volume and gasflow in the lungs of normal and diseased human subjects.* Am J Med, 1960. **29**: p. 672-89.
65. Jensen, J.I., S. Lyager, and O.F. Pedersen, *The relationship between maximal ventilation, breathing pattern and mechanical limitation of ventilation.* J Physiol, 1980. **309**: p. 521-32.
66. Sorli, J., et al., *Control of breathing in patients with chronic obstructive lung disease.* Clin Sci Mol Med, 1978. **54**(3): p. 295-304.
67. Loveridge, B., et al., *Alteration in breathing pattern with progression of chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1986. **134**(5): p. 930-4.
68. Montes de Oca, M. and B. Celli, Am J Respir Crit Care Med 2000. **161**: p. 880-885.
69. Spiro, S., et al., *An analysis of physiological strain of submaximal exercise in patients with chronic obstructive bronchitis.* Thorax, 1975. **30**: p. 415-25.
70. Loveridge, B., et al., *Breathing patterns in patients with chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1984. **130**(5): p. 730-3.
71. Tobin, M.J., et al., *Breathing patterns. 2. Diseased subjects.* Chest, 1983. **84**(3): p. 286-94.
72. Marino, P.L., *The ICU book*. 1998, Baltimore: Williams & Wilkins.
73. Krachman, S. and Tobin. M, *Chronic Obstructive Pulmonary Disease*, in *Respiratory-Circulatory Interactions in Health and Disease*, Magder. S, Editor. 2001, Marcel Dekker: New York. p. 651-679.
74. De Troyer, A. and T.A. Wilson, *Effect of acute inflation on the mechanics of the inspiratory muscles.* J Appl Physiol, 2009. **107**(1): p. 315-23.
75. Gorman, R.B., et al., *Diaphragm length during tidal breathing in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2002. **166**(11): p. 1461-9.
76. Pride, N. and Milic-Emil. J, *Lung Mechanics*, in *Chronic Obstructive Pulmonary Disease*, Calverley. P and Pride. N, Editors. 1995, Chapman & Hall: London. p. 135-160.
77. West, J., *Respiratory Physiology: The Essentials*. 2000, Philadelphia: Lippincott Williams & Wilkins.
78. Enright, P., *Diffusing capacity for carbon monoxide*. 2010, UptoDate.com.

79. Porth, C., *Disorders of ventilation and gas exchange.* Pathophysiology Concepts of Altered Health States 2005, Philadelphia Lippincott Williams & Wilkins.
80. Guyton, A. and J. Hall, eds. *Physical principles of gas exchange.* Textbook of Medical Physiology, ed. 10. 2000, W.B. Saunders Company: Philadelphia.
81. Calverley, P.M., *Chronic Obstrucive Pulmonary Disease*. 2003, New York: Oxford University Press.
82. Winn, R. and Chan. E, *Pulmonary Function Testing* in *Laboratory Evaluation*. 2007, McGraw-Hill Companies- Acces Medicine.
83. Snider, G.L., *Chronic Obstructive Pulmonary Disease*, in *Internal medicine*, Stein. J, Editor. 1998, Mosby: St. Louis.
84. McIvor, A., Bourbeau. J, and Borycki. E, *Assessment in COPD*, in *Comprehensive management of chronic obstructive pulmonary disease*, J. Bourbeau, Nault. D, and Borycki. E, Editors. 2002, BC Cecker: Hamilton. p. 19-31.
85. O'Donnell, D.E. and K.A. Webb, *Breathlessness in patients with severe chronic airflow limitation. Physiologic correlations.* Chest, 1992. **102**(3): p. 824-31.
86. Stubbing, D.G., et al., *Pulmonary mechanics during exercise in subjects with chronic airflow obstruction.* J Appl Physiol, 1980. **49**(3): p. 511-5.
87. Marin, J.M., et al., *Relationship of resting lung mechanics and exercise pattern of breathing in patients with chronic obstructive lung disease.* Chest, 1993. **104**(3): p. 705-11.
88. Belman, M.J., *Exercise in chronic obstructive pulmonary disease.* Clin Chest Med, 1986. **7**(4): p. 585-97.
89. Gallagher, C.G., *Exercise and chronic obstructive pulmonary disease.* Med Clin North Am, 1990. **74**(3): p. 619-41.
90. De Troyer, A., *Effect of hyperinflation on the diaphragm.* Eur Respir J, 1997. **10**(3): p. 708-13.
91. Wagner, P.D., H.A. Saltzman, and J.B. West, *Measurement of continuous distributions of ventilation-perfusion ratios: theory.* J Appl Physiol, 1974. **36**(5): p. 588-99.
92. Wagner, P.D. and Dantzker. D, *Ventilation-perfusion inequality in chronic obstructive pulmonary disease.* J Clin Invest 1977. **59** (2): p. 203-16.
93. Marthan, R., et al., *Gas exchange alterations in patients with chronic obstructive lung disease.* Chest, 1985. **87**(4): p. 470-5.
94. Barbera, J.A., et al., *Gas exchange during exercise in mild chronic obstructive pulmonary disease. Correlation with lung structure.* Am Rev Respir Dis, 1991. **144**(3 Pt 1): p. 520-5.
95. Palange, P., et al., *Ventilatory and metabolic adaptations to walking and cycling in patients with COPD.* J Appl Physiol, 2000. **88**(5): p. 1715-20.
96. Agusti, A.G. and J.A. Barbera, *Contribution of multiple inert gas elimination technique to pulmonary medicine. 2. Chronic pulmonary diseases: chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.* Thorax, 1994. **49**(9): p. 924-32.
97. Wagner, P.D., et al., *Ventilation-perfusion inequality in chronic obstructive pulmonary disease.* J Clin Invest, 1977. **59**(2): p. 203-16.
98. Barbera, J.A., et al., *Lung structure and gas exchange in mild chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1990. **141**(4 Pt 1): p. 895-901.

99. ATS., *Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society.* American Journal of Respiratory Critical Care Medicine, 1995. **152**: p. S77-S120.
100. Saey, D., et al., *Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2003. **168**(4): p. 425-30.
101. Casaburi, R., *Skeletal muscle dysfunction in chronic obstructive pulmonary disease.* Med Sci Sports Exerc, 2001. **33**(7 Suppl): p. S662-70.
102. Killian, K.J., et al., *Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation.* Am Rev Respir Dis, 1992. **146**(4): p. 935-40.
103. *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.
104. Gosker, H.R., et al., *Skeletal muscle dysfunction in chronic obstructive pulmonary disease and chronic heart failure: underlying mechanisms and therapy perspectives.* Am J Clin Nutr, 2000. **71**(5): p. 1033-47.
105. Casaburi, R., *Deconditioning*, in *Pulmonary Rehabilitation*, A. Fishman, Editor. 1996, Marcel Dekker: New York. p. 213–230.
106. Maltais, F., et al., *Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1996. **154**(2 Pt 1): p. 442-7.
107. Green, H.J., et al., *Operation Everest II: adaptations in human skeletal muscle.* J Appl Physiol, 1989. **66**(5): p. 2454-61.
108. Bigard, A.X., et al., *Myosin heavy chain composition of skeletal muscles in young rats growing under hypobaric hypoxia conditions.* J Appl Physiol, 2000. **88**(2): p. 479-86.
109. Howald, H., et al., *Effect of chronic hypoxia on muscle enzyme activities.* Int J Sports Med, 1990. **11 Suppl 1**: p. S10-4.
110. Pastoris, O., et al., *Modifications by chronic intermittent hypoxia and drug treatment on skeletal muscle metabolism.* Neurochem Res, 1995. **20**(2): p. 143-50.
111. Schols, A.M., et al., *Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease.* Thorax, 1996. **51**(8): p. 819-24.
112. Saltin, B., Gollnick, P., *Skeletal muscle adaptability: significance for metabolism and performance* Handbook of Physiology: Skeletal Muscle, ed. L. Peachey. 1986, Washington, DC: American Physiological Society. 555–631.
113. Man, W.D., et al., *Skeletal muscle dysfunction in COPD: clinical and laboratory observations.* Clin Sci (Lond), 2009. **117**(7): p. 251-64.
114. Langen, R.C., et al., *Muscle wasting and impaired muscle regeneration in a murine model of chronic pulmonary inflammation.* Am J Respir Cell Mol Biol, 2006. **35**(6): p. 689-96.
115. Agusti, A.G., et al., *Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2002. **166**(4): p. 485-9.

116. Gan, W.Q., et al., *Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis.* Thorax, 2004. **59**(7): p. 574-80.
117. Schols, A.M., et al., *Energy balance in chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1991. **143**(6): p. 1248-52.
118. Schols, A.M., et al., *Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial.* Am J Respir Crit Care Med, 1995. **152**(4 Pt 1): p. 1268-74.
119. Ferreira, I.M., et al., *Nutritional supplementation in stable chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2000(3): p. CD000998.
120. Decramer, M., et al., *Corticosteroids contribute to muscle weakness in chronic airflow obstruction.* Am J Respir Crit Care Med, 1994. **150**(1): p. 11-6.
121. Decramer, M., V. de Bock, and R. Dom, *Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1996. **153**(6 Pt 1): p. 1958-64.
122. Petersen, A.M., et al., *Smoking impairs muscle protein synthesis and increases the expression of myostatin and MAFbx in muscle.* Am J Physiol Endocrinol Metab, 2007. **293**(3): p. E843-8.
123. Montes de Oca, M., et al., *Peripheral muscle alterations in non-COPD smokers.* Chest, 2008. **133**(1): p. 13-8.
124. Reid, M.B., et al., *Reactive oxygen in skeletal muscle. II. Extracellular release of free radicals.* J Appl Physiol, 1992. **73**(5): p. 1805-9.
125. Creutzberg, E.C., et al., *Disturbances in leptin metabolism are related to energy imbalance during acute exacerbations of chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2000. **162**(4 Pt 1): p. 1239-45.
126. Takabatake, N., et al., *Circulating leptin in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1999. **159**(4 Pt 1): p. 1215-9.
127. Kim, H.C., M. Mofarrahi, and S.N. Hussain, *Skeletal muscle dysfunction in patients with chronic obstructive pulmonary disease.* Int J Chron Obstruct Pulmon Dis, 2008. **3**(4): p. 637-58.
128. Gea, J. and E. Barreiro, *[Update on the mechanisms of muscle dysfunction in COPD].* Arch Bronconeumol, 2008. **44**(6): p. 328-37.
129. Couillard, A. and C. Prefaut, *From muscle disuse to myopathy in COPD: potential contribution of oxidative stress.* Eur Respir J, 2005. **26**(4): p. 703-19.
130. Troosters, T., R. Gosselink, and M. Decramer, *Chronic obstructive pulmonary disease and chronic heart failure: two muscle diseases?* J Cardiopulm Rehabil, 2004. **24**(3): p. 137-45.
131. Franssen, F.M., E.F. Wouters, and A.M. Schols, *The contribution of starvation, deconditioning and ageing to the observed alterations in peripheral skeletal muscle in chronic organ diseases.* Clin Nutr, 2002. **21**(1): p. 1-14.
132. Bernard, S., et al., *Peripheral muscle weakness in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1998. **158**(2): p. 629-34.
133. Decramer, M., et al., *Muscle weakness is related to utilization of health care resources in COPD patients.* Eur Respir J, 1997. **10**(2): p. 417-23.

134. Gosselink, R., T. Troosters, and M. Decramer, *Peripheral muscle weakness contributes to exercise limitation in COPD.* Am J Respir Crit Care Med, 1996. **153**(3): p. 976-80.
135. Engelen, M.P., et al., *Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD.* Eur Respir J, 1994. **7**(10): p. 1793-7.
136. Schols, A.M., et al., *Body composition and exercise performance in patients with chronic obstructive pulmonary disease.* Thorax, 1991. **46**(10): p. 695-9.
137. Rochester, D.F., *Body weight and respiratory muscle function in chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1986. **134**(4): p. 646-8.
138. Sato, Y., et al., *Morphologic and histochemical evaluation of muscle in patients with chronic pulmonary emphysema manifesting generalized emaciation.* Eur Neurol, 1997. **37**(2): p. 116-21.
139. Gosker, H.R., et al., *Striking similarities in systemic factors contributing to decreased exercise capacity in patients with severe chronic heart failure or COPD.* Chest, 2003. **123**(5): p. 1416-24.
140. Man, W.D., et al., *Abdominal muscle and quadriceps strength in chronic obstructive pulmonary disease.* Thorax, 2005. **60**(9): p. 718-22.
141. Hamilton, A.L., et al., *Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders.* Am J Respir Crit Care Med, 1995. **152**(6 Pt 1): p. 2021-31.
142. Jakobsson, P., L. Jorfeldt, and J. Henriksson, *Metabolic enzyme activity in the quadriceps femoris muscle in patients with severe chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1995. **151**(2 Pt 1): p. 374-7.
143. Hildebrand, I.L., et al., *Does chronic hypoxaemia induce transformations of fibre types?* Acta Physiol Scand, 1991. **141**(3): p. 435-9.
144. Maltais, F., et al., *Altered expression of myosin heavy chain in the vastus lateralis muscle in patients with COPD.* Eur Respir J, 1999. **13**(4): p. 850-4.
145. Jobin, J., et al., *Chronic obstructive pulmonary disease: capillarity and fiber-type characteristics of skeletal muscle.* J Cardiopulm Rehabil, 1998. **18**(6): p. 432-7.
146. Simard, C., et al., *Mitochondrial and Capillarity Changes in Vastus Lateralis Muscle of Copd Patients: Electron Microscopy.* Med Sci Sports Exerc, 1996. **28**(5).
147. Saey, D., et al., *Contractile fatigue, muscle morphometry, and blood lactate in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2005. **171**(10): p. 1109-15.
148. Gosker, H.R., et al., *Skeletal muscle fibre-type shifting and metabolic profile in patients with chronic obstructive pulmonary disease.* Eur Respir J, 2002. **19**(4): p. 617-25.
149. Jakobsson, P., L. Jorfeldt, and A. Brundin, *Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD), with and without chronic respiratory failure.* Eur Respir J, 1990. **3**(2): p. 192-6.
150. Sala, E., et al., *Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1999. **159**(6): p. 1726-34.
151. Gosker, H.R., et al., *Reduced mitochondrial density in the vastus lateralis muscle of patients with COPD.* Eur Respir J, 2007. **30**(1): p. 73-9.

152. Maltais, F., et al., *Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD.* Am J Respir Crit Care Med, 1996. **153**(1): p. 288-93.
153. Serres, I., et al., *Skeletal muscle abnormalities in patients with COPD: contribution to exercise intolerance.* Med Sci Sports Exerc, 1998. **30**(7): p. 1019-27.
154. Jeffery Mador, M., T.J. Kufel, and L. Pineda, *Quadriceps fatigue after cycle exercise in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2000. **161**(2 Pt 1): p. 447-53.
155. Van't Hul, A., et al., *Quadriceps muscle endurance in patients with chronic obstructive pulmonary disease.* Muscle Nerve, 2004. **29**(2): p. 267-74.
156. Allaire, J., et al., *Peripheral muscle endurance and the oxidative profile of the quadriceps in patients with COPD.* Thorax, 2004. **59**(8): p. 673-8.
157. Warburton, D. and S. Mathur, *Skeletal muscle training in people with chronic heart failure or chronic obstructive pulmonary disease.* Physiother. Can., 2004. **56**: p. 143-157.
158. Kimura, J., *Electrodiagnosis in diseases of nerve and muscle*. 1983, Philadelphia, PA,: F.A. Davis Company.
159. Nazari, S., *Mechanical Events In Physiopathology Of Idiopathic Pulmonary Emphysema: A Theoretical Analysis.* The Internet Journal of Pathology, 2003. **2**(2).
160. Pitta, F., et al., *Activity monitoring for assessment of physical activities in daily life in patients with chronic obstructive pulmonary disease.* Arch Phys Med Rehabil, 2005. **86**(10): p. 1979-85.
161. Butler, J., et al., *Cause of the raised wedge pressure on exercise in chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1988. **138**(2): p. 350-4.
162. Buda, A.J., et al., *Effect of intrathoracic pressure on left ventricular performance.* N Engl J Med, 1979. **301**(9): p. 453-9.
163. Bauerle, O., C.A. Chrusch, and M. Younes, *Mechanisms by which COPD affects exercise tolerance.* Am J Respir Crit Care Med, 1998. **157**(1): p. 57-68.
164. Rossi, A., et al., *Intrinsic positive end-expiratory pressure (PEEPi).* Intensive Care Med, 1995. **21**(6): p. 522-36.
165. Potter, W.A., S. Olafsson, and R.E. Hyatt, *Ventilatory mechanics and expiratory flow limitation during exercise in patients with obstructive lung disease.* J Clin Invest, 1971. **50**(4): p. 910-9.
166. Rochester, D.F. and N.M. Braun, *Determinants of maximal inspiratory pressure in chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1985. **132**(1): p. 42-7.
167. O'Donnell, D.E. and P. Laveneziana, *Dyspnea and activity limitation in COPD: mechanical factors.* COPD, 2007. **4**(3): p. 225-36.
168. Loring, S.H., M. Garcia-Jacques, and A. Malhotra, *Pulmonary characteristics in COPD and mechanisms of increased work of breathing.* J Appl Physiol, 2009. **107**(1): p. 309-14.
169. Maltais, F., et al., *Oxidative enzyme activities of the vastus lateralis muscle and the functional status in patients with COPD.* Thorax, 2000. **55**(10): p. 848-53.
170. Edwards, R.H., et al., *Human skeletal muscle function: description of tests and normal values.* Clin Sci Mol Med, 1977. **52**(3): p. 283-90.

171. Edwards, R.H., *Human muscle function and fatigue*, in *Human muscle fatigue: Physiological mechanisms.*, Porter. H and Whelan. J, Editors. 1981, Pitman Medical: London. p. 1-18.
172. Polkey, M.I., et al., *Quadriceps strength and fatigue assessed by magnetic stimulation of the femoral nerve in man.* Muscle Nerve, 1996. **19**(5): p. 549-55.
173. Mador, M.J., et al., *Effect of pulmonary rehabilitation on quadriceps fatiguability during exercise.* Am J Respir Crit Care Med, 2001. **163**(4): p. 930-5.
174. Man, W.D., et al., *Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2003. **168**(5): p. 562-7.
175. Laveneziana, P., et al., *Exercise Limitation in Chronic Obstructive Pulmonary Disease.* Curr Resp Med Rev, 2008. **4**: p. 258-269.
176. Pepin, V., et al., *Walking versus cycling: sensitivity to bronchodilation in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2005. **172**(12): p. 1517-22.
177. Deschenes, D., et al., *Locus of symptom limitation and exercise response to bronchodilation in chronic obstructive pulmonary disease.* J Cardiopulm Rehabil Prev, 2008. **28**(3): p. 208-14.
178. Saey, D. and T. Troosters, *Measuring skeletal muscle strength and endurance, from bench to bedside.* Clin Invest Med, 2008. **31**(5): p. E307-11.
179. Casaburi, R., *Exercise training in chronic obstructive lung disease*, in *Principles and Practice of Pulmonary Rehabilitation*, R. Casaburi and T.L. Petty, Editors. 1993, Saunders: Philadelphia. p. 202-224.
180. Maltais, F., et al., *Metabolic and hemodynamic responses of lower limb during exercise in patients with COPD.* J Appl Physiol, 1998. **84**(5): p. 1573-80.
181. Weisman, M. and R. Zeballos, *Clinical Exercise Testing.*, in *Prog Respir Res.*, C. Bolliger, Editor. 2002, Karger: Basel. p. 138-158.
182. Guyton, A.C. and J.E. Hall, *Heart Muscle; The heart as a Pump*, in *Textbook of Medical Physiology*, A.C. Guyton and J.E. Hall, Editors. 2006, Elsevier Saunders Inc.: Philadelphia. p. 99.
183. Bassett, D.R., Jr. and E.T. Howley, *Limiting factors for maximum oxygen uptake and determinants of endurance performance.* Med Sci Sports Exerc, 2000. **32**(1): p. 70-84.
184. Faulkner, J.A., G.J. Heigenhauser, and M.A. Schork, *The cardiac output--oxygen uptake relationship of men during graded bicycle ergometry.* Med Sci Sports, 1977. **9**(3): p. 148-54.
185. Proctor, D.N., et al., *Influence of age and gender on cardiac output-VO2 relationships during submaximal cycle ergometry.* J Appl Physiol, 1998. **84**(2): p. 599-605.
186. Stewart, R.I. and C.M. Lewis, *Cardiac output during exercise in patients with COPD.* Chest, 1986. **89**(2): p. 199-205.
187. Bogaard, H.J., et al., *The haemodynamic response to exercise in chronic obstructive pulmonary disease: assessment by impedance cardiography.* Eur Respir J, 1998. **12**(2): p. 374-9.
188. Morrison, D.A., et al., *Right ventricular dysfunction and the exercise limitation of chronic obstructive pulmonary disease.* J Am Coll Cardiol, 1987. **9**(6): p. 1219-29.

189. Light, R.W., et al., *Hemodynamics of patients with severe chronic obstructive pulmonary disease during progressive upright exercise.* Am Rev Respir Dis, 1984. **130**(3): p. 391-5.
190. Sietsema, K., *Cardiovascular limitations in chronic pulmonary disease.* Med Sci Sports Exerc, 2001. **33**(7 Suppl): p. S656-61.
191. Jorgensen, K., et al., *Reduced intrathoracic blood volume and left and right ventricular dimensions in patients with severe emphysema: an MRI study.* Chest, 2007. **131**(4): p. 1050-7.
192. Holverda, S., et al., *Stroke volume increase to exercise in chronic obstructive pulmonary disease is limited by increased pulmonary artery pressure.* Heart, 2009. **95**(2): p. 137-41.
193. Matthay, R.A., et al., *Right ventricular function at rest and during exercise in chronic obstructive pulmonary disease.* Chest, 1992. **101**(5 Suppl): p. 255S-262S.
194. Baril, J., et al., *Does dynamic hyperinflation impair submaximal exercise cardiac output in chronic obstructive pulmonary disease?* Clin Invest Med, 2006. **29**(2): p. 104-9.
195. Richardson, R.S., et al., *Evidence of skeletal muscle metabolic reserve during whole body exercise in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1999. **159**(3): p. 881-5.
196. Sabapathy, S., et al., *Lower limb vasodilatory capacity is not reduced in patients with moderate COPD.* Int J Chron Obstruct Pulmon Dis, 2006. **1**(1): p. 73-81.
197. Oelberg, D.A., et al., *Systemic oxygen extraction during incremental exercise in patients with severe chronic obstructive pulmonary disease.* Eur J Appl Physiol Occup Physiol, 1998. **78**(3): p. 201-7.
198. Vassaux, C., et al., *Effects of hyperinflation on the oxygen pulse as a marker of cardiac performance in COPD.* Eur Respir J, 2008. **32**(5): p. 1275-82.
199. Montes de Oca, M., J. Rassulo, and B.R. Celli, *Respiratory muscle and cardiopulmonary function during exercise in very severe COPD.* Am J Respir Crit Care Med, 1996. **154**(5): p. 1284-9.
200. Tutar, E., et al., *Echocardiographic evaluation of left ventricular diastolic function in chronic cor pulmonale.* Am J Cardiol, 1999. **83**(9): p. 1414-7, A9.
201. Barr, R.G., et al., *Percent emphysema, airflow obstruction, and impaired left ventricular filling.* N Engl J Med, 2010. **362**(3): p. 217-27.
202. Watz, H., et al., *Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation.* Chest, 2010. **138**(1): p. 32-8.
203. Borghi-Silva, A., et al., *Respiratory muscle unloading improves leg muscle oxygenation during exercise in patients with COPD.* Thorax, 2008. **63**(10): p. 910-5.
204. Harms, C.A., et al., *Respiratory muscle work compromises leg blood flow during maximal exercise.* J Appl Physiol, 1997. **82**(5): p. 1573-83.
205. Harms, C.A., et al., *Effects of respiratory muscle work on exercise performance.* J Appl Physiol, 2000. **89**(1): p. 131-8.
206. Simon, M., et al., *Limitation of lower limb VO(2) during cycling exercise in COPD patients.* J Appl Physiol, 2001. **90**(3): p. 1013-9.
207. Stark-Leyva, K.N., K.C. Beck, and B.D. Johnson, *Influence of expiratory loading and hyperinflation on cardiac output during exercise.* J Appl Physiol, 2004. **96**(5): p. 1920-7.

208. Begin, P. and A. Grassino, *Inspiratory muscle dysfunction and chronic hypercapnia in chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1991. **143**(5 Pt 1): p. 905-12.
209. Fletcher, E.C., et al., *Survival in COPD patients with a daytime PaO2 greater than 60 mm Hg with and without nocturnal oxyhemoglobin desaturation.* Chest, 1992. **101**(3): p. 649-55.
210. Nonoyama, M.L., et al., *Oxygen therapy during exercise training in chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2007(2): p. CD005372.
211. Hoo, G.W., *Nonpharmacologic adjuncts to training during pulmonary rehabilitation: the role of supplemental oxygen and noninvasive ventilation.* J Rehabil Res Dev, 2003. **40**(5 Suppl 2): p. 81-97.
212. Nonoyama, M.L., et al., *Effect of oxygen on health quality of life in patients with chronic obstructive pulmonary disease with transient exertional hypoxemia.* Am J Respir Crit Care Med, 2007. **176**(4): p. 343-9.
213. Soguel Schenkel, N., et al., *Oxygen saturation during daily activities in chronic obstructive pulmonary disease.* Eur Respir J, 1996. **9**(12): p. 2584-9.
214. Dreher, M., et al., *Exercise in severe COPD: is walking different from stair-climbing?* Respir Med, 2008. **102**(6): p. 912-8.
215. Tarpy, S.P. and B.R. Celli, *Long-term oxygen therapy.* N Engl J Med, 1995. **333**(11): p. 710-4.
216. O'Donohue, W., *Oxygen therapy in pulmonary rehabilitation*, in *Pulmonary rehabilitation: guideliness for success*, J. Hodgkin, B. Celli, and G. Connors, Editors. 2000, Lippincott Williams & Wilkins: Philadelphia. p. 135-46.
217. Pepin, V., et al., *Exercise capacity in chronic obstructive pulmonary disease: mechanisms of limitation.* COPD, 2007. **4**(3): p. 195-204.
218. Saey, D., et al., *Pulmonary rehabilitation in chronic obstructive pulmonary disease.* Panminerva Med, 2009. **51**(2): p. 95-114.
219. Calverley, P.M., *Neuropsychological deficits in chronic obstructive pulmonary disease.* Monaldi Arch Chest Dis, 1996. **51**(1): p. 5-6.
220. O'Donnell, D.E., et al., *Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update.* Can Respir J, 2007. **14 Suppl B**: p. 5B-32B.
221. Lacasse, Y., G.H. Guyatt, and R.S. Goldstein, *The components of a respiratory rehabilitation program: a systematic overview.* Chest, 1997. **111**(4): p. 1077-88.
222. *Pulmonary rehabilitation-1999. American Thoracic Society.* Am J Respir Crit Care Med, 1999. **159**(5 Pt 1): p. 1666-82.
223. Casaburi, R., et al., *Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1997. **155**(5): p. 1541-51.
224. Vogiatzis, I., et al., *Effects of rehabilitative exercise on peripheral muscle TNFalpha, IL-6, IGF-I and MyoD expression in patients with COPD.* Thorax, 2007. **62**(11): p. 950-6.
225. Takigawa, N., et al., *Comprehensive pulmonary rehabilitation according to severity of COPD.* Respir Med, 2007. **101**(2): p. 326-32.
226. Coppoolse, R., et al., *Interval versus continuous training in patients with severe COPD: a randomized clinical trial.* Eur Respir J, 1999. **14**(2): p. 258-63.

227. Cortopassi, F., et al., *Comprehensive exercise training improves ventilatory muscle function and reduces dyspnea perception in patients with COPD.* Monaldi Arch Chest Dis, 2009. **71**(3): p. 106-12.
228. Disease, G.I.f.C.O.L. *Global Strategy for the Diagnosis, Management and Prevention of COPD*. 2009 January 16 [cited 2010 January 16]; http://www.goldcopd.org. :[
229. Gosselink, R., T. Troosters, and M. Decramer, *Exercise training in COPD patients: the basic questions.* Eur Respir J, 1997. **10**(12): p. 2884-91.
230. Maltais, F., et al., *Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1997. **155**(2): p. 555-61.
231. Emtner, M., et al., *Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients.* Am J Respir Crit Care Med, 2003. **168**(9): p. 1034-42.
232. Somfay, A., et al., *Dose-response effect of oxygen on hyperinflation and exercise endurance in nonhypoxaemic COPD patients.* Eur Respir J, 2001. **18**(1): p. 77-84.
233. Chiappa, G.R., et al., *Heliox improves oxygen delivery and utilization during dynamic exercise in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2009. **179**(11): p. 1004-10.
234. Laude, E.A., et al., *The effect of helium and oxygen on exercise performance in chronic obstructive pulmonary disease: a randomized crossover trial.* Am J Respir Crit Care Med, 2006. **173**(8): p. 865-70.
235. Bradley, J.M., et al., *A systematic review of randomized controlled trials examining the short-term benefit of ambulatory oxygen in COPD.* Chest, 2007. **131**(1): p. 278-85.
236. Palange, P., et al., *Supplemental oxygen and heliox: 'new' tools for exercise training in chronic obstructive pulmonary disease.* Curr Opin Pulm Med, 2005. **11**(2): p. 145-8.
237. O'Donnell, D.E., C. D'Arsigny, and K.A. Webb, *Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2001. **163**(4): p. 892-8.
238. Bye, P.T., et al., *Ventilatory muscle function during exercise in air and oxygen in patients with chronic air-flow limitation.* Am Rev Respir Dis, 1985. **132**(2): p. 236-40.
239. Woodcock, A.A., E.R. Gross, and D.M. Geddes, *Oxygen relieves breathlessness in "pink puffers".* Lancet, 1981. **1**(8226): p. 907-9.
240. O'Donnell, D.E., D.J. Bain, and K.A. Webb, *Factors contributing to relief of exertional breathlessness during hyperoxia in chronic airflow limitation.* Am J Respir Crit Care Med, 1997. **155**(2): p. 530-5.
241. Maltais, F., et al., *Effects of oxygen on lower limb blood flow and O2 uptake during exercise in COPD.* Med Sci Sports Exerc, 2001. **33**(6): p. 916-22.
242. Fujimoto, K., et al., *Benefits of oxygen on exercise performance and pulmonary hemodynamics in patients with COPD with mild hypoxemia.* Chest, 2002. **122**(2): p. 457-63.
243. Stein, D.A., B.L. Bradley, and W.C. Miller, *Mechanisms of oxygen effects on exercise in patients with chronic obstructive pulmonary disease.* Chest, 1982. **81**(1): p. 6-10.

244. Swinburn, C.R., J.M. Wakefield, and P.W. Jones, *Relationship between ventilation and breathlessness during exercise in chronic obstructive airways disease is not altered by prevention of hypoxaemia.* Clin Sci (Lond), 1984. **67**(5): p. 515-9.
245. Bradley, B.L., et al., *Oxygen-assisted exercise in chronic obstructive lung disease. The effect on exercise capacity and arterial blood gas tensions.* Am Rev Respir Dis, 1978. **118**(2): p. 239-43.
246. Scano, G., et al., *Effect of oxygen on breathing during exercise in patients with chronic obstructive lung disease.* Eur J Respir Dis, 1982. **63**(1): p. 23-30.
247. Payen, J.F., et al., *Muscular metabolism during oxygen supplementation in patients with chronic hypoxemia.* Am Rev Respir Dis, 1993. **147**(3): p. 592-8.
248. Criner, G.J. and B.R. Celli, *Ventilatory muscle recruitment in exercise with O2 in obstructed patients with mild hypoxemia.* J Appl Physiol, 1987. **63**(1): p. 195-200.
249. Bye, P.T., et al., *Ventilatory muscles during exercise in air and oxygen in normal men.* J Appl Physiol, 1984. **56**(2): p. 464-71.
250. Pardy, R.L. and P.T. Bye, *Diaphragmatic fatigue in normoxia and hyperoxia.* J Appl Physiol, 1985. **58**(3): p. 738-42.
251. Somfay, A., et al., *Effect of hyperoxia on gas exchange and lactate kinetics following exercise onset in nonhypoxemic COPD patients.* Chest, 2002. **121**(2): p. 393-400.
252. Cotes, J.E., Z. Pisa, and A.J. Thomas, *Effect of Breathing Oxygen Upon Cardiac Output, Heart Rate, Ventilation, Systemic and Pulmonary Blood Pressure in Patients with Chronic Lung Disease.* Clin Sci, 1963. **25**: p. 305-21.
253. Olvey, S.K., et al., *First pass radionuclide assessment of right and left ventricular ejection fraction in chronic pulmonary disease. Effect of oxygen upon exercise response.* Chest, 1980. **78**(1): p. 4-9.
254. Vogiatzis, I., et al., *Effect of helium breathing on intercostal and quadriceps muscle blood flow during exercise in COPD patients.* Am J Physiol Regul Integr Comp Physiol, 2011. **300**(6): p. R1549-59.
255. Siqueira, A.C., et al., *Effects of hyperoxia on the dynamics of skeletal muscle oxygenation at the onset of heavy-intensity exercise in patients with COPD.* Respir Physiol Neurobiol, 2010. **172**(1-2): p. 8-14.
256. Garrod, R., E.A. Paul, and J.A. Wedzicha, *Supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia.* Thorax, 2000. **55**(7): p. 539-43.
257. Fichter, J., et al., *[Effect of oxygen (FI02: 0.35) on the aerobic capacity in patients with COPD].* Pneumologie, 1999. **53**(3): p. 121-6.
258. Wadell, K., K. Henriksson-Larsen, and R. Lundgren, *Physical training with and without oxygen in patients with chronic obstructive pulmonary disease and exercise-induced hypoxaemia.* J Rehabil Med, 2001. **33**(5): p. 200-5.
259. Rooyackers, J.M., et al., *Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise.* Eur Respir J, 1997. **10**(6): p. 1278-84.
260. Langer, D., et al., *A clinical practice guideline for physiotherapists treating patients with chronic obstructive pulmonary disease based on a systematic review of available evidence.* Clin Rehabil, 2009. **23**(5): p. 445-62.
261. Papamoschou, D., *Theoretical validation of the respiratory benefits of helium-oxygen mixtures.* Respir Physiol, 1995. **99**(1): p. 183-90.

262. Yanai, M., et al., *Site of airway obstruction in pulmonary disease: direct measurement of intrabronchial pressure.* J Appl Physiol, 1992. **72**(3): p. 1016-23.
263. Martin, D., et al., *Effects of breathing a normoxic helium mixture on exercise tolerance of patients with cystic fibrosis.* Pediatr Pulmonol, 1994. **18**(4): p. 206-10.
264. Eves, N.D., et al., *Helium-hyperoxia, exercise, and respiratory mechanics in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2006. **174**(7): p. 763-71.
265. Esposito, F. and G. Ferretti, *The effects of breathing He-O2 mixtures on maximal oxygen consumption in normoxic and hypoxic men.* J Physiol, 1997. **503 (Pt 1)**: p. 215-22.
266. Hunt, T., et al., *Heliox, dyspnoea and exercise in COPD.* European Respiratory Review, 2010. **19**: p. 30-38.
267. Eves, N. and Ford. G, *Helium–oxygen: A versatile therapy to "lighten the load" of chronic obstructive pulmonary disease (COPD).* Respiratory Medicine: COPD Update, 2007. **3**(3): p. 87-94.
268. Gainnier, M. and J.M. Forel, *Clinical review: use of helium-oxygen in critically ill patients.* Crit Care, 2006. **10**(6): p. 241.
269. Valli, G., et al., *Clinical use of Heliox in asthma and COPD.* Monaldi Arch Chest Dis, 2007. **67**(3): p. 159-64.
270. Babb, T.G., *Breathing He-O2 increases ventilation but does not decrease the work of breathing during exercise.* Am J Respir Crit Care Med, 2001. **163**(5): p. 1128-34.
271. Amann, M., et al., *Impact of pulmonary system limitations on locomotor muscle fatigue in patients with COPD.* Am J Physiol Regul Integr Comp Physiol, 2010. **299**(1): p. R314-24.
272. Oelberg, D.A., et al., *Ventilatory and cardiovascular responses to inspired He-O2 during exercise in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1998. **158**(6): p. 1876-82.
273. Palange, P., et al., *Effect of heliox on lung dynamic hyperinflation, dyspnea, and exercise endurance capacity in COPD patients.* J Appl Physiol, 2004. **97**(5): p. 1637-42.
274. Marciniuk, D.D., et al., *The effects of helium-hyperoxia on 6-min walking distance in COPD: a randomized, controlled trial.* Chest, 2007. **131**(6): p. 1659-65.
275. Spahija, J., et al., *Downregulation of diaphragm activation with pressure support ventilation (PSV) in COPD and healthy subjects during exercise.* Am J Respir Crit Care Med, 2007. **175**: p. A224.
276. Maltais, F., H. Reissmann, and S.B. Gottfried, *Pressure support reduces inspiratory effort and dyspnea during exercise in chronic airflow obstruction.* Am J Respir Crit Care Med, 1995. **151**(4): p. 1027-33.
277. Diaz, O., et al., *Effects of noninvasive ventilation on pulmonary gas exchange and hemodynamics during acute hypercapnic exacerbations of chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1997. **156**(6): p. 1840-5.

278. Pollack, C., Jr., M.T. Torres, and L. Alexander, *Feasibility study of the use of bilevel positive airway pressure for respiratory support in the emergency department.* Ann Emerg Med, 1996. **27**(2): p. 189-92.
279. Lloyd-Owen, S.J., et al., *Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey.* Eur Respir J, 2005. **25**(6): p. 1025-31.
280. Caples, S.M. and P.C. Gay, *Noninvasive positive pressure ventilation in the intensive care unit: a concise review.* Crit Care Med, 2005. **33**(11): p. 2651-8.
281. Spahija, J., et al., *Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist.* Crit Care Med, 2010. **38**(2): p. 518-26.
282. Petrof, B.J., et al., *Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1990. **141**(2): p. 281-9.
283. Brochard, L., et al., *Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation.* Am Rev Respir Dis, 1989. **139**(2): p. 513-21.
284. Brochard, L., et al., *Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask.* N Engl J Med, 1990. **323**(22): p. 1523-30.
285. Kallet, R.H. and J.V. Diaz, *The physiologic effects of noninvasive ventilation.* Respir Care, 2009. **54**(1): p. 102-15.
286. Schiller, O., et al., *Bi-level positive airway pressure ventilation in pediatric oncology patients with acute respiratory failure.* J Intensive Care Med, 2009. **24**(6): p. 383-8.
287. Ambrosino, N., G. Palmiero, and S.K. Strambi, *New approaches in pulmonary rehabilitation.* Clin Chest Med, 2007. **28**(3): p. 629-38, vii.
288. O'Donnell, D.E., et al., *Effect of continuous positive airway pressure on respiratory sensation in patients with chronic obstructive pulmonary disease during submaximal exercise.* Am Rev Respir Dis, 1988. **138**(5): p. 1185-91.
289. Costa, D., et al., *Influence of noninvasive ventilation by BiPAP on exercise tolerance and respiratory muscle strength in chronic obstructive pulmonary disease patients (COPD).* Rev Lat Am Enfermagem, 2006. **14**(3): p. 378-82.
290. Borghi-Silva, A., et al., *Noninvasive ventilation acutely modifies heart rate variability in chronic obstructive pulmonary disease patients.* Respir Med, 2008. **102**(8): p. 1117-23.
291. Borghi-Silva, A., et al., *Non-invasive ventilation improves peripheral oxygen saturation and reduces fatigability of quadriceps in patients with COPD.* Respirology, 2009. **14**(4): p. 537-44.
292. Borghi-Silva, A., et al., *Adjuncts to physical training of patients with severe COPD: oxygen or noninvasive ventilation?* Respir Care, 2010. **55**(7): p. 885-94.
293. Toledo, A., et al., *The impact of noninvasive ventilation during the physical training in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).* Clinics (Sao Paulo), 2007. **62**(2): p. 113-20.
294. Reuveny, R., et al., *Ventilatory support during training improves training benefit in severe chronic airway obstruction.* Isr Med Assoc J, 2005. **7**(3): p. 151-5.

295. Johnson, J.E., D.J. Gavin, and S. Adams-Dramiga, *Effects of training with heliox and noninvasive positive pressure ventilation on exercise ability in patients with severe COPD.* Chest, 2002. **122**(2): p. 464-72.
296. Kohnlein, T., et al., *Noninvasive ventilation in pulmonary rehabilitation of COPD patients.* Respir Med, 2009. **103**(9): p. 1329-36.
297. Brochard, L., *Pressure support ventilation.*, in *Principles and practice of mechanical ventilation.*, M.J. Tobin, Editor. 1994, McGraw-Hill inc: New York. p. 239–256.
298. van 't Hul, A., et al., *Training with inspiratory pressure support in patients with severe COPD.* Eur Respir J, 2006. **27**(1): p. 65-72.
299. van 't Hul, A., et al., *Acute effects of inspiratory pressure support during exercise in patients with COPD.* Eur Respir J, 2004. **23**(1): p. 34-40.
300. Keilty, S.E., et al., *Effect of inspiratory pressure support on exercise tolerance and breathlessness in patients with severe stable chronic obstructive pulmonary disease.* Thorax, 1994. **49**(10): p. 990-4.
301. Younes, M., *Proportional assist ventilation, a new approach to ventilatory support. Theory.* Am Rev Respir Dis, 1992. **145**(1): p. 114-20.
302. Hernandez, P., et al., *Proportional assist ventilation may improve exercise performance in severe chronic obstructive pulmonary disease.* J Cardiopulm Rehabil, 2001. **21**(3): p. 135-42.
303. Dolmage, T.E. and R.S. Goldstein, *Proportional assist ventilation and exercise tolerance in subjects with COPD.* Chest, 1997. **111**(4): p. 948-54.
304. Hawkins, P., et al., *Proportional assist ventilation as an aid to exercise training in severe chronic obstructive pulmonary disease.* Thorax, 2002. **57**(10): p. 853-9.
305. Bianchi, L., et al., *Lack of additional effect of adjunct of assisted ventilation to pulmonary rehabilitation in mild COPD patients.* Respir Med, 2002. **96**(5): p. 359-67.
306. Lellouche, F. and L. Brochard, *Advanced closed loops during mechanical ventilation (PAV, NAVA, ASV, SmartCare).* Best Pract Res Clin Anaesthesiol, 2009. **23**(1): p. 81-93.
307. Younes, M., et al., *Proportional assist ventilation. Results of an initial clinical trial.* Am Rev Respir Dis, 1992. **145**(1): p. 121-9.
308. Petrof, B.J., E. Calderini, and S.B. Gottfried, *Effect of CPAP on respiratory effort and dyspnea during exercise in severe COPD.* J Appl Physiol, 1990. **69**(1): p. 179-88.
309. Kyroussis, D., et al., *Respiratory muscle activity in patients with COPD walking to exhaustion with and without pressure support.* Eur Respir J, 2000. **15**(4): p. 649-55.
310. Polkey, M.I., et al., *Inspiratory pressure support prolongs exercise induced lactataemia in severe COPD.* Thorax, 2000. **55**(7): p. 547-9.
311. Highcock, M.P., J.M. Shneerson, and I.E. Smith, *Increased ventilation with NiIPPV does not necessarily improve exercise capacity in COPD.* Eur Respir J, 2003. **22**(1): p. 100-5.
312. Bianchi, L., et al., *Effects of proportional assist ventilation on exercise tolerance in COPD patients with chronic hypercapnia.* Eur Respir J, 1998. **11**(2): p. 422-7.
313. Spahija, J., et al., *Downregulation of diaphragm activation with pressure support ventilation (PSV) in COPD and healthy subjects during exercise.* 2007.

314. Spahija, J., et al., *Effect of increased diaphragm activation on diaphragm power spectrum center frequency.* Respir Physiol Neurobiol, 2005. **146**(1): p. 67-76.
315. Sinderby, C., J. Spahija, and J. Beck, *Changes in respiratory effort sensation over time are linked to the frequency content of diaphragm electrical activity.* Am J Respir Crit Care Med, 2001. **163**(4): p. 905-10.
316. Spahija, J., Beck. J, and Sinderby. C, *Respiratory failure and diaphragm function*, in *Yearbook of Intensive Care and Emergency Medicine*, J.L. Vicente, Editor. 2004, Springer-Verlag: Berlin, Heidelberg, New York. p. 325-332.
317. Evison, H. and R.M. Cherniack, *Ventilatory cost of exercise in chronic obstructive pulmonary disease.* J Appl Physiol, 1968. **25**(1): p. 21-7.
318. Harms, C.A., et al., *Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise.* J Appl Physiol, 1998. **85**(2): p. 609-18.
319. Oliveira, C.C., et al., *Influence of respiratory pressure support on hemodynamics and exercise tolerance in patients with COPD.* Eur J Appl Physiol, 2010. **109**(4): p. 681-9.
320. Borghi-Silva, A., et al., *Effects of respiratory muscle unloading on leg muscle oxygenation and blood volume during high-intensity exercise in chronic heart failure.* Am J Physiol Heart Circ Physiol, 2008. **294**(6): p. H2465-72.
321. Pinsky, M.R., G.M. Matuschak, and M. Klain, *Determinants of cardiac augmentation by elevations in intrathoracic pressure.* J Appl Physiol, 1985. **58**(4): p. 1189-98.
322. Duke, G.J. and A.D. Bersten, *Non.invasive ventilation for adult acute respiratory failure. Part I.* Crit Care Resusc, 1999. **1**(2): p. 198.
323. Kong, W., et al., *Effects of extrinsic positive end-expiratory pressure on cardiopulmonary function in patients with chronic obstructive pulmonary disease.* Chin Med J (Engl), 2001. **114**(9): p. 912-5.
324. Corner, E. and R. Garrod, *Does the addition of non-invasive ventilation during pulmonary rehabilitation in patients with chronic obstructive pulmonary disease augment patient outcome in exercise tolerance? A literature review.* Physiother Res Int, 2010. **15**(1): p. 5-15.
325. Costes, F., et al., *Noninvasive ventilation during exercise training improves exercise tolerance in patients with chronic obstructive pulmonary disease.* J Cardiopulm Rehabil, 2003. **23**(4): p. 307-13.
326. Palange, P., et al., *Recommendations on the use of exercise testing in clinical practice.* Eur Respir J, 2007. **29**(1): p. 185-209.
327. *ATS/ACCP Statement on cardiopulmonary exercise testing.* Am J Respir Crit Care Med, 2003. **167**(2): p. 211-77.
328. Dowson, L.J., et al., *Exercise capacity predicts health status in alpha(1)-antitrypsin deficiency.* Am J Respir Crit Care Med, 2001. **163**(4): p. 936-41.
329. Oga, T., et al., *Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status.* Am J Respir Crit Care Med, 2003. **167**(4): p. 544-9.
330. Carter, R., et al., *Peak physiologic responses to arm and leg ergometry in male and female patients with airflow obstruction.* Chest, 2003. **124**(2): p. 511-8.
331. LoRusso, T.J., et al., *Prediction of maximal exercise capacity in obstructive and restrictive pulmonary disease.* Chest, 1993. **104**(6): p. 1748-54.

332. Brown, S.E., et al., *Reproducibility of VO2max in patients with chronic air-flow obstruction.* Am Rev Respir Dis, 1985. **131**(3): p. 435-8.
333. Cox, N.J., et al., *Reproducibility of incremental maximal cycle ergometer tests in patients with mild to moderate obstructive lung diseases.* Lung, 1989. **167**(2): p. 129-33.
334. Silverman, M., et al., *Variability of the perceived sense of effort in breathing during exercise in patients with chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1988. **137**(1): p. 206-9.
335. Noseda, A., et al., *Lung function, maximum and submaximum exercise testing in COPD patients: reproducibility over a long interval.* Lung, 1989. **167**(4): p. 247-57.
336. Burki, N.K., *Dyspnea.* Lung, 1987. **165**(5): p. 269-77.
337. Killian, K.J. and N.L. Jones, *Mechanisms of exertional dyspnea.* Clin Chest Med, 1994. **15**(2): p. 247-57.
338. Schwartzstein, R. and L. Cristiano, *Qualities of respiratory sensation.* Respiratory sensation, ed. L. Adams and A. Guz. 1996, New York: Marcel Dekker Inc. 125-154.
339. Borg, G.A., *Psychophysical bases of perceived exertion.* Med Sci Sports Exerc, 1982. **14**(5): p. 377-81.
340. O'Donnell, D.E. and K.A. Webb, *Exertional breathlessness in patients with chronic airflow limitation. The role of lung hyperinflation.* Am Rev Respir Dis, 1993. **148**(5): p. 1351-7.
341. Belman, M.J., et al., *Variability of breathlessness measurement in patients with chronic obstructive pulmonary disease.* Chest, 1991. **99**(3): p. 566-71.
342. Mador, M.J., A. Rodis, and U.J. Magalang, *Reproducibility of Borg scale measurements of dyspnea during exercise in patients with COPD.* Chest, 1995. **107**(6): p. 1590-7.
343. Muza, S.R., et al., *Comparison of scales used to quantitate the sense of effort to breathe in patients with chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1990. **141**(4 Pt 1): p. 909-13.
344. Skinner, J.S., et al., *The validity and reliability of a rating scale of perceived exertion.* Med Sci Sports, 1973. **5**(2): p. 94-6.
345. O'Donnell, D.E., M. Lam, and K.A. Webb, *Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1998. **158**(5 Pt 1): p. 1557-65.
346. Yan, S., D. Kaminski, and P. Sliwinski, *Reliability of inspiratory capacity for estimating end-expiratory lung volume changes during exercise in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1997. **156**(1): p. 55-9.
347. Murariu, C., et al., *Exercise limitation in obstructive lung disease.* Chest, 1998. **114**(4): p. 965-8.
348. Polkey, M.I., et al., *Are voluntary manoeuvres maximal in routine clinical testing?* Am J Respir Crit Care Med, 1996(153:A785).
349. Kufel, T.J., L.A. Pineda, and M.J. Mador, *Comparison of potentiated and unpotentiated twitches as an index of muscle fatigue.* Muscle Nerve, 2002. **25**(3): p. 438-44.

350. Sinderby, C., et al., *Diaphragm activation during exercise in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2001. **163**(7): p. 1637-41.
351. Sinderby, C., et al., *Voluntary activation of the human diaphragm in health and disease.* J Appl Physiol, 1998. **85**(6): p. 2146-58.
352. Fukuba, Y., et al., *The curvature constant parameter of the power-duration curve for varied-power exercise.* Med Sci Sports Exerc, 2003. **35**(8): p. 1413-8.
353. *Standardization of Spirometry, 1994 Update. American Thoracic Society.* Am J Respir Crit Care Med, 1995. **152**(3): p. 1107-36.
354. Knudson, R.J., et al., *The maximal expiratory flow-volume curve. Normal standards, variability, and effects of age.* Am Rev Respir Dis, 1976. **113**(5): p. 587-600.
355. Gagnon, P., et al., *Impact of preinduced quadriceps fatigue on exercise response in chronic obstructive pulmonary disease and healthy subjects.* J Appl Physiol, 2009. **107**(3): p. 832-40.
356. Baecke, J.A., J. Burema, and J.E. Frijters, *A short questionnaire for the measurement of habitual physical activity in epidemiological studies.* Am J Clin Nutr, 1982. **36**(5): p. 936-42.
357. Serres, I., et al., *Impaired skeletal muscle endurance related to physical inactivity and altered lung function in COPD patients.* Chest, 1998. **113**(4): p. 900-5.
358. Voorrips, L.E., et al., *A physical activity questionnaire for the elderly.* Med Sci Sports Exerc, 1991. **23**(8): p. 974-9.
359. Babb, T.G., et al., *Effect of mild-to-moderate airflow limitation on exercise capacity.* J Appl Physiol, 1991. **70**(1): p. 223-30.
360. O'Donnell, D.E., et al., *Ventilatory assistance improves exercise endurance in stable congestive heart failure.* Am J Respir Crit Care Med, 1999. **160**(6): p. 1804-11.
361. Polkey, M.I., et al., *Inspiratory pressure support reduces slowing of inspiratory muscle relaxation rate during exhaustive treadmill walking in severe COPD.* Am J Respir Crit Care Med, 1996. **154**(4 Pt 1): p. 1146-50.
362. Krishnan, B., et al., *Lack of importance of respiratory muscle load in ventilatory regulation during heavy exercise in humans.* J Physiol, 1996. **490 (Pt 2)**: p. 537-50.
363. Levison, H. and R.M. Cherniack, *Ventilatory cost of exercise in chronic obstructive pulmonary disease.* J Appl Physiol, 1968. **25**(1): p. 21-7.
364. Pardy, R.L., et al., *The effects of inspiratory muscle training on exercise performance in chronic airflow limitation.* Am Rev Respir Dis, 1981. **123**(4 Pt 1): p. 426-33.
365. Kyroussis, D., et al., *Abdominal muscle fatigue after maximal ventilation in humans.* J Appl Physiol, 1996. **81**(4): p. 1477-83.
366. Moga, A.M., et al. *The effect of pressure support ventilation on operational lung volumes and breathing pattern in COPD and healthy individuals during exercise*. in *12th Rehabilitation Research Colloquium*. 2010. McGill University: McGill University Press.
367. Ranieri, V.M., et al., *Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation.* Am Rev Respir Dis, 1993. **147**(1): p. 5-13.

368. Martin, J.G., S. Shore, and L.A. Engel, *Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma.* Am Rev Respir Dis, 1982. **126**(5): p. 812-7.
369. Paton, J.Y., et al., *Expiratory muscle endurance and the oxygen cost of expiration in normal adults.* Am. Rev. Respir. Dis. , 1989. **139**(A345).
370. Lofaso, F., et al., *Evaluation of carbon dioxide rebreathing during pressure support ventilation with airway management system (BiPAP) devices.* Chest, 1995. **108**(3): p. 772-8.
371. Garrard, C.S. and C. Emmons, *The reproducibility of the respiratory responses to maximum exercise.* Respiration, 1986. **49**(2): p. 94-100.
372. Lord, S.R., et al., *The effect of a 12-month exercise trial on balance, strength, and falls in older women: a randomized controlled trial.* J Am Geriatr Soc, 1995. **43**(11): p. 1198-206.
373. Covey, M.K., et al., *Test-retest reliability of symptom-limited cycle ergometer tests in patients with chronic obstructive pulmonary disease.* Nurs Res, 1999. **48**(1): p. 9-19.
374. Ikeda, A., et al., *Oxitropium bromide improves exercise performance in patients with COPD.* Chest, 1994. **106**(6): p. 1740-5.