Effect of Pressure Support Ventilation on maximum exercise capacity in individuals with COPD

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DEDICATIONS

This thesis is dedicated to my lovely wife, Happiness, who has been my greatest gift in life; to my two lovely kids Delight and David, who do their best to keep me away from my books with humour and joy, and to my parents who taught me determination and focus.

ABSTRACT

RATIONALE: Non-invasive mechanical ventilation (NIMV) has been used as adjunct to exercise in pulmonary rehabilitation but its acute effect on maximum exercise capacity is not fully understood. Whether NIMV delivered during exercise using a level of ventilatory support titrated to comfort is better than a fixed level of assist is also unknown.

OBJECTIVE: The objective of the current study was to evaluate the effect of a fixed and an individually optimized level of pressure support ventilation (PSV) delivered during a symptom-limited incremental bicycle test on maximum exercise capacity, breathing pattern, end-expiratory lung volume (EELV), metabolic parameters, exercise limiting symptoms and respiratory comfort in individuals with COPD.

METHODS: Individuals with stable COPD, who do not use supplemental O_2 and without known conditions that could limit exercise were recruited. Participants performed three incremental bicycle exercise tests (workload increased by 5 watts/minute) until exhaustion. Tests, separated by 48 hours, were performed in a randomized order (i) without a ventilator (NV), (ii) with 10cmH_2O PSV (PSV10) and (iii) with PSV level titrated to patient comfort (PSVt) using a Maquet SERVO-i ventilator in a crossover design. Maximum exercise workload (WLmax), breathing pattern, mouth pressure (Pmo), EELV, metabolic parameters, dyspnea, leg effort, and respiratory comfort were measured and compared using a one-way ANOVA.

RESULTS: Eleven individuals (8 males, 3 females) with COPD (FEV_1: 49±16% predicted; age: 64±7 years) were studied. The mean PSVt level was 8.2 ± 4.5 cmH_2O. There was no difference in the WLmax achieved during the three tests. At rest, PSV10 increased tidal volume ($p=0.001$) compared to NV, whereas PSVt did not. Inspiratory duration was lower ($p=0.009$; $p=0.004$), minute ventilation higher ($p=0.001$; $p=0.02$), mean inspiratory flow higher ($p<0.001$; $p=0.006$), EELV higher ($p=0.003$; $p=0.002$), and end-tidal CO_2 lower ($p<0.001$; $p=0.005$) with PSV10 and PSVt, respectively. These differences were not observed at peak exercise. Oxygen uptake, Carbon dioxide production, exercise limiting symptoms at peak exercise, and respiratory comfort were not different between the three tests. Mean inspiratory Pmo was lower at peak exercise compared to resting breathing (PSV10: $p=0.034$, PSVt: $p<0.001$) and to 50% of WLmax (PSV10: $p<0.006$, PSVt: $p<0.001$), despite sustained peak Pmo values. These results suggest that the respiratory muscle unloading, evident with PSV at rest, progressively decreased with increasing exercise.

CONCLUSION: Titrated and fixed levels of assist using non-invasive PSV did not improve WLmax due to a progressive decrease in respiratory muscle unloading as exercise intensity increased.

ABRÉGÉ

RATIONNEL: La ventilation mécanique non-invasive (VMNI) est utilisée comme thérapie complémentaire à la réadaptation pulmonaire. Toutefois, son effet sur la capacité maximale d'exercice n'est pas entièrement compris. En effet, l'impact de la VMNI fourni lors de l'exercice en utilisant un niveau de support ventilatoire ajusté au confort, plutôt qu'un niveau fixe demeure inconnu.

L'objectif de la présente étude est d'évaluer l'effet d'un niveau de ventilation de pression de support (VPS) fixe et optimisé individuellement durant un exercice de capacité maximal avec symptômes limités sur bicyclette, le profile respiratoire, les volumes pulmonaires en fin d'expiration, les paramètres métaboliques, les symptômes limitant l'exercice et le confort respiratoire chez les personnes atteintes de maladie pulmonaire obstructive chronique (MPOC).

MÉTHODES: Les personnes avec MPOC stable, n'utilisant pas d'oxygène supplémentaire et sans autres problèmes médicaux connues affectant la capacité à faire de l'exercice ont été recrutées. Les participants ont effectué trois épreuves d'effort à vélo (charge augmentée de 5 watts / minute) jusqu'à l'épuisement. Les épreuves, effectués à intervalle de 48 heures, ont été réalisés dans un ordre aléatoire: 1) sans ventilateur (SV), 2) avec 10cm H_2O VPS (VPS10) et 3) un niveau de VPS ajusté selon le confort du patient (VPSt) en utilisant ventilateur Maquet SERVO-i utilisant un plan d'étude croisé. La charge de travail maximale d'exercice (WLmax), le profile respiratoire, la pression buccale, les volumes pulmonaires en fin d'expiration, les paramètres métaboliques, la dyspnée, l'effort de la jambe et le confort respiratoire ont été mesurés et comparés à l'aide d'une analyse de variance à un facteur.

RESULTATS: Onze personnes (8 hommes, 3 femmes) avec MPOC ($VEMS_1$: 49 ± 16 % prédit; âge : 64 ± 7 ans) ont été étudiés. Le niveau VPSt moyen était de 8,2 ± 4,5 cm de H_2O. Aucune différence n'a été mesurée dans la WLmax dans les trois tests. Au repos, avec VPS10 le volume courant a augmenté en comparaison avec le SV ($p = 0.001$), alors que le VPSt demeure in-changé. La durée inspiratoire était plus basse ($p=0.009$; $p=0.004$), la ventilation minute plus élevée ($p=0.001$; $p=0.02$), le débit inspiratoire moyen plus haut ($p<0.001$; $p=0.006$), les volumes pulmonaires en fin d'expiration plus élevés ($p=0.003$; $p=0.002$), and CO_2 de fin d'expiration plus bas ($p<0.001$; $p=0.005$) avec le VPS10 et VPSt respectivement. Ces différences n'ont pas été observées lors de l'exercice maximal. La consommation d'oxygène, la production de dioxyde de carbone, les symptômes limitant l'effort maximal de pointe et le confort respiratoire n'étaient pas

différents entre les trois épreuves. La pression buccale inspiratoire moyenne était inférieure pour l'exercice maximal comparé à la respiration au repos (VPS10: $p = 0.034$, VPSt: $p < 0.001$) et à 50 % de WLmax (VPS10: $p < 0.006$, VPSt: $p < 0.001$), malgré des valeurs de pression buccale maximales soutenues. Ces résultats suggèrent que le déchargement des muscles respiratoires, évident avec le VPS au repos, diminue progressivement avec l'augmentation de l'exercice.

CONCLUSION : Les niveaux d'assistance titrée et fixe utilisant une ventilation non-invasive n'a pas améliorés la WLmax dû à une diminution progressive de la décharge des muscles respiratoires avec l'augmentation de l'intensité de l'exercice.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
BiPAP	Bi-level positive airway pressure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EELV	End-expiratory lung volume;
FEV_1	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
GOLD	Global initiative for chronic Obstructive Lung Disease
IC	Inspiratory capacity
NIMV	Non-invasive mechanical ventilation
PAV	Proportional assist ventilation
PEEPe	Extrinsic positive end-expiratory pressure
PEEPi	Intrinsic positive end-expiratory pressure
Pmo	Mouth pressure
PSV	Pressure support ventilation
RR	Respiratory rate
SaO_2	Arterial Oxygen saturation
Te	Expiratory time
Ti	Inspiratory time
VCO_2	Carbon dioxide production
V_E	Minute ventilation
VO_2	Oxygen consumption
VT	Tidal volume
WLmax	Maximum exercise capacity
PSV10	Pressure support ventilation of 10 cm H_2O
PSVt	Pressure support ventilation titrated to comfort

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PREFACE

This study was born out of the passion to make contribution to knowledge that will improve the life of people with Chronic Obstructive Pulmonary Disease (COPD). This patient population is commonly limited in their ability to do exercise which leads to a vicious cycle of functional decline. Pulmonary rehabilitation which incorporates exercise training has been shown to improve functional outcome in COPD, but exercise intolerance can limit their maximal benefit from any pulmonary rehabilitation program. It has also been shown that ability to do exercise is the largest single predictor of mortality in this patient population. Exercise tolerance in COPD can be secondary to ventilatory limitation or limitation due to muscle fatigue. This study evaluated the effect of using NIMV as an adjunct to increase maximum exercise performance in people with COPD. Non-invasive mechanical ventilation is anticipated to ameliorate the ventilatory component of their exercise limitation and to improve exercise performance.

Chapter one of the thesis contains an introduction. Chapter two is a review of literature on COPD. Chapter three contains the rationale for the manuscript, chapter four is the manuscript entitled “Effect of Pressure Support Ventilation on Maximum Exercise Capacity in Individuals with COPD”, and chapter five is the conclusion.

AUTHORS CONTRIBUTION

Anekwe, David was responsible for coordinating the overall activities of the study including arranging for recruitment, scheduling of the tests, running of the study, as well as data collection and analysis and writing of the manuscript. Dr. Spahija supervised and assisted throughout the study period to ensure the quality of the study and an accurate delivery of NIVS during exercise. She also provided holistic and procedural guidance throughout the study, assisted in patient recruitment and during the studies, proofread and edited all documents as well as the final thesis. Dr. de Marchie conducted the medical screening of all recruited participants, provided clinical supervision during the exercise tests, and offered necessary feedback and advice before and during the study. He also reviewed the thesis and documents that were translated into French.

CHAPTER ONE: INTRODUCTION

1. BACKGROUND

Breathing is one of the most vital and important functions of human life. According to the Public Health Agency of Canada [1], there is no life without breath. Life decreases in quality and expectancy when adequate breath can no longer be maintained or sustained. Yet for individuals with chronic obstructive pulmonary disease (COPD), breathing is a difficult task and forms the basis on which the disease progresses and gives rise to systemic consequences that can lead to disability and death. COPD is a pulmonary condition that is characterized by chronic obstruction of lung airflow [2] that is usually progressive [3] and is not fully reversible [2].

Individuals with COPD develop lung and airway impairments and ventilatory limitations, which limit their ability to do exercise [4, 5], and in turn contribute to a vicious circle of physical inactivity that negatively impacts health-related quality of life [6]. COPD currently has no cure; therefore, for the management of the disease, emphasis is placed on decelerating the rate of decline in lung function and physical ability, as well as improving symptoms and health-related quality of life [7].

There is strong scientific evidence for the use of physical exercise training to improve health-related quality of life and functional capacity in individuals with COPD [8]; but, unfortunately, many such individuals are limited in the extent to which they can benefit from physical exercise training because of exercise intolerance [9-11]. In response, a number of adjuncts to exercise training have been developed in an attempt to improve exercise tolerance in individuals with COPD [9-11].

Non-invasive mechanical ventilation (NIMV) is one of the adjuncts suggested for use during physical training , however, findings from a recent study [12], which looked at the acute effect of non-invasive ventilatory support on maximum exercise capacity in individuals with COPD, revealed that bi-level positive airway pressure (BiPAP) ventilation using a standard exhalation device resulted in a reduced maximum exercise capacity compared to no ventilatory assist. The BiPAP ventilator has single limb tubing for inspiration and expiration, making it prone to CO_2 re-breathing during ventilation with a standard exhalation device. Re-breathed CO_2 can stimulate

breathing, increasing the work of breathing, and subsequently decreasing maximum exercise capacity. Use of a plateau valve has been proposed in order to help alleviate CO_2-rebreathing during BiPAP ventilation, although use of such a valve may also add some resistance during expiration [12,13]. The Maquet SERVO-i ventilator has a separate limb for inspiration and expiration and hence does not pose the risk of CO_2 re-breathing during ventilation. Some earlier studies [13, 14] that evaluated the acute effects of mechanical ventilation during exercise used a fixed level of inspiratory assist. To date, however, it is unknown whether a fixed level of inspiratory assist or an individually tailored level of inspiratory is optimal in the use of NIMV as an adjunct to exercise training in COPD patients. The purpose of the current study is to evaluate the effect of a fixed level and an individually optimized level of pressure support ventilation, delivered during a symptom-limited incremental bicycle test, on maximum exercise capacity, breathing pattern, metabolic parameters and exercise limiting symptoms in individuals with moderate to severe COPD in comparison to unassisted exercise.

CHAPTER TWO: LITERATURE REVIEW

2. CHRONIC OBSTRUCTIVE PULMONARY DISEASE

2.1 What is COPD?

COPD is a common and preventable lung disease characterized by persistent airflow limitation that is usually progressive, not fully reversible, and associated with enhanced chronic inflammatory response in the airways and lungs to noxious particles and gases [2, 3]. This definition, which comes partly from the Global Initiative for Chronic Obstructive Lung Diseases (GOLD), shows that airflow limitation in COPD is caused by pathologies of the airways and lungs. In the airways, there may be structural changes (remodelling) and narrowing of small airways resulting from chronic inflammation [15-17], while in the lungs, there may be loss of elastic recoil due to destruction of lung parenchyma and alveolar attachments to the small airways as a result of inflammatory processes [16, 18]. The occurrence of COPD is secondary to the presence of two distinct independent disease pathologies, chronic bronchitis and emphysema [3]. Chronic bronchitis refers to chronic or recurrent excessive mucous secretion in the bronchial tree, diagnosed clinically by the presence of a cough with expectoration for three months in two consecutive years that is not attributable to other lung diseases [3, 19]. Individuals with chronic bronchitis can present with normal spirometry and no evidence of airflow limitation [3, 20]; but when the chronic inflammation in chronic bronchitis causes structural changes and narrowing of small airways resulting in airflow limitation with FEV_1/FVC ratio less than 70%, then a diagnosis of COPD can be made. Emphysema, which is the abnormal permanent enlargement of the airspaces distal to the terminal bronchioles accompanied by destruction of their walls and without obvious fibrosis, is also one of many other pathological processes leading to the development of airflow limitation [3]. COPD may also include chronic asthma, bronchiolitis and cystic fibrosis. Asthma ordinarily consists of reversible airflow limitation. In its chronic form, however, repeated airway inflammation and bronchial hyper-responsiveness result in hypertrophy and remodelling of the smooth muscles of the airways, which causes narrowing of the airways and obstruction of airflow that is not fully reversible [21].

2.2 Diagnosis and Classification of COPD

The diagnosis for COPD is objectively made based on findings from spirometry [22]. Persistent airflow limitation is confirmed by as post bronchodilator FEV_1/FVC ratio that is less than 70% [3]. Peak expiratory flow rate is another test that can be used to screen and detect individuals with COPD in the community [22]. Peak expiratory flow rate has a high sensitivity for detecting individuals with airflow limitation, but its appreciable rate of false positive results makes its specificity low [3, 22]; therefore, the British Thoracic Society and the Global Initiative for Chronic Obstructive Lung Disease do not recommend it alone for diagnosing patients as having COPD [3, 22].

Clinically, COPD can be suspected on the basis of a patient's symptoms and from other key indicators that can be obtained from the subjective history of the patient. The Global Initiative for Chronic Obstructive Lung Disease recommends that COPD be considered if a patient above 40 years of age presents with any of the following conditions: (i) dyspnea that is progressive, persistent, or worse with exercise, (ii) chronic cough, (iii) chronic sputum production, (iv) history of smoking or exposure to dust, chemicals and smoke from biofuels, or (v) a family history of COPD [3]. Fatigue, weight loss, anorexia, wheezing, chest tightness and prolonged lung infections are other symptoms that may be associated with COPD [3, 23].

Classification of the severity of COPD is based on the post bronchodilator FEV_1 values of the individual after airflow limitation has been objectively ascertained. Four classes—mild, moderate, severe and very severe— are known according to the GOLD classification shown in Table 2.1 below.

Table 2.1 : Classification of the Severity of Airflow Limitation in COPD (Based on Post Bronchodilator FEV_1 in Patients with FEV_1/FVC < 0.7)

GOLD 1 : Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2 : Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3: Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4: Very Severe	$FEV_1 < 30\%$ predicted or <50% normal with chronic respiratory failure present

FEV_1 = Forced Expiratory Volume in one second, FVC = Forced Vital Capacity
Adapted from Gold Guidelines [3]

2.3 Epidemiology of COPD

2.3.1 Incidence

Studies on the incidence of COPD have reported a wide variation because of the differences in the definition of COPD used [24, 25]. Based on the GOLD definition of COPD, Johannessen et al [26] reported an incidence of 7 per 1000 of the general population from a 9-year cumulative incidence of COPD in a Norwegian community. Data from a self-reported COPD database in Canada showed a decrease in the incidence of COPD from 11.5/1000 to 8.5/1000 annually between 1996 and 2007 [27]. Though the definition of COPD in this database is based on International Classification Diseases codes, the reported incidence in the Canadian population study is higher than that from the Norwegian community.

2.3.2 Prevalence

The 2008 Global Burden of Disease publication of the World Health Organization estimated that 64 million people had COPD in 2004 [28]. An international survey, the Burden of Obstructive Lung Disease (BOLD), estimated a global prevalence of 10.1% for stage II COPD severity or higher [29]. Data from a Canadian study which covered the period of 1996 to 2007 showed a 64.8% increase in prevalence of COPD despite a decrease in its incidence within the same 11-year period [27]. Increasing prevalence despite decreasing incidence may be the result of increased scientific knowledge and improvement in medical care that has helped individuals with COPD to live longer. Statistics from the Public Health Agency of Canada showed the highest prevalence of COPD to be in individuals aged 75 years and above [30, 31]. A 2011 report from Statistics Canada [32] revealed that about 779,355 individuals (4.1% of Canadians) consisting of 319,753 (3.5%) males and 459,602 (4.7%) females reported having had a clinician diagnose COPD. Available evidence suggests that the prevalence and severity of COPD is underreported by as much as 50% in individuals aged 40 years and above [31, 33]. The 2008 Lung Association COPD research reported about 1.5 million Canadians with COPD [34], while their previous estimates from the Lung Health Test [35] estimated about 3.1 million Canadians with the disease [34], corresponding to about 50% underreporting as speculated by the Public Health Agency of Canada [31].

2.3.3 Morbidity and Mortality

COPD is a major cause of chronic morbidity and mortality across the world [24, 36, 37]. The World Health Organization reported about 3 million deaths from COPD in 2005 alone, and this number comprised 5% of all global deaths from all sources in the same year [28]. A United States study showed that in the year 2000, COPD was responsible for 8 million physician office and hospital outpatient visits, 1.5 million emergency department visits, 726,000 hospitalizations, and 119,000 deaths within United States alone [38]. Epidemiologic data shows that COPD moved to become the fourth leading cause of death in the year 2004 [39, 40], and it is predicted to become the world's third leading cause of death by the year 2030 [41]. In 1990, COPD was identified as the twelfth leading cause of Disability-Adjusted Life Year(s) (DALYs – a metric that combines years of life lost due to a disease [mortality] and years lived with disability due to same disease [morbidity]), and it is projected to become the seventh leading cause of DALYs worldwide by the year 2030 [42].

2.3.4 Burden

According to a study published by the World Bank/WHO, COPD is projected to rank fifth worldwide in the burden of diseases by the year 2020 [3]. A report on the economic burden of COPD in Canada shows an annual hospitalization cost of about $1.5 billion a year [43], while in the United States, the Morbidity and Mortality: 2012 Chart Book of the National Heart, Lung and Blood Institute put the cost associated with the burden of COPD/Asthma at $68.0 billion [44]. The 2009 Chart Book of the same institute estimated a total of $49.9 billion as the direct and indirect costs associated with the burden of COPD alone [3].

The implication of all these findings is that COPD continues to be a common and important health problem among Canadian adults and worldwide, and the number of individuals with COPD is likely to increase as the population ages [31]. This projection calls for a concerted effort in tackling the challenge to help the growing number of aging Canadian adults and the world at large to improve their quality of life despite the physiological consequences of this disease.

2.4 Pathology, Pathogenesis and Pathophysiology of COPD

2.4.1 Lung and Airways Impairment

The Global Initiative for Chronic Obstructive Lung Diseases (GOLD) describes two major mechanisms of airflow limitation in COPD: i) loss of elastic recoil of the lungs due to destruction of the lung parenchyma and its alveolar attachments to the small airways by inflammatory processes [16, 18] and ii) structural changes (remodelling) and narrowing of small airways resulting from chronic inflammation [15-17].

2.4.1.1 Destruction of the Lung Parenchyma

The pathogenesis of COPD is associated with damage of the lung tissue caused by exaggerated chronic inflammatory response to noxious gases [3, 45]. Inhaled cigarette smoke has been identified as the major trigger for this exaggerated inflammatory response [3, 45-48]. Other noxious gases and indoor pollution, such as smoke from biomass fuel, have been identified as potential precursors of this exaggerated inflammatory response [3, 46, 49]. One predominant characteristic feature of the exaggerated inflammatory response in COPD is the persistent presence of the inflammatory cells (T cells) in the lungs years after the initial assault from the cigarette smoke has been stopped [36, 50-52]. Amplification of this inflammatory repair response in the lung tissues has been linked to an abnormality of the immune system (autoimmune disease) [47, 53, 54] that is most likely genetically determined [3, 48, 55]. The amplified inflammatory response interferes with tissue repair in the lungs [56]. Interruption of the tissue repair process predisposes the lungs to irreversible destruction of the lung parenchyma (emphysema) from injury imposed by cigarette smoke and other noxious gas particles [4, 57]. The destruction of the lung parenchyma leads to the loss of parenchymal alveolar attachments to the distal airways [55, 58, 59], thus predisposing them to narrowing and closure during the expiratory phase of breathing [3, 48, 55] (Figure 2.1).

Destruction of the elastic fibers of the lung parenchyma can also occur without the trigger factor of cigarette smoke or noxious gases in individuals with Alpha 1-antitrypsin deficiency. Alpha 1-antitripsin deficiency is a genetic disorder in which deficiency of the elastase inhibitor causes an autoimmune breakdown of the elastic fibers of the lungs by elastase [60]. This may accelerate the onset of COPD in smokers or result in COPD even in non-smokers. Individuals with COPD resulting from Alpha 1-antitrypsin deficiency therefore have a different form of COPD from

smokers, because of the difference in pathogenesis (though the two forms of the same disease can coexist).

2.4.1.2 Chronic Inflammation of the Airways

The exaggerated chronic inflammatory response to cigarette smoke in COPD is not limited to the lung parenchyma. The peripheral and central airways are not spared from the exaggerated inflammatory process [48, 55]. In the small airways, the chronic inflammation results in thickening and distortion of the airway wall (fibrosis) and occlusion of the airway lumen by mucus and inflammatory exudates [48, 55, 61] (Figure 2.1). The consequence of these events is narrowing of the lumen of the small airways and concomitant increase in airway resistance. In the central airways, a similar process as in the small airways takes place, with mucus gland hypertrophy, hypersecretion and cilliary dysfunction [48, 55, 61, 62]. The resulting obstruction to airflow from these processes and the increased airflow resistance are contributors to the almost irreversible airflow obstruction seen in COPD.

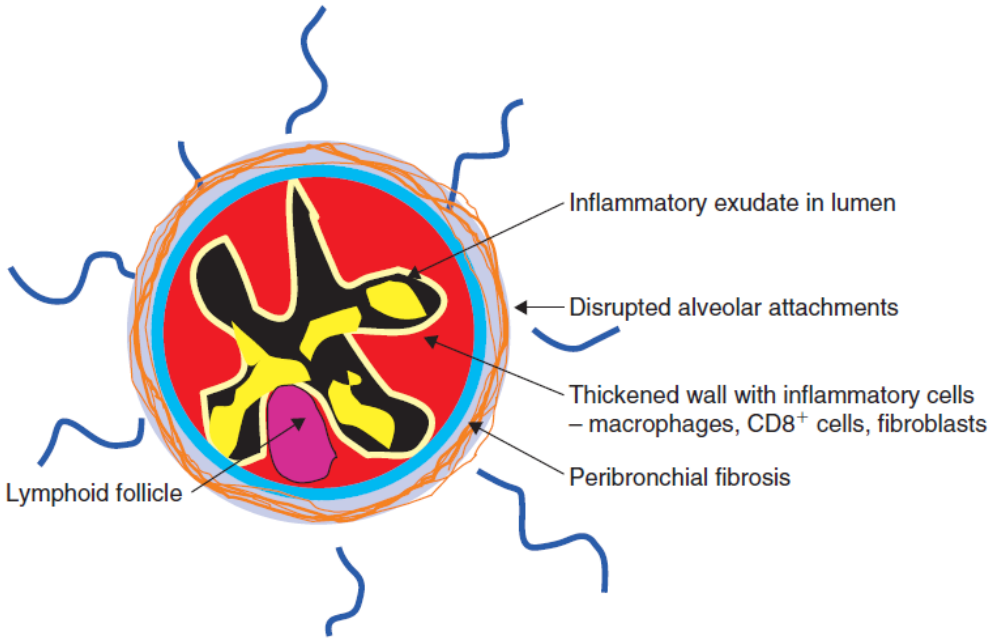


Figure 2.1: Mechanism of airflow limitation in small airway of COPD patients

Small airways are obstructed as a result of loss of alveolar attachments, thickening and distortion of the airway wall resulting from inflammation and fibrosis, and occlusion of the airway lumen by mucus and inflammatory exudates. Adapted from Barnes [48]

2.4.2 Hyperinflation

One of the net effects of the above-mentioned pathological changes is static hyperinflation and air trapping within the lungs [59]. Hyperinflation is an abnormal increase in the volume of gas resident in the lungs at the end of tidal expiration (which implies increase in the functional residual capacity [FRC] of the lungs) [63]. Destruction of the alveolar walls of the lung parenchyma causes a decrease in the elasticity of the lungs [55] and results in marked distal airspace enlargement [56] due to air trapping. During normal breathing, FRC is determined at the balance between the outward recoil pressure of the chest wall and the inward recoil pressure of the lungs [59]. With decreased elasticity of lungs, the equilibrium between the inward elastic recoil pressure of lungs and the outward recoil pressure of the chest cage is reset at a higher resting FRC [5, 59], which results in static hyperinflation [59] (Figure 2.2).

Beyond static hyperinflation, COPD patients also develop dynamic hyperinflation [4, 59], which can occur in addition to or independent of static hyperinflation [59]. Dynamic hyperinflation is a key component of COPD pathology in patients with all severities of COPD, unlike static hyperinflation whose adverse effect is eventful mainly in patients with very severe COPD (GOLD 4) and individuals with α_1-antitrypsin deficiency [59]. Expiratory airflow obstruction in COPD increases the time needed for expiration; and with increased respiratory rate (as is common during exercise), inspiration commences before full expiration of the preceding tidal volume is achieved leading to dynamic hyperinflation [4, 64]. Consequently, the end-expiratory lung volume (EELV) is no longer at the point of equilibrium between the inward elastic recoil pressure of the lungs and the outward recoil pressure of the chest cage (because full exhalation is not achieved). This leads to further air being trapped within the lungs with each breath and development of an intrinsic positive end-expiratory pressure (PEEPi) at the end of expiration [59].

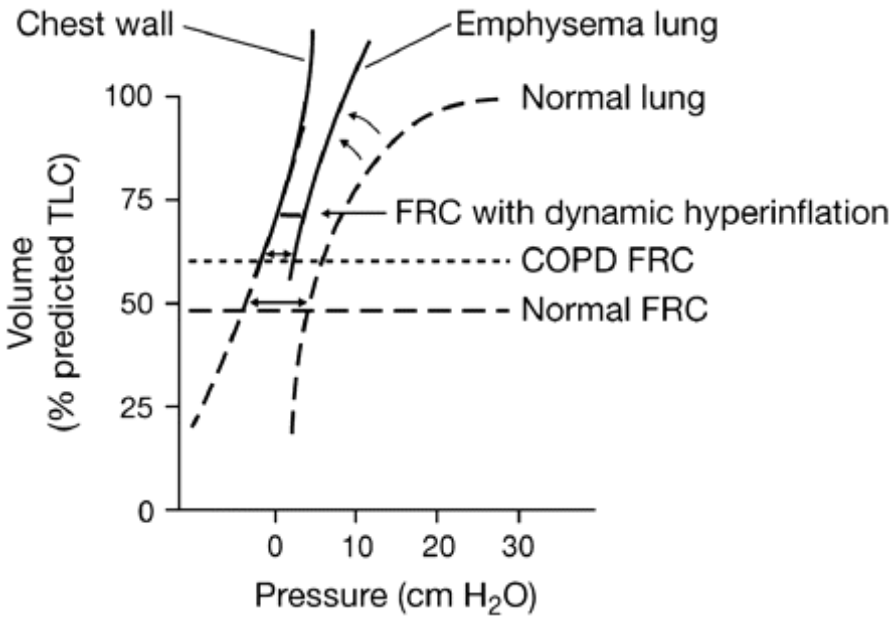


Figure 2.2: Effect of decreased elastic recoil pressure of the lungs on FRC

FRC in normal lungs occurs at the lung volume where equilibrium between recoil pressures of the chest wall and lungs is achieved with the respiratory muscles at rest (long-dashed lines). This is also called the resting volume. Loss of lung elasticity due to emphysema in COPD reduces the lung recoil pressure. Consequently, FRC or resting volume occurs at a higher volume, which defines static hyperinflation (short-dashed lines). Dynamic hyperinflation occurs when end-expiratory lung volume (EELV) or FRC is unable to return to the resting volume, resulting in a positive end-expiratory pressure (PEEP). TLC = total lung capacity. From Ferguson et al [59]

2.4.2.1 Adverse Effect of Hyperinflation on the Respiratory System

Hyperinflation causes several deleterious effects to the respiratory system and the mechanics of breathing. Hyperinflation increases PEEPi, which necessitates an increased inspiratory pressure to be generated before inspiratory airflow can occur [59, 65], thus increasing the elastic work of breathing [4, 59].

The diaphragm is shaped like a parachute and operates from a mechanically highly advantageous position by virtue of its shape and insertion on the costal margins of the ribs, the sternum, xiphoid process and the vertebrae. During inspiration, contraction of the diaphragm causes the dome to move caudally, expanding the chest cavity at a low energy cost of breathing. In COPD, hyperinflation causes an increase in the cephalic to caudal dimension of the chest cavity. This

results in depression of the diaphragm dome and shortening of the muscle. The altered diaphragm functional position decreases the range of motion of its piston-like movement during inspiration and impedes its inspiratory action [66].

Changes in chest wall geometry due to hyperinflation also causes a decrease in the zone of apposition of the diaphragm [67]. The reduction in the zone of apposition reduces the area of the rib cage that is exposed to the positive abdominal pressure produced by diaphragmatic contraction, limiting the capacity of the diaphragm to produce rib cage expansion [68].

Hyperinflation also reduces the pressure-generating ability of the intercostal inspiratory muscles, such as the parasternal intercostals [69]. This reduction is partly due to the length-tension relationship as seen in the diaphragm, but also due to the fact that the direction of rib displacement is altered in hyperinflation[70]. This change in intercostal muscle orientation with increasing lung volume affects the effectiveness of the muscles in pulling the ribs cranially.

2.4.3 Pulmonary Gas Exchange Abnormalities in COPD

The destruction of the alveolar walls of the lungs in individuals with COPD also results in pulmonary gas exchange abnormalities [37]. Since the alveolar surfaces are the predominant areas for gas exchange in the lungs, destruction of the alveolar walls results in a smaller surface area available for gaseous exchange. There is, as well, accompanying destruction of the pulmonary capillary bed in areas of alveolar wall destruction [37, 71]. Loss in gas exchange surface area can decrease gaseous exchange and the effect of the loss in the pulmonary capillary bed is ventilation to perfusion (V/Q) mismatching [4, 72]. Wagner et al [73] showed that COPD patients with predominantly emphysematous pathology have increased ventilation of poorly perfused lung units (i.e., a high V/Q ratio) and hence increased physiological dead space. Since the level of destruction of parenchymal, alveolar wall, and pulmonary capillary bed progresses with the disease, the V/Q mismatch is more pronounced in advanced cases of the disease [37, 74]. During exercise, alveolar hypoventilation secondary to dynamic hyperinflation [75] leads to poor ventilation of perfused lung areas (i.e. low V/Q ratio). The resulting V/Q mismatch is another contributory factor to exertional hypoxemia in COPD [37]. Pulmonary gas exchange abnormalities can lead to the development of chronic arterial hypoxemia as the disease condition progresses [37].

Chronic hypoxemia in COPD patients can lead to a cascade of adverse sequelae. One of the adverse effects of hypoxia is pulmonary hypertension [37, 76]. Pulmonary hypertension occurs secondary to vasoconstriction resulting from hypoxemia [37, 61, 77, 78]. Pulmonary hypertension can also be as a result of emphysematous obliteration of the pulmonary capillary bed in COPD [37, 61, 76]. Chronic hypoxia can also lead to secondary polycythemia [37, 76], systemic inflammation, and skeletal muscle dysfunction [37]. These factors contribute to diminished quality of life, reduced exercise tolerance, increased risk of cardiovascular morbidity, and greater risk of death in the population of people with COPD [37].

2.4.4 Work of Breathing in COPD

Several factors such as shortened inspiratory muscles, increased resistance to airflow and intrinsic PEEP contribute to increased work of breathing in COPD. Shortening of the fibres of the diaphragm secondary to hyperinflation reduces the efficiency of the diaphragm as a pressure generator which requires a greater neural input to generate air inflow during inspiration. Reduced airway diameter results in increased inspiratory flow resistance, which increases the workload against which the respiratory muscles must work to ventilate the lungs. Patients with COPD have been reported to have a more than a fourfold increase in inspiratory flow resistance compared to healthy individuals [79]. Intrinsic PEEP also requires greater force generation by the inspiratory muscles before inspiratory flow can begin thereby increasing the work of breathing [80]. In individuals with COPD who have impaired gas exchange, resting minute ventilation is increased to compensate for impaired gas exchange [81] and this increase can also contribute to increase in the work of breathing.

All these factors contribute to an increased demand on the respiratory system of individuals with COPD, making the system overlaboured, ineffective, and inefficient. In an effort to maintain respiration despite these abnormalities, there is an associated increase in the respiratory muscle work of breathing that is accompanied by an increase in neural respiratory drive; and these two factors contribute to the development of the feeling of dyspnea, which is often a limiting factor to exercise in individuals with COPD [4, 5].

2.5 Exercise Intolerance

Individuals with COPD are therefore limited in their ability to do exercise by dyspnea secondary to increased wok of breathing (ventilatory limitation) [82, 83], or by leg fatigue resulting from skeletal muscle dysfunction secondary to systemic inflammation [83, 84].

2.5.1 Ventilatory Limitation to Exercise

In individuals with moderate to severe airflow obstruction, dyspnea (breathlessness) has been noted as the primary symptom that limits their ability to exercise [4, 85, 86]. Dyspnea, which is a sensation of difficulty in breathing, is generated by neuromechanical uncoupling resulting from a neural respiratory output in the brain not being commensurate with the mechanical response of the ventilatory system [4, 87]. During exercise, dynamic hyperinflation is the principal precursor of this neuromechanical dissociation which, in turn, gives rise to dyspnea limitation during exercise performance [88].

2.5.1.1 Reduced Ventilatory Capacity

During exercise in healthy adults, the ventilatory system responds to the increased metabolic demands of exercise by first increasing the depth of breathing, followed by an increased respiratory rate. In contrast, individuals with COPD tend to increase minute ventilation by predominantly increasing their respiratory rate. This results in less time being available for expiration, which consequently leads to air trapping within the lungs (dynamic hyperinflation). The resulting dynamic hyperinflation causes a reduction in the inspiratory reserve volume and further limits the ability to increase tidal volumes, thereby limiting the ability of the respiratory system to meet the ventilatory requirements of the exercise and limiting exercise capacity [89].

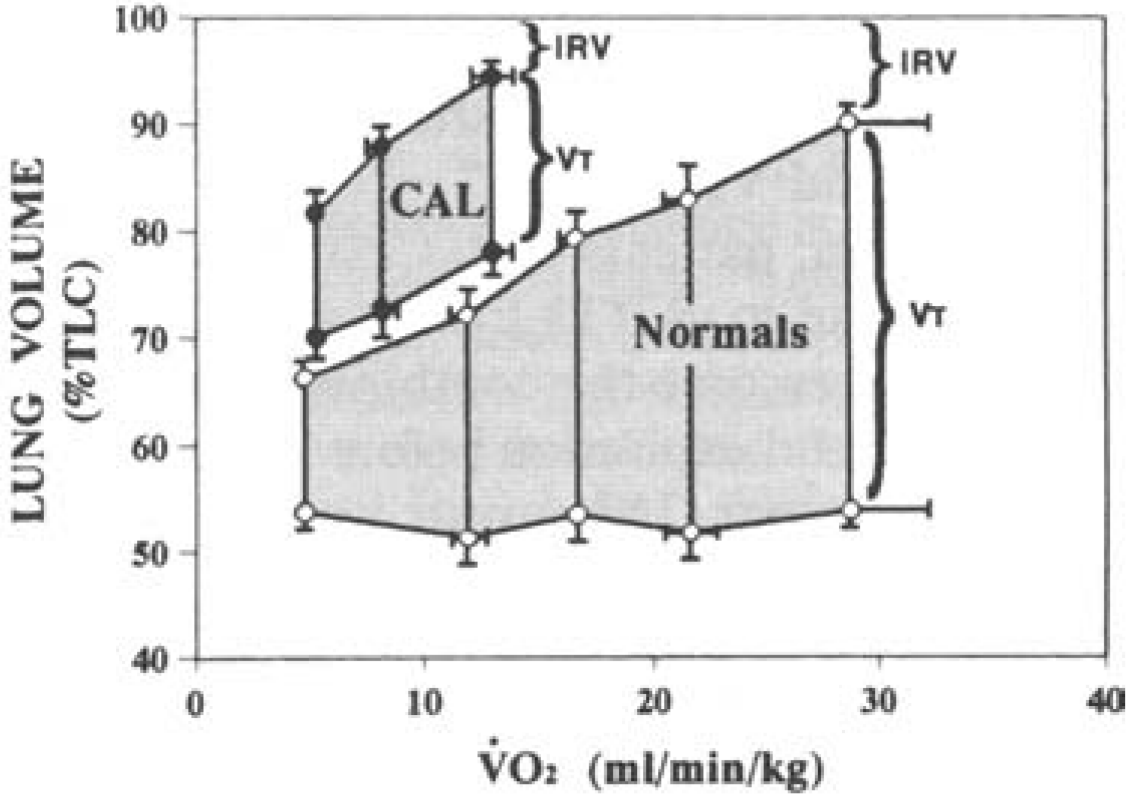


Figure 2.3: Limited ventilatory increase in COPD

Secondary to hyperinflation, V_T cannot increase and respond to increased ventilatory demands when there is a need for increase in VO_2. CAL = Chronic Airflow Limitation. Adapted from O'Donnell [90]

2.5.1.2 Hypoxemia secondary to alveolar hypoventilation

COPD patients may be hypoxemic at rest or develop oxygen desaturation with exercise [91]. At rest, hypoxemia occurs secondary to a ventilation-to-perfusion mismatch that results from destruction of the gas exchanging alveolar walls and from obstructed airways[91]. Hypoxemia can be further worsened during exercise in COPD patients with a pre-existing V/Q mismatch because of the decreased transit time of blood through the pulmonary capillaries as cardiac output increases [91]. In severely affected COPD patients, increased ventilatory demands from normal activities of daily living can worsen gas exchange abnormalities and lead to hypoxemia [92]. Exercise-induced hypoxemia has been noted as a possible exercise-limiting factor in both COPD patients [93] and normal subjects [94-96]. Hypoxemia results in increased ventilatory

drive, vascular bed dilation, increased cardiac output, and tachycardia [91], all of which can affect maximum exercise capacity. Chronic hypoxemia can also result in pulmonary hypertension (secondary to hypoxic vasoconstriction of the pulmonary vasculature) and *cor pulmonale*, which affects cardiac output and oxygen delivery and results in a decrease in the functional exercise reserve [97].

2.5.2 Limitation to Exercise Secondary to Leg Fatigue

Other than the respiratory limitation to exercise in COPD patients, leg fatigue [9] secondary to peripheral muscle dysfunction or reduced peripheral oxygen delivery [11] also contributes to exercise limitation in this patient group.

2.5.2.1 Peripheral Muscle Dysfunction

Peripheral muscle dysfunction is another limiting factor to exercise capacity in individuals with COPD [98-101]. It is associated with reduced muscle strength [102-104] and endurance [105-107], as well as increased contractile fatigability [83, 106]. The mechanism of peripheral muscle dysfunction includes, but is not limited to, a shift in the number of predominantly energy efficient type I fibers to a predominance of fatigue-prone type II fibers [106, 108]. This shift is accompanied by a decrease in oxidative capacity [109] because of the shift from oxidative to glycolytic fibers [106, 110], a decrease in mitochondrial density [111], and decreased capillarization [108, 112].

2.5.2.2 Peripheral Oxygen Delivery

The evidence available shows that decreased oxygen supply to the exercising peripheral muscles is a contributory factor to exercise limitation in COPD [100, 113-115]. In individuals with COPD, expiratory pressures may increase excessively during increased ventilatory efforts due to expiratory flow limitation, and this occurs along with an increase in intrathoracic pressure (increase in abdominal, pleural and alveolar pressures), thereby limiting venous return [116, 117]. Decreased venous return leads to a lower cardiac output as a result of a smaller stroke volume and duty cycle [116, 117]. With lower cardiac output, oxygen supply to the respiratory and exercising peripheral muscles is reduced leading to a decrease in exercise capacity.

2.5.2.3 Increased Work of Breathing and Respiratory Steal

Available evidence suggests that in instances of increased metabolic demand by the respiratory muscles, blood is preferential supplied to the respiratory muscles in preference to the exercising peripheral muscles (a phenomenon known as respiratory steal) [118-120]. This limited supply of blood to the exercising muscle limits oxygen availability and this in turn limits the exercise intensity level that can be achieved by the exercising muscles [116, 119, 121, 122].

In conclusion, it is evident that exercise capacity is limited in COPD patients by complex and multi-factorial pathophysiological mechanisms. This limitation in exercise capacity has been discovered to be the greatest single predictor of mortality among individuals with COPD [123].

2.6 Current Trend in the Management and Rehabilitation of Individuals with COPD (Pulmonary Rehabilitation)

There is currently strong clinical and scientific evidence for the use of pulmonary rehabilitation in the management of individuals with COPD and other chronic lung diseases [9, 10, 124-129]. These programs employ a multidisciplinary approach to improve physical and social functioning in individuals with chronic respiratory disease [125, 130, 131]. According to the British Thoracic Society Standards of Care Subcommittee on Pulmonary Rehabilitation, the goals of pulmonary rehabilitation are to reduce symptoms, activity limitation, and participation restriction, and to improve functional independence in people with lung disease [124, 125]. Conventionally, a pulmonary rehabilitation process must incorporate a structured program with intense physical training, educational instructions, and other psychosocial and behavioural components to improve exercise performance/endurance, muscle strength, quality of life, dyspnea and reduce hospitalizations [10, 91, 124]. Exercise training is the chief cornerstone of any pulmonary rehabilitation program [132-135]. Exercise training reduces energy expenditure, work of breathing, and dyspnea while improving muscle strength and endurance [91].

A systematic review from the Cochrane Airways Group showed that pulmonary rehabilitation produced significant improvements in dyspnea, fatigue and emotional function among individuals with COPD [128]. In contrast, the effect of pulmonary rehabilitation on functional exercise capacity and maximum exercise capacity in the same review was noted to be small and slightly below the threshold of clinical significance for the six-minute walking distance test [128].

Casaburi et al (REF here) showed that a higher exercise intensity (80% of baseline peak work rate) is more effective than a lower exercise intensity (50% of baseline peak work rate) in the training of individuals with obstructive lung disease, even when the same total workload is performed [136, 137]. However, many patients with severe obstructive airflow limitation may not able to exercise at the intensity (80% of baseline peak work rate) required for maximum benefit from exercise training [9-11, 89, 138, 139].

2.7 Non-invasive Mechanical Ventilation

In an attempt to address the exercise limitation in individuals with COPD and assist them to achieve higher exercise intensities in order to produce greater benefits from exercise during pulmonary rehabilitation, several studies have looked at the effect of adjuncts such as NIMV, supplemental oxygen and helium oxygen on exercise capacity in the COPD population [13, 91, 93, 140-142].

Non-invasive mechanical ventilation acts as an adjunct by addressing the ventilatory components of limitation in exercise among COPD patients [139]. As an adjunct to exercise, NIMV is theoretically expected to unload the inspiratory muscles (principally the diaphragm), thereby decreasing the work of breathing, decreasing dyspnea and hence increasing exercise capacity [10, 91].

2.7.1 Effects of Non-invasive Mechanical Ventilation on the Respiratory System of Individuals with COPD

2.7.1.1 General Non-Specific Effects of NIMV

2.7.1.1.1 Effect on Hyperinflation

The ability of NIMV to reduce dynamic hyperinflation was suggested in the literature by the findings of Elliot et al [143] more than two decades ago when they observed a decrease in gas trapping in COPD patients after six months of domiciliary NIMV.

Application of NIMV provides an extrinsic positive end-expiratory pressure (PEEPe) [144, 145], either in the form of continuous positive airway pressure (CPAP), expiratory positive airway pressure (EPAP), or PEEPe, depending on the mode of NIMV used. This PEEPe counters PEEPi caused by dynamic hyperinflation and helps to keep the airways open during expiration [144, 145]. Imposition of PEEPe in spontaneously breathing patients counterbalances the inspiratory

threshold load imposed by PEEPi through increased intraluminal pressure in the airways, which results in a shift of the equal pressure point from the distal to the proximal airways and hence prevents or attenuates dynamic airway collapse [146, 147]. PEEPe achieves this without causing a further increase in lung volume and alveolar and intrathoracic pressure until a critical value of PEEP (P_{crit}) is reached [145]. Hence application of NIMV with an appropriate level of PEEP/EPAP should help to moderate the occurrence of dynamic hyperinflation in COPD patients during exercise. If the PEEPe in smaller than the PEEPi then NIMV is expected to have no effect on dynamic hyperinflation and if PEEPe is more than PEEPi, then NIMV is expected to further increase in EELV [148, 149].

2.7.1.1.2 Effect on V/Q mismatch

There are indications that NIMV improves ventilation-to-perfusion matching of functional alveolar units in patients with COPD. Some earlier studies have shown improvements in blood gases with NIMV both with long-term use [150-152] and during exercise [151, 153], without alluding to the possibility of a direct effect on the ventilation-to-perfusion ratio. In contrast, functional imaging studies from the work of De Backer et al [154] have provided evidence that in stable hypercapnic COPD patients with localized emphysema, NIMV can improve the ventilation of healthier lung lobes and lead to an improvement in V/Q matching, with a resultant increase in gas exchange. Their study also suggests that with prolonged use of NIMV, there is a regional mass flow redistribution towards areas with higher vessel density and less emphysema (which are the areas with better perfusion) and hence further optimization of gas exchange [154].

2.7.1.1.3 Effect on Work of Breathing

Non-invasive mechanical ventilation reduces the work of breathing during exercise by unloading the respiratory muscles. It has been shown that in patients with severe COPD, there is slowing of maximum relaxation rate of the inspiratory muscles during exhaustive treadmill exercise, which is an indication that these muscles become heavily loaded, initiating the fatigue process that further limits exercise [155]. Polkey et al [156] showed that when patients with COPD walked to exhaustion, NIMV reduced slowing of inspiratory muscle maximum relaxation rate suggesting a considerable unloading of the inspiratory muscles. Use of inspiratory assist in patients has also been shown to be associated with reduction in diaphragm electrical activity [157],

transdiaphragmatic pressure-time product [89, 158] and esophageal pressure-time product [158], suggesting a reduction in the work performed by the major inspiratory muscles.

2.7.1.2 Specific Acute Effects of NIMV during Exercise

From the limited available literature on the acute effects of NIMV in patients with chronic obstructive airflow limitation, NIMV has been reported to acutely reduce the feeling of breathlessness and improve minute ventilation [89, 159, 160], improve oxygenation, decrease dyspnea, increase walking distance [153], reduce inspiratory effort [89], and improve exercise performance and endurance [139, 153, 160, 161].

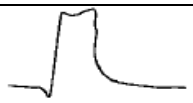
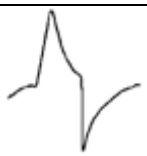
2.7.2 Ventilators and Modes of Non-invasive Mechanical Ventilation

Non-invasive positive pressure ventilation involves ventilatory assistance administered by delivering pressurized gas to the upper airway through the use of non-invasive interface such as a mask, nasal cannula or mouth piece and thereby increasing transpulmonary pressure and inflating the lungs. Exhalation occurs by means of elastic recoil of the lungs or active force exerted by the expiratory muscles as the situation may require.

2.7.2.1 Pressure-limited Modes

Non-invasive mechanical ventilation is usually delivered in a pressure-limited mode. Pressure-limited modes of ventilation support breathing by generating a preset positive pressure in the airway, which causes airflow [162, 163]. Pressure is therefore fixed while the volume of air delivered is variable and depends on the interaction between the predefined pressure, patient's inspiratory effort, and compliance and resistance of the respiratory system [163]. Airflow is also varied to maintain a constant pressure (being brisk at the beginning of inspiration and decelerating as the pressure gradient between the ventilator and the respiratory circuit narrows) [163]. Since maintaining a constant pressure that in turn generates airflow is the target in pressure-limited modes of ventilation, these ventilators are therefore able to compensate for air leaks in the respiratory circuit [162-164]. Common available pressure-limited modes of ventilation include BiPAP, pressure support ventilation (PSV), proportional assist ventilation (PAV), and CPAP ventilation. PSV and BiPAP are the most commonly used pressure-limited modes of ventilation in rehabilitation and will be discussed in further sections.

Table 2.2: Characteristics of pressure-targeted ventilators

	Pressure-targeted
Pressure curve pattern	
Flow curve pattern	
Type of ventilatory assistance delivered	Fixed pressure. Tidal volume may vary with changes in C and R
Controlled variable	Maintains a constant inspiratory preset pressure
Breath-to-breath adjustments	Possible: flow and volume can be varied in a breath-to-breath basis
Possibility to guarantee a fixed delivered tidal volume	No
Peak airway pressure	Limited (useful in patients at risk of barotrauma or gastric distension
Leak compensation	Good for mild to moderate leaks

Adapted from Rabec et al [174]

2.7.2.2.1 Bi-level Positive Airway Pressure

BiPAP is one of the most common modes of non-invasive ventilation used in the outpatient setting for long term non-invasive positive pressure ventilation [165]. It must be distinguished from BiPAP®, which is the name of a portable ventilator manufactured by Respironics Corporation that can deliver both the BiPAP mode of ventilation and other modes such as PAV and CPAP.

The BiPAP mode of ventilation is a pressure-limited mode that oscillates between a preset higher inspiratory positive airway pressure (IPAP) during inspiration and a preset lower expiratory positive airway pressure (EPAP) during expiration [164, 166]. IPAP and EPAP are delivered

through single limb tubing for both inspiration and expiration in the BiPAP® ventilator [165]. The level of pressure support during BiPAP ventilation is equivalent to the pressure difference between the IPAP and EPAP. The BiPAP mode maintains a constant flow in the respiratory circuit during expiration by delivering an expiratory positive airway pressure (EPAP). The EPAP level is similar and serves the same function as the CPAP level in the CPAP mode and the PEEP level in the pressure support ventilatory mode. Addition of inspiratory pressure during inspiration raises the pressure to the IPAP level, so expiration and inspiration are cycled through the pressure levels of EPAP and IPAP respectively.

Standard ICU ventilators with double limb tubing possess an integrated expiratory valve for venting of expired air [163], but the BiPAP® ventilator uses a standard exhalation device to vent expired air out of its one limb respiratory circuit [167, 168]. The standard exhalation device of the BiPAP (called the whisper swivel) is a calibrated intentional leak device that is located on the distal end of in the respiratory circuit [163]; despite use of this device, there is evidence from laboratory lung model bench studies [167, 168] and in clinical studies of patients with acute respiratory failure [159, 167] that CO2 re-breathing may still occur with BiPAP ventilation. To reduce such CO_2 re-breathing, a minimal EPAP level of 4cm H_20 has been advocated [163]. The amount of CO_2 rebreathing has also been shown to increase with increased respiratory rate (shorter expiratory time) [167] as can be expected during exercise.

Use of the BiPAP® ventilator as an adjunct to exercise using the whisper swivel exhalation device may however be counterproductive, since rebreathed CO_2 can increase respiratory drive via activation of the retrotrapezoid nucleus (RTN) of the medulla [169-171]. The increased respiratory drive may increase the energy demand of the respiratory muscles [12].

This may be a possible reason for the results of an earlier study [12] which looked at the effect of BiPAP on symptom-limited maximum exercise in COPD patients. The authors found that using BiPAP support of 0cm H_20 (EPAP of 4cm H_20 and IPAP 4cm H_20) or 10cm H_20 (EPAP of 4cm H_20 and IPAP 14cm H20) with a standard exhalation device, resulted in reduced maximum exercise capacity compared to no ventilator, while other physiological parameters (minute ventilation, VO_2, VCO_2 and tidal volume) were also higher with BiPAP at 0 and 10cm H_20 in comparison to no ventilator, showing that there may have been an increased respiratory work

despite lower maximum exercise capacity. Dyspnea and EELV were similar at peak exercise with or without the ventilator in their work.

2.7.2.2.2 Pressure Support Ventilation (PSV)

Pressure support ventilation (PSV) is pressure limited and patient triggered [172]. With the spontaneous breath initiated by the patient, the patient controls the beginning and end of inspiration as well as the respiratory rate while the ventilator delivers a preset pressure to assist the patient during inspiration. The inspiratory flow and tidal volume are determined by the interaction between patient's inspiratory effort, respiratory mechanics, inspiratory and expiratory times, and the preset pressure support level [173]. Timing of the inspiratory support is triggered by the patient [163, 172] when the pressure or flow sensor of the ventilator senses a decrease in airway pressure or a change in flow as the patient gets to the end of expiration [172]. PSV is usually flow cycled, and therefore once triggered, pressure is maintained at the preset support level until flow falls below a preset ventilator-determined threshold level and then expiration begins [163, 172]. Parameters such as inspiratory trigger sensitivity, and percentage threshold of peak flow for cycling to expiration may be adjustable and clinician selected in certain ventilators, but with all ventilators, inspiratory pressure support level must be selected [163].

The inspiratory pressure support level in PSV is equivalent to the difference between the IPAP and EPAP in the BiPAP ventilatory mode. With PSV, there is also the option of adding an extrinsic PEEP which resembles the EPAP in the BiPAP ventilatory mode [166]. Unlike the BiPAH however, a standard ventilator for delivery of PSV in the intensive care unit has two different limbs for inspiration and expiration and hence does not pose a risk of CO2 re-breathing during ventilation.

The Maquet SERVO-i ventilator is a standard ICU ventilator which has the option for both flow and pressure triggering with adjustable flow trigger sensitivity level 0 – 100% (fraction of bias flow) and pressure trigger sensitivity -20 – 0 cm H_20 [174]. The adult inspiratory flow range in the universal model of the Maquet SERVO-i is between 0 to 3.3 l/s and expiratory flow range is 0 to 3.2 l/s [174]. Inspiratory tidal volume is between 100 – 4000 ml and inspiratory minute volume 0.5 – 60(l/min) [174]. The pressure support level (above PEEP) in the NIV mode of the Maquet SERVO-i ranges from 0 – (32 - PEEP) cm H2O, while the PEEP in NIV is between 2 – 20 cm H2O [174]. Oxygen can be blended from a concentration 21 – 100 % [174].

2.8 Inspiratory Assist Levels

Some previous studies have investigated the effect of NIMV on exercise performance in individuals with COPD using inspiratory assist levels tailored to the individuals comfort [175-177] whereas others have used fixed levels of the same parameters [12, 161, 178]. A study by Van 't Hul et al [161] showed that exercise endurance was not significantly different when exercise was performed with a fixed inspiratory assist level of 5 cm H_2O compared to unassisted exercise, whereas it was increased with 10 cm H_2O of assist [161]. This gives an indication that the level of inspiratory assist chosen can influence the effect of NIMV during exercise. Several other studies with fixed level of inspiratory pressure support during assisted exercise have likewise used 10 cm H_2O [12, 161]. Nava et al [179] compared the effects of two levels of nasal pressure support (10 cm H_2O and 20 cm H_2O) on diaphragmatic activity in patients with COPD at rest, and observed that the application of 20 cm H_20 of inspiratory assist was not tolerated by one patient, whereas in another patient, it resulted in a small positive deflection of Pes suggesting an excess level of PS. The study concluded that it may be reasonable to individually titrate the level of ventilatory support for each patient [179]. Most studies have used a set level of PEEP, independent of whether or not the level of assist was comfortable for the patients [13, 14, 161, 175, 176]. It is as yet unknown whether a fixed level of inspiratory pressure support or a level titrated and tailored to the individual's comfort is optimal in the use of NIMV as an adjunct to exercise training in people with COPD.

2.9 Conclusion

COPD is a chronic disease with a global increasing prevalence, a major cause of morbidity and mortality all over the world and very high economic burden in developed countries of the world such as the US and Canada. The demand of the disease on the health system in Canada is alarming. Scientific and clinical evidence have shown pulmonary rehabilitation as an effective therapy for the rehabilitation of individuals with chronic pulmonary diseases with consequent reduction in morbidity, mortality, and economic and health burden of the disease.

Exercise therapy is the mainstay of any pulmonary rehabilitation program but individuals with COPD possess multiple local and systemic pathologies that limit their ability to perform exercise and therefore limit them from benefiting maximally from pulmonary rehabilitation programs. Scientific search for adjuncts that can address the ventilatory and systemic limitations to exercise

in COPD has been on the increase. NIMV has been theoretically identified as one of the possible adjuncts to address some of the ventilatory limitations to exercise in COPD. Scientific studies on the effect of exercise training with NIMV have produced conflicting results. With several types of ventilators, modes, modalities and options available in NIMV, it has become necessary to evaluate the effect of NIMV in an acute study protocol and gain insight into the physiological basis of the effectiveness or ineffectiveness of NIMV as an adjunct to exercise.

With limited published studies on the acute effects of NIMV, the recent study from our lab which looked at the acute effect of BiPAP ventilation on maximum exercise capacity in patients with COPD showed ineffectiveness of the BiPAP (using the standard valve) to increase maximum exercise capacity.

Previous literature has shown the standard exhalation device of the BiPAP to predispose patients with acute respiratory failure to CO_2 re-breathing. Since the previous study used the standard exhalation device (Whisper Swivel), it is possible that the participants re-breathed CO_2 during BiPAP ventilation which may have caused the minute ventilation to increase and maximum exercise capacity to be reduced compared to no ventilator. It may also be that the BiPAP is ineffective as an adjunct to acutely increasing exercise capacity in individuals with COPD.

PSV with PEEP is similar to BiPAP in terms of the level of support it provides and the ability to counteract PEEPi with PEEPe (or EPAP in the BiPAP), but the flow from the different ventilators is different. In an exercise scenario, level of flow of the ventilator is important since there is a high demand from the respiratory system. Standard PSV ventilators, unlike the BiPAP have dual limb tubing (one for inspiration and another for expiration) with true exhalation valves and so do not pose the risk for CO_2 re-breathing. PSV operates with valves that open and close in inspiration and expiration to control flow. Inspiratory effort from the patient is required to open the inspiratory valve (trigger) before flow can begin. Flow continues as long as the patient maintains an inspiratory effort. Enough flow is provided by the ventilator to maintain pre-set pressure once the inspiratory valve is open. Diminishing flow secondary to reduced inspiratory effort from the patient causes the inspiratory valve to close and the ventilator cycles into expiratory phase. This dynamic interaction between the patient and the ventilator is important to the success of PSV.

Fixed versus individually optimized levels of inspiratory assist may be another interesting point of consideration in the use of NIMV as an adjunct for exercise training in COPD. To the best of our knowledge, no study has compared the effect of fixed and individually tailored levels of inspiratory assist on maximum exercise capacity in individuals with COPD.

CHAPTER III: RATIONALE AND OBJECTIVES FOR THE STUDY

Pulmonary rehabilitation programs have been shown to be beneficial to individuals with chronic pulmonary diseases. Exercise training is the major component of any pulmonary rehabilitation program and because individuals with COPD have a reduced exercise tolerance (due to ventilatory and other systemic factors), they may not benefit maximally from a pulmonary rehabilitation program. Efforts have been made in scientific studies to find adjuncts to exercise training that will enhance exercise performance in individuals with COPD. Non-invasive mechanical ventilation is one such adjunct to exercise training that addresses the ventilatory component of exercise limitation in individuals with COPD.

BiPAP ventilation is one of the common modes of NIMV. A recent study that looked at the acute effect of BiPAP (using the standard exhalation valve) found maximum exercise capacity to be lower with BiPAP ventilation in comparison to unassisted exercise. The standard exhalation valve has been shown in literature to cause CO_2 re-breathing in patients with acute respiratory failure and in lung model bench studies. Re-breathed CO_2 can lower maximum exercise capacity. In comparison to the BiPAP ventilator, standard ICU ventilators have a separate limb for inspiration and expiration and therefore do not pose the risk for CO_2 re-breathing. Earlier studies investigating the effect of NIMV on exercise performance have used either fixed levels of inspiratory assist or inspiratory assist levels tailored to individual's comfort, but which one of these is methods is optimal in the use of NIMV as an adjunct for increasing maximum exercise capacity in COPD population remains unknown.

Since improving exercise capacity is very important in individuals with COPD, the aim of this study was to evaluate the effect of a fixed level and an individually optimized level of pressure support ventilation delivered during a symptom-limited incremental bicycle test on maximum exercise capacity, breathing pattern, metabolic parameters and exercise limiting symptoms in individuals with moderate to severe COPD in comparison to unassisted exercise.

CHAPTER IV: EFFECT OF PRESSURE SUPPORT VENTILATION ON MAXIMUM EXERCISE CAPACITY IN INDIVIDUALS WITH COPD

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5.1: ABSTRACT

RATIONALE: Non-invasive mechanical ventilation (NIMV) has been used as adjunct to exercise in pulmonary rehabilitation but its acute effect on maximum exercise capacity is not fully understood. Whether NIMV delivered during exercise using a level of ventilatory support titrated to comfort is better than a fixed level of assist is also unknown.

OBJECTIVE: The objective of the current study was to evaluate the effect of a fixed and an individually optimized level of pressure support ventilation (PSV) delivered during a symptom-limited incremental bicycle test on maximum exercise capacity, breathing pattern, end-expiratory lung volume (EELV), metabolic parameters, exercise limiting symptoms and respiratory comfort in individuals with COPD.

METHODS: Individuals with stable COPD, who do not use supplemental O_2 and without known conditions that could limit exercise were recruited. Participants performed three incremental bicycle exercise tests (workload increased by 5 watts/minute) until exhaustion. Tests, separated by 48 hours, were performed in a randomized order (i) without a ventilator (NV), (ii) with 10cmH_2O PSV (PSV10) and (iii) with PSV level titrated to patient comfort (PSVt) using a Maquet SERVO-i ventilator in a crossover design. Maximum exercise workload (WLmax), breathing pattern, mouth pressure (Pmo), EELV, metabolic parameters, dyspnea, leg effort, and respiratory comfort were measured and compared using a one-way ANOVA.

RESULTS: Eleven individuals (8 males, 3 females) with COPD (FEV_1: 49±16% predicted; age: 64±7 years) were studied. The mean PSVt level was 8.2 ± 4.5 cmH_2O. There was no difference in the WLmax achieved during the three tests. At rest, PSV10 increased tidal volume ($p=0.001$) compared to NV, whereas PSVt did not. Inspiratory duration was lower ($p=0.009$; $p=0.004$), minute ventilation higher ($p=0.001$; $p=0.02$), mean inspiratory flow higher ($p<0.001$; $p=0.006$), EELV higher ($p=0.003$; $p=0.002$), and end-tidal CO_2 lower ($p<0.001$; $p=0.005$) with PSV10 and PSVt, respectively. These differences were not observed at peak exercise. Oxygen uptake, Carbon dioxide production, exercise limiting symptoms at peak exercise, and respiratory comfort were not different between the three tests. Mean inspiratory Pmo was lower at peak exercise compared to resting breathing (PSV10: $p=0.034$, PSVt: $p<0.001$) and to 50% of WLmax (PSV10: $p<0.006$, PSVt: $p<0.001$), despite sustained peak Pmo values. These results suggest that the respiratory muscle unloading, evident with PSV at rest, progressively decreased with increasing exercise.

CONCLUSION: Titrated and fixed levels of assist using non-invasive PSV did not improve WLmax due to a progressive decrease in respiratory muscle unloading as exercise intensity increased.

5.2: INTRODUCTION

Individuals with COPD are often limited in their ability to perform exercise due to the sensation of dyspnea [4, 5] and peripheral muscle dysfunction [98-101]. Exercise intolerance in this population is associated with reduced muscle strength [102-104] and endurance [105-107] and increased contractile fatigability [83, 106]. Exercise intolerance is also the greatest single predictor of mortality in this patient population [180]. There is strong clinical and scientific evidence for the use of pulmonary rehabilitation in the management of COPD [9, 10, 124-127]; such a program should incorporate physical training for improvement of exercise performance, health status and dyspnea [10, 124]. High intensity exercise (80% of baseline peak work-rate) has been shown to be more effective than low intensity exercise (50% of baseline peak work-rate) in the training of individuals with COPD [136, 137]. However, many patients with severe obstructive airflow limitation may not able to exercise at the high intensity (80% of baseline peak work-rate) that is required to enable them to obtain maximum benefit from exercise training [9-11, 89, 138].

Adjuncts such as NIMV, supplemental oxygen and heliox have been used in an attempt to increase exercise capacity in the COPD population by addressing the respiratory component of their limitation in exercise [91, 140]. NIMV as an adjunct to exercise is theoretically expected to unload the inspiratory muscles, to thereby decrease the work of breathing, decrease dyspnea and increase exercise capacity [10]. Although there is evidence that NIMV can reduce breathlessness, improve ventilatory capacity [89, 153, 159], prevent exercise induced hypoxemia [153] and improve exercise endurance [153, 161, 181], a previous study that evaluated the acute effect of BiPAP ventilation using the standard exhalation valve during exercise, found that maximum exercise workload (WLmax) was lower with assist compared to exercise without ventilatory assist [12]. The authors concluded that since the BiPAP ventilator delivers pressure support through a single limb tube for both inspiration and expiration, it is possible that the participants re-breathed CO_2 which stimulated respiratory drive, increased minute ventilation (V_E) and resulted in a decreased maximum exercise capacity.

Many standard ICU ventilators can deliver PSV in a non-invasive mode. Unlike the BiPAP ventilator, standard ICU ventilators have two separate limb tubes, one for inspiration and the other for expiration, and hence do not pose a risk for CO_2 re-breathing during ventilation. With

PSV, the ventilator is triggered by patient effort; the patient controls the tidal volume and respiratory rate while the ventilator delivers a preset pressure to assist the patient during inspiration. It is anticipated therefore that use of this ventilator will eliminate CO_2 re-breathing and may be more useful in promoting an increased WLmax when used acutely during exercise.
Certain studies have previously investigated the effect of NIMV on exercise endurance in individuals with COPD using fixed ventilatory assist levels (commonly 10 cm H_2O) [148, 168, 187], whereas others have used inspiratory assist levels tailored to the individual's comfort [175, 176]. Nava et al [179] compared the effects of 10 cm H_2O and 20 cm H_2O nasal pressure support on diaphragmatic activity in patients with COPD at rest, and found that comfort may be altered with pressure level. The study suggested that it may be reasonable to find a pressure level that is comfortable for each subject (titration) [179]. It remains unknown whether a fixed level of inspiratory pressure support or a level titrated and tailored to the individual's comfort is optimal in the use of NIMV as an adjunct to exercise training in people with COPD given that no study to date has looked at the effect of fixed and individually tailored levels of PSV on maximum exercise capacity.

The purpose of the current study was therefore to evaluate the effect of PSV delivered using a fixed assist level as well as an individually titrated level on maximum exercise capacity, breathing pattern, metabolic parameters, EELV, exercise limiting symptoms and respiratory comfort in individuals with moderate to severe COPD in comparison to unassisted exercise. We hypothesized that 1) NIMV using PSV (both fixed and optimised assist levels) would substantially improve exercise capacity and metabolic parameters in comparison to unassisted exercise, and 2) PSV delivered using an assist level that was tailored to an individual's comfort would result in a higher maximum exercise capacity compared to PSV delivered with ventilatory assist fixed at 10 cm H_2O.

5.3: METHODS

5.3.1: Study design: A randomized, crossover design was used in this study.

5.3.2: Population and recruitment

Individuals aged 55 to 75 years with stable moderate to severe COPD based on medical history and pulmonary function (FEV_1<80% predicted normal and FEV_1/FVC<70%) according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [2], were recruited into

the study. Stable disease was operationally defined as 'no exacerbation, respiratory symptoms and medications unchanged four weeks prior to study'. Individuals with neuromuscular and neurodegenerative diseases, orthopaedic conditions, cognitive dysfunction, and any cardiovascular disorders and other conditions that could limit ability to do exercise in the last one year were excluded from the study. Subjects who required supplemental oxygen during exercise, who had participated in a pulmonary rehabilitation program in the last six months as well as individuals who were unable to give informed consent, were also excluded from the study. Participants were encouraged to adhere to their medications throughout the study. They were also asked to refrain from smoking on the day of their tests and to avoid eating for at least 3 hours prior to the test. Participants were recruited from Hôpital du Sacré-Coeur de Montréal (HSCM) and the Jewish Rehabilitation Hospital (JRH). Ethics approval was obtained from the ethics board of HSCM and Centre de Recherche Interdisciplinaire en Réadaptation.

5.3.3: Procedure

Three visits were scheduled for each participant (as shown in Figure 5.1). During the first visit, demographic, medical and anthropometric characteristics were measured. Pulmonary function tests (spirometry, lung volumes, single breath diffusion capacity, maximum respiratory mouth pressures) (Medical Graphics, USA) and a resting 12-lead electrocardiogram test were performed. Maximum inspiratory and expiratory muscle pressures were measured at functional residual capacity (FRC) and total lung capacity (TLC), respectively.

During each of the three visits, participants performed a symptom limited-incremental exercise test on a bicycle. They were positioned comfortably and securely on the bicycle ergometer and asked to breath at rest for 6 minutes. This was followed by a 1-min warm-up exercise period consisting of unloaded pedaling, after which the exercise work rate was increased by 5 watts every minute until a symptom limited end-point was reached. The participants were encouraged to maintain a pedaling rate of 60 ± 8 revolutions per minute throughout exercise as was done in previous studies [13, 93, 182, 183]. Patients were asked to rate their dyspnea using a Borg scale. The scale was explained to the participants before the start of the exercise and assessment was done at the last 15 seconds of every minute. Individuals were asked to perform inspiratory capacity (IC) manoeuvres at rest, every minute during the exercise, and at peak exercise. To avoid possible effects of performing IC manoeuvres on dyspnea intensity, IC manoeuvres were

always performed after completing the symptom intensity ratings. Immediately after reaching the exercise endpoint, the participants performed 1 minute of unloaded cycling (cool down) and then stopped pedaling. On completion of the test, participants were asked "What made you stop the exercise: shortness of breath, leg effort or both?" to identify the locus of symptom limitation. At end exercise, a visual analogue scale (VAS) was used to assess the patient's level of breathing comfort with anchors of worst comfort and best comfort on either end.

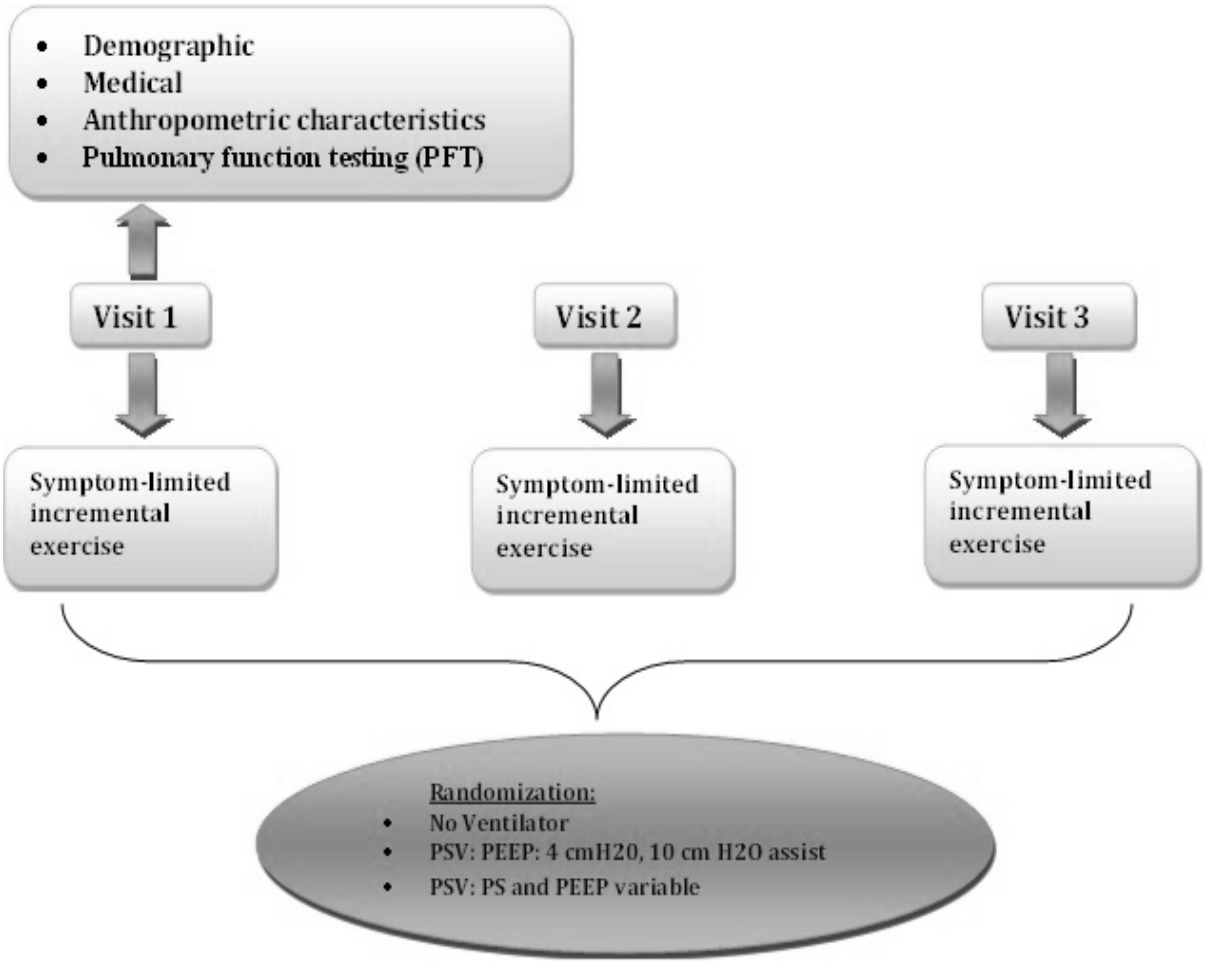

Figure 5.1: Schedule of Participants Clinical Visits

The three visits (exercise tests) were separated by at least 48 hours (two days) and were performed in a randomised fashion (i) without a ventilator, (ii) with 10 cm H_2O inspiratory assist using pressure support ventilation and (iii) with individually tailored level of inspiratory assist using pressure support ventilation. The randomization schedule was determined via randomly picked slips in an opaque envelope. The PEEP on the ventilator was set at 4 cm H_2O, rate of rise

at 0.2 seconds and cycling was set at 50% for all the assisted exercises. All incremental exercise tests were performed with a mouthpiece connected to a respiratory circuit consisting of a pneumotachograph and also connected to a pulmonary gas exchange analyzer. For the visits where exercise was performed with a ventilatory support, a Maquet SERVO-i ventilator (PSV mode) was added to the circuit to allow for delivery of the inspiratory assistance.

5.3.4: Instrumentation and measurements *(see annex b for more detailed information)*

All the symptom limited-incremental exercise tests were performed on a bicycle ergometer (Lode, Groningen, the Netherlands) with subjects breathing through a mouthpiece (VBite, Hans Rudolph) with nose clips on. The mouthpiece was connected to a respiratory circuit consisting of a pneumotach, a pulmonary gas exchange analyzer and a Hans Rudolph three-way sliding-type valve (manual direction control valve 2870 series).

5.3.4.1: *Maximum exercise capacity*

Maximum exercise capacity was taken as the highest WLmax reached and maintained for at least 30 seconds on the incremental exercise test on the bicycle ergometer. Test-retest reliability of symptom-limited cycle ergometer tests has been shown to be as reliable in patients with COP as in apparently healthy subjects [184]. Isoload was defined as the lowest of the three maximum exercise workloads achieved in the three symptom-limited incremental exercise tests for each individual.

5.3.4.2: *Breathing pattern and ventilator pressure*

Breathing pattern was assessed at rest and during exercise by measuring inspiratory and expiratory airflow using a pneumotach (Pneumotachograph, model 4813; Hans Rudolph, Kansas City, MO, USA) and a differential pressure transducer (TSD160A - Differential Pressure, 2.5 cm H20, DA100C, Biopac Systems, Santa Barbara, CA, USA). Volume was obtained by digital integration of the flow signal. Mouth pressure was recorded from a side port of the mouthpiece connected to a separate pressure transducer (TSD160E - Differential Pressure, 350 cm H20, DA100C, Systems, Santa Barbara, CA, USA). Calibration of the flow and pressure signals from the differential pressure transducers were done before each test using a 3 litre syringe and 20 cm H_2O pressure from a U-tube manometer respectively. In all trials, the flow and pressure signals were acquired online on a personal computer at a sampling rate of 1000 Hz using a 16-bit A/D

converter (MP 100A-CE, Biopac Systems, Santa Barbara, CA, USA), and were stored on a personal computer for offline analysis.

5.3.4.3: *Metabolic Parameters*

Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) [indicators of gas exchange] were measured at rest and during exercise with a COSMED system (COSMED K4b2, Rome, Italy). Calibration of the COSMED K4b2 system was performed, immediately before each test with a 3-liter syringe for the turbine, and using a gas reference gas mixture (16% O_2 and 5% CO_2; balanced N_2) for its gas analyzers. Heart rate and oxygen saturation was also measured continuously at rest and during exercise using a pulse oximeter (COSMED K4b2, Rome, Italy), while ECG was being monitored online during the test. The validity, reliability and linearity of these instruments for use in the human respiratory system and COPD population has been shown in published studies [185-193].

5.3.4.4: *Operational Lung Volumes PEEP*

End-expiratory lung volume (EELV) was obtained by subtracting the IC volume from measures of TLC previously obtained during pulmonary function testing. Changes in IC reflect changes in dynamic EELV [194]. Therefore, serial measurements of IC mirror changes in operational lung volumes. Serial IC measurements during exercise have been shown to be reproducible, responsive and correlate with changes in exertional dyspnea [199].

5.3.4.5: *Dyspnea and Leg Fatigue Symptoms*

The modified 10-point Borg scale was used to assess the perception of dyspnea and leg fatigue. Validity of the Borg Scale has been established by a high degree of correlation ($r < 0.92$) with both oxygen uptake and minute ventilation during exercise [195, 196]. A very good reproducibility ($r=0.96$) for rating respiratory sensations at peak exercise has also been found in COPD patients [195, 196]. The modified 10-point Borg scale of dyspnea was shown to be highly reproducible and responsive during bicycle exercise in individuals with stable advanced COPD and the Borg ratings of perceived leg discomfort scale was also reported to be highly reproducible [194, 197].

5.3.4.6: *Respiratory Comfort*

At the end of each exercise test, a VAS comfort scale, with anchors of 'worst comfort' and 'best comfort' on either end, was used to assess the patient's level of breathing comfort during the exercise.

5.3.4.6: *Off-Line Data Analysis:*

Off-line breath by breath analysis was performed on the flow, volume and pressure signals from the Biopac. For each individual respiratory rate (RR), minute ventilation (VE), mouth pressure (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 and pressure tracings. Tidal volume (V_T) was obtained by digital integration of flow and mean and peak inspiratory and expiratory pressures were obtained from the pressure signal. Peak inspiratory and expiratory Pmo were taken as the highest and lowest pressure in inspiration and expiration, respectively. 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.

5.3.5: *Statistical Analysis*

Outcome measures (maximum exercise capacity, operational lung volumes, metabolic parameters, breathing pattern, and other physiological parameters) were compared between exercise conditions of (i) no ventilator, (ii) PSV with inspiratory assist of 10 cm H_2O (PSV10) (iii) PSV with assist level titrated to comfort (PSVt) at rest, isoload and peak exercise. Comparisons were done with a one-way repeated measures analysis of variance (ANOVA) using the Statistical Package for the Social Sciences (IBM SPSS, Inc. Chicago) version 19. Analysis was followed up with post hoc contrasts of significant effects using the least significant difference analysis. The level of significance for all statistical tests was set at α=0.05 for all tests. Results are reported as means ± SD unless otherwise indicated.

5.4: RESULTS

5.4.1: Participant characteristics

Eleven individuals with COPD (8 males and 3 females) aged 64.18±7.12 years took part in this study. Participants had moderate to very severe airflow limitation as defined by the GOLD

guidelines [3]. They also had static hyperinflation with increased FRC and TLC, respiratory muscle weakness as indicated by a reduced PImax and PEmax and a reduced diffusion capacity. Nine participants had a BMI < 31.0 with two participants presenting with obesity (BMI of 42.86 and 37.55). Ten participants were ex-smokers while one participant (with BMI of 42.86) was a current smoker. Participants also showed a decreased baseline exercise capacity as captured by a mean 6-minute walk distance of 464.49±99.88. Table 5.1 summarizes the main characteristics of the study participants.

5.4.2: Primary outcome:

Maximum exercise capacity

Figure 5.2 shows the WLmax of each individual in the three conditions studied (NV, PSV10 and PSVt) as well as the mean WLmax values. Compared to exercise without ventilatory assist, with PSV10, WLmax was higher in 3 participants (range: 5w), unchanged in 5 participants and lower in 3 others (range: 5-30w), whereas with PSVt it was higher in 7 participants (range: 5-15w), lower in 3 (range: 5-10w), and unchanged in 1. The mean WLmax achieved was 51.36±20.01w, 48.64±20.14w and 54.09±22.23w with NV, PSV10 and PSVt, respectively. There was no difference in WLmax achieved in the three conditions $F(2, 20) = 2.384$, $p=0.118$

5.4.3: Secondary outcomes:

Ventilator pressure measured at the mouth

Figure 5.3 shows the individual levels of PSV chosen by participants above and below 10 cm H_2O. Four patients with COPD felt that a level of PSV higher than 10 cm H_2O was optimal for them during titration of pressure, whereas 7 chose a lower level of assist. Interestingly, during exercise, all four subjects who chose a higher level of assist achieved a higher maximum exercise workload during PSVt assisted exercise compared to PSV10 assisted exercise workload.

Mean and peak inspiratory and expiratory mouth pressures (Pmo) during conditions of NV, PSV10 and PSVt, are shown in Figure 5.4. The mean inspiratory Pmo with PSV10 was 10.26±1.50 and 8.19±2.21 at rest and peak exercise, respectively, whereas it averaged 9.46±3.56 and 6.07±4.06 with PSVt. During expiration, the mean Pmo with PSV10 was 5.03±0.42 and 7.23±1.65 at rest and peak exercise, respectively, while it was 5.04±0.45 and 7.62±1.76 at rest and peak exercise with PSVt, respectively.

Without ventilatory assist, the peak and mean inspiratory pressures increased progressively from rest to 50% of exercise to peak exercise. With ventilatory assistance, peak inspiratory pressures were maintained at rest, 50% of exercise and peak exercise, but mean inspiratory pressure decreased from rest to 50% of exercise and to peak exercise. The mean expiratory mouth pressure increased progressively from rest, to 50% of exercise and to levels higher than the set PEEP at peak exercise. The decreased mean inspiratory pressure at peak exercise suggests reduced inspiratory muscle unloading whereas the increased mean expiratory pressure suggests an increased expiratory work of breathing.

Figures 5.5, 5.6 and 5.7 show Pmo tracings with corresponding flows and volumes in three subjects: one individual who had PSVt higher than PSV10 (the highest PSVt in our sample), one with PSVt lower than PSV10 (the lowest PSVt in our sample) and the third with PSVt close to PSV10 (average value of PSVt in our sample), respectively. Pressure support ventilators are known to generate a positive square wave on inspiration and maintain a PEEP on expiration. Our Pmo tracings showed a change in the wave pattern of the ventilator as the patient progressed from resting breathing to peak exercise. At resting breathing, the pressure of the ventilator increased early in inspiration, maintained a plateau for a substantial time of the inspiratory phase, before cycling off to expiration where a plateau was also maintained close to the set PEEP. As exercise progressed to peak, the pressure wave pattern was observed to increase with a slope for most of the inspiratory phase and only reached the target pressure at end-inspiration. Loss of the capacity to increase pressure early in inspiration and maintain a plateau before cycling off as the patient approached peak exercise suggests that the participants may have been out driving the ventilator (ventilator unable to supply adequate flow to maintain pressure) with increased respiratory demand. The ventilator thus was unable to maintain the target pressure for most of the inspiratory time (Pmo tracing not a square wave). Moreover, the tracings further show that with very low support level during PSVt, subjects out-drove the ventilator earlier during exercise as shown by the pressure curve pattern seen at 50% in the subject with a PSVt level of 3 cm H_2O compared to PSV10 (Figure 5.6), and that high support level during PSVt (Figure 5.5, PSVt of 15 cm H2O), does not necessarily improve the capability of the ventilator to maintain effective assist during inspiration at peak exercise. The Pmo tracings also illustrate that at peak exercise, the ventilator could not maintain the set PEEP on expiration and that there was an increase in the expiratory pressure at peak exercise suggestive of an increased expiratory muscle recruitment in

that phase. Furthermore, large negative deflections indicative of triggering delay can be seen at on the Pmo signal as peak exercise, which were not present during resting breathing. This is suggestive of trigger performance issues with the ventilator at peak exercise.

Comparison across the upper and lower panels (PSV10 and PSVt of same individual) and between graphs shows that a higher pressure during titration was associated with higher flow and V_T. V_T, mean and peak inspiratory and expiratory flows as seen in table 5.2 and 5.3 also shows higher V_T and flow with PSV10 (10 cm H_2O) compared with PSVt (average mean inspiratory pressure of 8.18±4.49 cm H_2O).

Breathing Pattern at Rest, Isoload and Peak Exercise

Breathing pattern responses at rest, peak exercise, and isoload are shown in tables 5.2, 5.3 and 5.4 respectively and in Figure 5.8.

Tidal volume (V_T) was significantly higher with PSV10 at both rest and isoload and with PSVt only at isoload. A similar trend was seen at peak exercise though it did not reach statistical significance. There was no difference in the respiratory rate (RR) at rest, but it was significantly lower with both PSV10 and PSVt PSV at isoload and peak exercise. Our participants therefore took slower deeper breaths during exercise when assisted with PSV. Minute ventilation was higher with PSV10 and PSVt during resting breathing; however, it was not different in all three conditions at isoload and peak.

Inspiratory time was significantly lower with ventilatory assist at rest but at isoload and peak exercise, there was no difference between assisted and unassisted exercise. There was no significant difference in expiratory time in all conditions at rest but at isoload and peak exercise, expiratory time and total time was higher with exercise assisted with PSV.

Flow Rate

Mean and peak inspiratory flow rate was significantly higher with assisted exercise at rest but there was no difference at isoload and peak exercise.

Mean and peak expiratory flow rate was significantly higher with assisted exercise at rest and isoload but at peak exercise, only peak expiratory flow was significantly higher.

Operational Lung Volumes

Figure 5.9, illustrates the operational lung volumes from resting breathing to peak exercise during unassisted and assisted exercise. EELV increased during exercise in all three conditions. During resting breathing, EELV was higher with ventilatory assist, but at peak exercise there was no significant difference in EELV between the three conditions. Increased V_T with PSV also resulted in higher end inspiratory lung volume at peak exercise.

Metabolic Parameters

As can be seen in Tables 5.2, 5.3 and 5.4and Figure 5.10, end-tidal CO_2 was significantly lower with both PSV10 and PSVt compared to no assist during resting breathing. It was 18% and 25% lower with PSV10 and PSVt, respectively during resting breathing. But at isoload and peak exercise, there was no difference in end-tidal CO_2.

There was no significant difference in oxygen uptake and carbon dioxide output between the three conditions at rest and peak exercise, but carbon dioxide output was significantly lower with PSV at isoload.

Lower end-tidal CO_2 with a similar VO_2 and VCO_2 for a higher V_E at rest with PSV is an indication that mechanical ventilation was effectively unloading the inspiratory muscles at rest. At isoload, V_E was not different between the three conditions but VCO_2 was lower with PSV and at peak exercise, there was no difference in end-tidal CO_2, VO_2 and VCO_2 and V_E. This suggests decreased level of inspiratory muscle unloading as participants progressed with exercise.

Exertional Symptoms

There was no difference in the Borg ratings of dyspnea and fatigue at rest, isoload and at peak exercise in the three exercise conditions (Tables 5.2, 5.3 and 5.4 and Figure 5.11). Maximum exercise capacity was limited by dyspnea in 3 individuals, leg fatigue in 7 individuals and combination of both in 1 one individual when they exercised with unassisted, while 4 people were limited by dyspnea, 6 by leg fatigue and 1 by both with PSV10 and 3 people by dyspnea, 5 people by leg fatigue and 2 people by both while exercising PSVt.

Comfort of Breathing

Mean ratings of respiratory comfort were 66.18±21.25 cm, 67.91±21.63 cm, and 77.60±18.33 cm for NV, PSV10 and PSVt respectively. Mean respiratory comfort ratings were not

significantly different for the different ventilatory strategies used, however as shown in Figure 5.12, more individuals found PSVt more comfortable than PSV10.

Cardiovascular Parameters

As shown in Table 5.2, 5.3, 5.4 heart rate and arterial oxygen saturation were not different between the three ventilatory assist conditions at rest, isoload and peak exercise.

5.5: DISCUSSION

This pilot study compared the effect of PSV delivered using a fixed assist level as well as individually titrated levels of inspiratory assist on maximum exercise capacity, breathing pattern, metabolic parameters and exercise limiting symptoms individuals with moderate to severe COPD. The main findings of this study is that a fixed level pressure support ventilation of 10 cmH_2O and levels titrated to comfort administered using Maquet servo-i ventilator delivered through a mouth piece did not improve maximum exercise capacity in comparison to unassisted exercise. At rest, PSV10 increased tidal volume compared to NV, whereas PSVt did not. At rest, PSV also decreased inspiratory duration, increased minute ventilation, increased mean inspiratory flow, resulted in higher EELV higher, and lower end-tidal CO_2. These differences which were evident during resting breathing were not observed at peak exercise. Oxygen uptake, Carbon dioxide production, exercise limiting symptoms at peak exercise, EELV at peak exercise and respiratory comfort were not different between the three tests. Mean inspiratory Pmo was lower at peak exercise compared to resting breathing and to 50% of WLmax, despite sustained peak Pmo values. These results suggest that the respiratory muscle unloading, evident with PSV at rest, progressively decreased with increasing exercise.

In this study, pressure support was administered using a Maquet SERVO-i ventilator. The rationale for our choice of ventilator was borne out of findings from a previous study in our lab which looked at the acute effect of BiPAP on symptom-limited maximum exercise capacity in COPD patients and found that 80% of the participants had a lower maximum exercise capacity with BiPAP [12]. In that study, minute ventilation and metabolic parameters were higher at isoload and peak exercise with BiPAP compared to no assist, and dyspnea was the exercise limiting factor in all BiPAP assisted exercise tests. BiPAP has previously been shown to cause CO_2 re-breathing in laboratory bench lung model studies [167, 168] and in clinical studies [159, 167]. CO_2 is a known respiratory stimulator that can increase respiratory drive and put more demand on the respiratory muscles, and thereby affect maximum exercise capacity with earlier onset of dyspnea. The current study eliminated any possible effect of CO_2 rebreathing by using the Maquet SERVO-i ventilator given that the ventilator has separate tubing for inspiration and expiration and hence does not pose risk for CO_2 re-breathing. We chose 10 cm H_2O for the fixed

level because similar levels have been used in previous studies that evaluated the acute effect of NIMV during exercise [12, 13, 89, 198].

5.5.1 Effect of NIMV on exercise capacity

As an assist to exercise, NIMV is theoretically expected to unload the inspiratory muscles (principally the diaphragm), thereby decreasing the work of breathing, decreasing dyspnea and hence increasing exercise capacity [10, 91, 199]. Some studies have shown NIMV to be beneficial as an adjunct to exercise training in individuals with COPD [13, 141], but studies which looked at acute effects of NIMV in individuals with COPD have shown a high degree of variability in its effect on exercise tolerance [161, 200]. While 4-5 cmH2O of CPAP significantly increased exercise endurance time in one study[201], other studies that used 5-6 cm H_2O of CPAP [177, 178] or PAV delivered with a volume assist of 6 cmH_2O/L and a flow assist of 3 $cmH_2O/L/s$ [178] found no such improvement. Studies in critically ill patients have shown that several factors such as level of support, mode of mechanical ventilation, type of mechanical ventilator, patients' related factors and patient-ventilator interaction alters the physiologic effect of NIMV on the respiratory system [202, 203].

5.5.2 Exercise and patient-ventilator interaction

Results from this current study suggests that participants could not increase their maximum exercise capacity during PSV assisted exercise because there was a decrease in efficiency of the Maquet servo-i ventilator as subjects progressed from resting breathing to peak exercise. Qualitative analysis of the Pmo tracing shows three progressive changes suggestive of decreased unloading of the inspiratory muscles, increased expiratory work of breathing, and patient ventilator asynchrony as subjects progressed from resting breathing to 50% of exercise and to peak exercise. First, we saw a decrease in the inspiratory rise time of the Pmo curve in inspiration resulting in loss of the normal square wave. Secondly, we saw an increase in pressure during expiration and thirdly, we had a larger negative deflection at end-expiration before the triggering of the ventilator.

Inspiratory rise time is a user adjustable criterion (0.0-0.4 seconds) on the Maquet servo-i ventilator. The inspiratory rise time refers to the time set for the ventilator to reach the target pressure support level. In some ventilator models, the inspiratory rise time is a function of user-adjustable 'pressurization rate' [204]. Decreasing the inspiratory rise time will result in a steeper

ramp of the pressure signal by increasing the initial peak inspiratory flow rate and vice versa. For this study, we chose inspiratory rise time of 0.2 seconds because a shorter inspiratory rise time was not tolerated by our study participants. Earlier studies also reported extremes of high and low peak inspiratory flow rates (result of extremely short and long inspiratory rise time respectively) to be associated with discomfort and with a possible increase in the work of breathing in healthy and mechanically ventilated patients [205-207]. Ideally, the ventilator should increase pressure to the set level within the specified rise time and maintain it till the specified cycling off criteria is reached at the end of neural inspiration. As our subjects progressed with exercise, the ventilator could not meet the set pressure till the end of the inspiratory time. The initial ramp profile of a pressure support ventilator depends primarily on the initial peak flow rate [207] and the efficacy of PSV is determined by the interaction between the patient's respiratory mechanics and the ventilator [208]. If the initial peak flow rate of a ventilator is insufficient to meet a patient's ventilatory demand, it will result in flow asynchrony [209] and the steepness of the ramp of the observed Pmo signal will be reduced [210]. The Maquet SERVO-i has a maximum inspiratory flow rate of 3.3 l/s before the resistance provided by the respiratory circuit. Our Pmo tracing therefore suggests that as our study participants approached peak exercise, the ventilator could not meet their flow demand leading to a longer inspiratory rise time. Increased inspiratory rise time has been shown to be associated with a decrease in the area under the curve in inspiration which is an indication of increased patient work of breathing [208]. We therefore conclude that greater flow demand from the participants during exercise, changed the positive square wave of PSV leading to a reduction in mean inspiratory pressure [211], decreased unloading of the inspiratory muscles and increased inspiratory work of breathing which affected maximum exercise capacity in our participants. Results of mean inspiratory Pmo at rest and peak exercise also give evidence to the fact that there was decreased unloading of the inspiratory muscles because of decreased mean pressures. Similar Pmo tracing to those observed in our study were also obtained by Dolmage et al [178] in patients exercising at 60-70% of their workrate. They also reported that the Pmo became progressively less than targeted as ventilation increased during the exercise, despite the fact that they recruited severely impaired subjects in whom ventilation during exercise was not expected to exceed the capability of the ventilator. That end-tidal CO_2 was lower with PSV at rest but not at isoload and peak exercise also gives evidence to the fact that the unloading of the inspiratory

muscles by PSV diminished as exercise progressed. At isoload, our finding of a lower VCO_2 at the same level of minute ventilation suggests that PSV still had an unloading effect on the inspiratory muscles, but not at a level to increase maximum exercise capacity.

We chose in the current study to set the extrinsic PEEP (PEEPe) level to 4 cm H_2O. Use of PEEPe has been associated with a reduction in the PEEPi level and has been shown to result in less inspiratory effort in mechanically ventilated COPD patients in the ICU [80, 212]. The increase in the expiratory Pmo (above set PEEP) in our subjects, as exercise intensity increased, indicates a progressive recruitment of the expiratory muscles. Expiratory muscle activity in exercising COPD subjects has likewise been reported by Dodd et al [213] and may in part be an attempt by individuals to counteract the effects of high respiratory resistance and can contribute to increasing the PEEPi [214]. Expiratory muscle activity can also occur with patient-ventilator asynchrony (specifically delayed cycling) [215, 216], which might have developed as our subjects progressed in exercise. If mechanical inflation from the ventilator extends beyond the patients' neural inflation (delayed termination), the length of time available for lung emptying becomes reduced, leading to dynamic hyperinflation and expiratory muscle activity [80, 215, 216]. The ventilator in the current study was set to cycling at 50% of peak inspiratory flow, which is reasonable considering that Chiumello et al [80] reported higher cycling-off criteria (40% vs 5%) to be associated with a smaller PEEPi, reduced ventilator cycling-off delays and a lower inspiratory work of breathing in mechanically ventilated COPD patients.

Triggering delays may also have interfered with exercise performance during pressure support ventilation in the current study as evidenced by the progressively larger negative pressure needed to trigger the ventilator as exercise intensity increased from resting breathing to 50%, 70% and peak exercise. Traditional ventilators have been shown to be associated with triggering asynchrony both in bench model studies [217, 218] and in clinical studies [219, 220]. Although adjusting the trigger sensitivity may improve triggering asynchrony in pressure support ventilation [217] the inspiratory trigger of the Maquet SERVO-i is nonadjustable in the NIMV mode and functions on a first-come first-served system corresponding to either a pressure decrease of 1 cm H2O under the PEEPe level or an expiratory flow decrease of 6 mL during 100 ms [219]. Our Pmo tracings and peak expiratory Pmo values show that the inspiratory trigger was about 4-5 cm H_2O below PEEPe at peak exercise in our study participants.

5.5.3 Effect of Titration on Maximum Exercise Capacity and Respiratory Comfort

To the best of our knowledge, this is the first study that compared the effect of a fixed and titrated levels of pressure support during exercise on maximum exercise capacity. The rationale for this comparison was borne out of the fact that patient comfort and compliance are critical to the success of non-invasive ventilation [162] and that previous studies have shown that comfort varies with level of support [179, 203, 221]. Compared with studies by Biachi et al and Keilty et al in which they confined titration of PSV level to a range of 12-15 cm H_2O during constant work rate exercise, participants in this study chose a wide range of PSVt levels from 3-15 cm H_2O.

WLmax was higher with PSVt than with the fixed level of 10 cm H_2O in seven of our participants, unchanged in three and decreased in one of them but the difference was not significant. Compared to NV application of 10 cm H_2O inspiratory support increased WLmax in 3 of 11 (27%) participants while titration of level of support to comfort increased it in 7 of 11 participants (64%). Findings from this study also show no difference in respiratory comfort during exercise with PSVt compared to PSV10 and NV. In this study, titration to comfort was done at rest and our results show that adjusting the ventilator pressure to comfort at rest is not generally sufficient for exercise. Further studies will be needed to know if titration of support during exercise improves WLmax and/or alters the respiratory comfort during exercise. Other modes of NIMV, such as neurally adjusted ventilatory assist (NAVA) and PAV, which can adjust assist level to respiratory demand in a systematic and proportional fashion might also help improve WLmax and respiratory comfort. But the use of NAVA may be limited in pulmonary rehabilitation because it requires insertion of esophageal electrode and PAV may also be limited because it cannot keep up with changes in resistance and compliance that occurs during exercise.

During PSVt titration, about 5 participants could not distinguish any difference in respiratory comfort, so support level was increased till a point where they felt a slight sensation of discomfort and then the level was lowered about 1-2 cm H_2O till the participant felt comfortable again.

5.5.4 Breathing Pattern

During resting breathing with PSV, there was an increase in the V_E predominantly through an increase in V_T. PSV has been shown to increase V_T in COPD patients during resting breathing

[222] and in exercise [89, 223]. At isoload, V_T remained significantly higher and V_E was unchanged, whereas at peak exercise there was no difference in V_T or V_E. This is another indicator that the effectiveness of the ventilator decreased as participants progressed in exercise. This is in agreement with some earlier studies on the acute effects of PSV [161, 224] which had shown similar findings on V_T and V_E at isotime and end-exercise. PSV also lowered respiratory rate at isoload and peak exercise with an increase in expiratory time. Decrease in respiratory rate showed that our participants achieved the same minute ventilation at a lower rate of breathing with concomitant longer expiratory time which is important for individuals with airflow obstruction.

5.5.5 Exercise Limiting Symptoms

Unlike some earlier studies [199, 201, 225] which found difference in dyspnea ratings at end exercise with the use of NIMV during constant work rate exercise, our study[178] found no difference in Borg rating of dyspnea and leg fatigue both at isoload and peak exercise. Similar dyspnea levels with PSV in this present study may be explained by evidence of decreased unloading at peak exercise.

5.5.6 Operational Lung Volumes

Our finding that PSV increased EELV during resting breathing and exercise concurs with earlier studies [12, 223] that evaluated the acute effects of NIMV on exercise. Dynamic hyperinflation occurs in COPD patients during exercise when expiratory flow limitation is compounded by incomplete lung emptying because of decreased expiratory time [4, 64]. At isoload and peak exercise, there was no difference in EELV between PSV assisted exercise and unassisted exercises similar to other earlier studies [89, 199, 226]. Increased EELV at resting breathing might be secondary to the fixed 4 cm H_2O PEEPe level that we used in our study. Ideally, the PEEPe level should be set on the ventilator to match the level of PEEPi so as to reduce the inspiratory threshold imposed by PEEPi on the respiratory system [227]. Our study focused on the use of PSV as an adjunct for exercise in pulmonary rehabilitation and it was not feasible to measure PEEPi in this patient population. We therefore chose an estimated average of PEEPe value of 4 cm H_2O for all our participants since a study in mechanically ventilated COPD patients previously demonstrated that 6 cm H_2O of PEEPe compared to no PEEPe, decreased dynamic PEEP and inspiratory effort [80].

5.6: METHODOLOGICAL CONSIDERATIONS

There are a few limitations inherent in the design of this study: Firstly, the researchers were not blinded to the experimental scenarios that the subjects were performing at each of their visit. The study was limited to the acute effect of NIMV and therefore is not applicable to the effect NIMV on exercise capacity when it is used as an adjunct over a period of time. Only PSV was studied and hence the results cannot be generalized to other modes of NIMV. This study is pilot study and used only 11 participants. Finally, individuals in this study had a mouthpiece and so there was no need for the use of leak compensation on the ventilator which would be necessary in circumstances when individuals had a face mask. Given that rehab studies would likely use face mask, other studies would be needed to verify if leak compensation would alter the results of the outcomes.

5.7: CONCLUSIONS

Our study demonstrated that a fixed level of pressure support ventilation does not systematically increase exercise workload. This study, to the best of our knowledge, is the first study to show progressive emergence of patient-ventilator asynchronies as exercise increases during the use of PSV as an adjunct to improve maximum exercise capacity. It is also the first study to show that titration of PSV level to comfort at rest does not seem to increase maximum exercise capacity and respiratory comfort during exercise. This study also suggests that the capacity of conventional ventilators designed for patients breathing at rest may not be sufficient to provide respiratory assistance in some COPD patients at peak exercise. Our findings also suggest that pressure support level titrated to patient's comfort during resting breathing may not be sufficient to provide enough assist at peak exercise.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

AUTHORS CONTRIBUTION

Anekwe, David was responsible for coordinating the overall activities of the study including arranging for recruitment, scheduling of the tests, running of the study, as well as data collection and analysis and writing of manuscripts. Dr. Spahija supervised and assisted throughout the study period to ensure the quality of the study and an accurate delivery of NIVS during exercise. She also provided holistic and procedural guidance throughout the study, assisted in patient recruitment and during the studies, proofread and edited all documents as well as the final thesis. Dr. de Marchie participated in the clinical supervision during the exercise tests, translation of all documents to French language, review of selected medical files and medical screening of all recruited participants, necessary feedback and advice before and during the study, as well as review of the manuscript.

Tables and figures:

Table 5:1: Characteristics of the 11 patients with COPD

Variable	Mean ± SD or N (%)
Anthropometric data	
Age, years	64 ± 7
Height, m	1.67 ± 0.06
Weight, kg	77.54 ± 26.95
BMI, kg/m^2	27.5 ± 8.1
Baseline exercise capacity	
6MWD, m	464.49 ± 99.88
Pulmonary function	
FEV_1, L (% pred)	1.37 ± 0.34 (49 ± 16)
FEV_1/FVC, %	43 ± 9
FRC, L (% pred)	4.62 ± 1.30 (143.73 ± 37.35)
TLC, L (% pred)	7.12 ± 1.40 (119.73 ± 20.79)
RV, L (% pred)	3.83 ± 1.33 (164.55 ± 47.03)
RV/TLC, %	52 ± 9
PImax, cm H_2O (% pred)	76.00 ± 36.44 (74 ± 30)
PEmax, cm H_2O (% pred)	94.55 ± 45.55 (51 ± 20)
DLCO, ml/mmHg/min (% pred)	12.66 ± 3.91 (51± 14)
SaO2, %	96 ± 2

Values are means ± SD. Definitions of abbreviations: BMI = body mass index; 6MWD = 6-minute walk distance; FEV_1 = forced expiratory volume in 1st second; FVC = forced vital capacity; FRC = functional residual capacity, RV = residual volume; TLC = total lung capacity; PImax = maximum inspiratory pressure; PEmax = maximum expiratory pressure; DLCO = diffusion capacity of the lung for carbon monoxide, SaO_2= arterial oxygen saturation.

Table 5:2: Physiological parameters at rest in 11 patients with COPD

Variable	NV	PSV10 (10 cm H_2O)	PSVt (average of 8.1 ± 4.5 cm H2O)	P ANOVA
VT, L	0.83±0.29	1.13±0.38*	1.03±0.45	0.007
RR, cycles/min	16.42±5.48	16.74±5.99	17.24±4.96	0.602
VE, L/min	12.24±2.55	17.10±3.63*	15.83±4.92*	0.002
Ti, s	1.58±0.52	1.22±0.36*	1.21±0.23*	0.001
Te, s	2.62±1.14	2.88±1.29	2.59±0.84	0.146
TT, s	4.20±1.60	4.10±1.63	3.80±1.05	0.220
VT/Ti , L/s	0.53±0.09	0.93±0.21**	0.84±0.30*	<0.001
VT/Te , L/s	-0.34±0.09	-0.41±0.09*	-0.41±0.13	0.042
PIF, L/s	0.77±0.13	1.37±0.13**	1.21±0.13*	<0.001
PEF, L/s	-0.65±0.18	-0.81±0.22*	-0.76±0.26	0.041
IC, L	2.39±0.65	1.98±0.74*	1.84±0.56*	<0.001
ET CO_2, %	4.51±1.04	3.68±0.84**	3.37±1.10*	0.004
VO_2, L/min	403.20±107.17	427.49±116.0	383.75±105.29	0.208
VCO_2, L/min	291.00±70.33	303.05±100.6	253.56±105.62	0.306
HR, bpm	88.10±15.77	95.60±17.78*	92.90±13.72	0.005
SpO_2, %	96.10±2.92	96.40±1.78	96.60±2.01	0.752
Dyspnea	0.09±0.20	0.32±0.51	0.64±1.00	0.115

Values are means ± SD. VT, tidal volume; RR, respiratory rate; VE, minute ventilation; Ti, inspiratory time; Te, expiratory time; TT, total breath time; VT/Ti, mean inspiratory flow; VT/Te, mean expiratory flow ; PIF, peak inspiratory flow; PEF, peak expiratory flow; iPm, inspiratory mouth pressure; ePm, expiratory mouth pressure, IC, inspiratory capacity; ET CO_2, end tidal CO_2; VO_2, oxygen uptake; VCO_2, carbon dioxide output; SpO_2 arterial oxygen saturation; HR, heart rate.

For post-hoc contrasts: *p< 0.05, relative to without NV; **p< 0.001, relative to without NV; † p< 0.05, relative to PSV10; ǂ p< 0.001, relative to PS10.

Table 5:3: Physiological parameters at isoload in 11 patients with COPD

Variable	NV	PSV10 (10 cm H_2O)	PSVt (average of 8.1 ± 4.5 cm H2O)	P ANOVA
VT, L	1.23±0.33	1.38±0.35*	1.33±0.40*	0.035
RR, cycles/min	27.49±6.63	24.51±5.66*	24.18±6.97*	0.008
VE, L/min	32.89±10.10	32.75±9.22	30.16±9.65	0.091
Ti, s	0.90±0.18	0.91±0.97	0.97±0.25	0.232
Te, s	1.43±0.42	1.70±0.51*	1.76±0.65*	0.002
TT, s	2.34±0.56	2.61±0.65*	2.73±0.89*	0.007
VT/Ti , L/s	1.40±0.43	1.53±0.36	1.41±0.42	0.194
VT/Te , L/s	-0.89±0.28	-0.85±0.26	-0.79±0.24*	0.033
Mean iPm, cmH_2O	-0.16±0.14	8.58±2.22**	7.45±4.13**	<0.001
Mean ePm, cmH_2O	0.00±0.01	7.03±1.49**	6.89±1.30**	<0.001
PIF, L/s	2.06±0.71	2.14±0.43	1.99±0.58	0.607
PEF, L/s	-1.62±0.59	-1.41±0.47	-1.22±0.41*†	0.001
IC, L	1.87±0.42	1.71±0.66	1.63±0.55	0.141
ET CO_2, %	5.08±1.08	4.94±1.17	4.75±1.17	0.233
VO_2, L/min	1165.11±483.49	1254.78±520.83	1160.46±495.63	0.046
VCO_2, L/min	914.49±366.10	856.45±355.37	819.89±339.76*	0.034
HR, bpm	112.80±23.86	114.90±23.57	112.90±22.03	0.633
SpO_2, %	93.60±4.35	94.40±4.01	93.50±3.78	0.606
Dyspnea	3.80 ± 1.87	4.32 ± 2.12	3.70 ± 1.54	0.620
Leg Fatigue	3.95 ± 1.50	4.55 ± 1.06	4.09 ± 1.74	0.213

Values are means ± SD. VT, tidal volume; RR, respiratory rate; VE, minute ventilation; Ti, inspiratory time; Te, expiratory time; TT, total breath time; VT/Ti, mean inspiratory flow; VT/Te, mean expiratory flow ; PIF, peak inspiratory flow; PEF, peak expiratory flow; iPm, inspiratory mouth pressure; ePm, expiratory mouth pressure; IC, inspiratory capacity; ET CO_2, end tidal CO_2; VO_2, oxygen uptake; VCO_2, carbon dioxide output; SpO_2 arterial oxygen saturation; HR, heart rate.

For post-hoc contrasts: *p< 0.05, relative to without NV; **p< 0.001, relative to without NV; † p< 0.05, relative to PSV10; ‡ p< 0.001, relative to PS10.

Table 5:4: Physiological parameters at peak exercise in 11 patients with COPD

Variable	NV	PSV10 (10 cmH_2O)	PSVt (average of 8.1 ± 4.5 cmH2O)	P ANOVA
VT, L	1.28± 0.36	1.39± 0.35	1.34± 0.38	0.059
RR, cycles/min	28.40±6.64	25.28±6.30*	27.40±7.21†	0.006
VE, L/min	35.62±11.75	34.24±10.16	34.59±11.84	0.776
Ti, s	0.85± 0.17	0.88± 0.19	0.84± 0.18	0.437
Te, s	1.40±0.42	1.67±0.54*	1.52±0.51*	0.002
TT, s	2.25±0.57	2.55±0.69*	2.36±0.67	0.007
VT/Ti , L/s	1.54±0.47	1.59±0.35	1.61± 0.46	0.698
VT/Te , L/s	-0.95±0.34	-0.89±0.30	-0.92±0.31	0.511
PIF, L/s	2.28±0.71	2.23±0.44	2.25±0.58	0.958
PEF, L/s	-1.74±0.60	-1.44±0.48*	-1.38±0.48*	0.003
IC, L	1.82±0.42	1.71±0.63	1.52±0.51*	0.043
ET CO_2, %	5.10±1.04	4.95±1.15	4.75±1.12	0.223
VO_2, L/min	1258.14±519.05	1321.49±545.95	1305.49±510.73	0.520
VCO_2, L/min	996.57±357.77	914.15±392.38	954.19±373.20	0.315
HR, bpm	115.60±23.20	117.70±24.91	118.70±24.07	0.592
SpO_2, %	93.40±4.30	94.30±3.92	93.30±3.97	0.414
Dyspnea	5.40±1.66	6.00±1.69	6.09±1.59	0.290
Leg Fatigue	6.05±2.08	6.68±1.86	6.05±2.22	0.407

Values are means ± SD. VT, tidal volume; RR, respiratory rate; VE, minute ventilation; Ti, inspiratory time; Te, expiratory time; TT, total breath time; VT/Ti, mean inspiratory flow; VT/Te, mean expiratory flow ; PIF, peak inspiratory flow; PEF, peak expiratory flow; iPm, inspiratory mouth pressure; ePm, expiratory mouth pressure; IC, inspiratory capacity; ET CO_2, end tidal CO_2; VO_2, oxygen uptake; VCO_2, carbon dioxide output; SpO_2 arterial oxygen saturation; HR, heart rate.

For post-hoc contrasts: *p< 0.05, relative to without NV; **p< 0.001, relative to without NV; † p< 0.05, relative to PSV10; ǂ p< 0.001, relative to PS10.

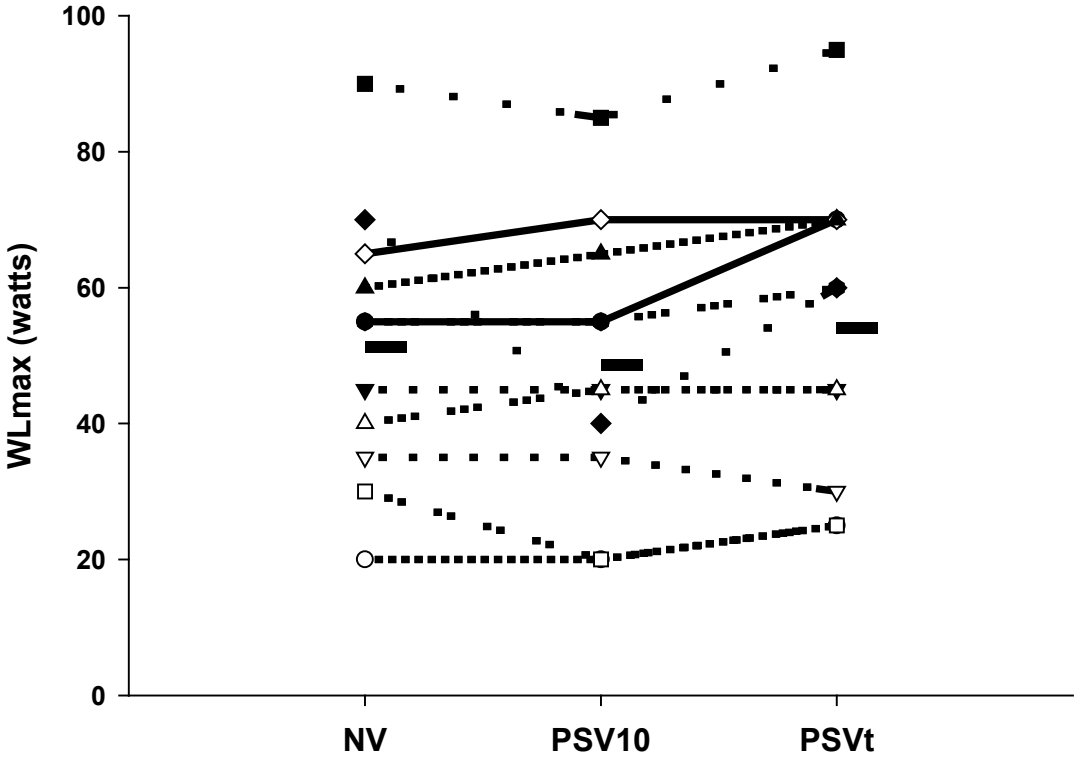

Figure 5.2: Individual workload max performances with NV, PSV10 and PSVt
WLmax =maximum workload achieved; NV = no ventilator; PSV10 = pressure support ventilation 10 cm H_2O of assist; PSVt = pressure support ventilation titrated to comfort; horizontal bars are the mean WLmax achieved.

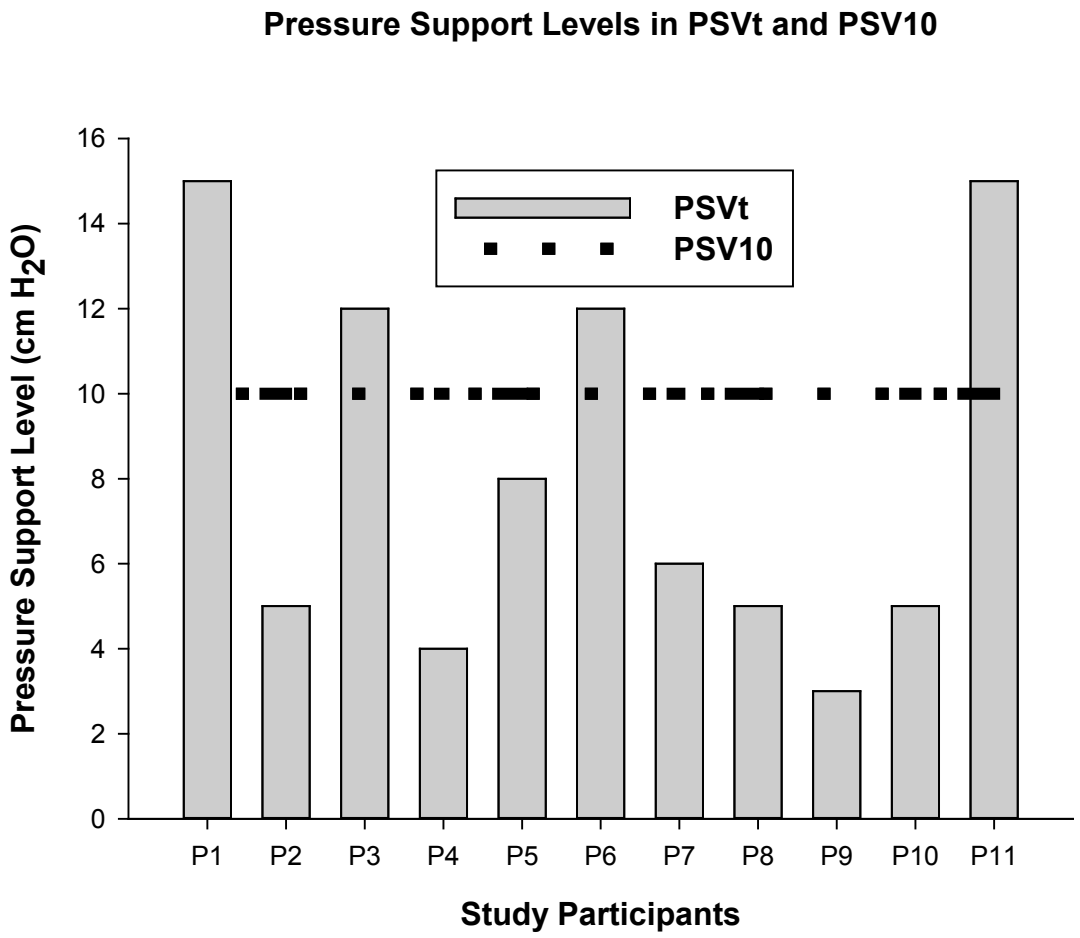

Figure 5.3: Pressure support levels titrated to patient comfort (PSVt)
PSV10= pressure support ventilation with assist of 10 cm H_2O,

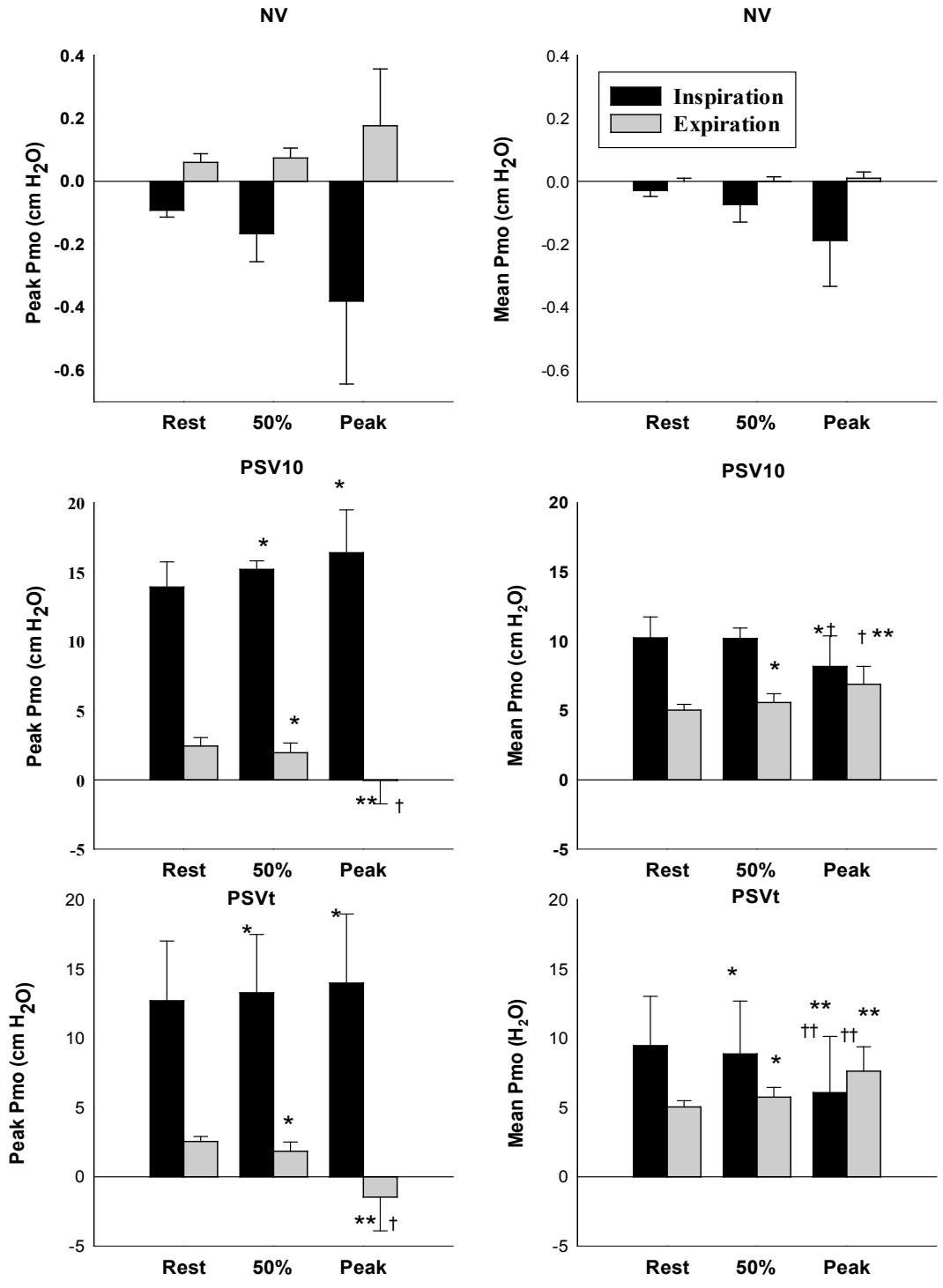

Figure 5.4: Peak inspiratory and expiratory (left) and mean inspiratory and expiratory mouth pressures with NV, PSV10 and PSVt

*NV = no ventilator; PSV10 = pressure support ventilation 10 cm H_2O of assist; PSVt = pressure support ventilation titrated to comfort. For post-hoc contrasts: *p< 0.05, relative to without NV; **p< 0.001, relative to without NV; †p< 0.05, relative to PSV10; †† p< 0.001, relative to PS10*

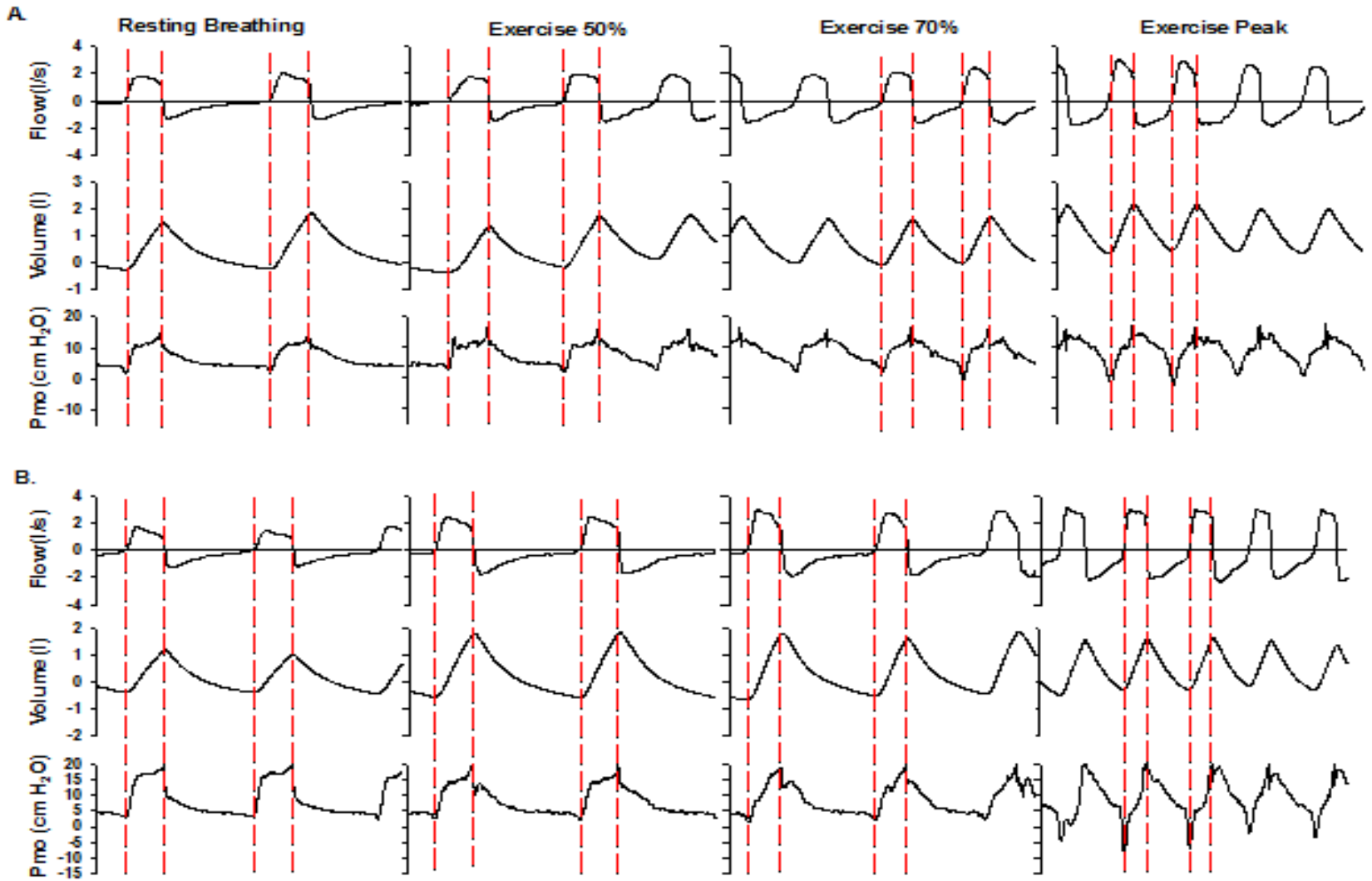

Figure 1.4: Flow, volume and mouth pressure signal at resting breathing, 50% exercise, 70% exercise and at peak exercise in Participant 11 during PSV10 (panel A) and higher titrated pressure of 15 cm H_2O (panel B)

PSV10 is pressure support ventilation of 10 cm H_2O. Pmo is mouth pressure.

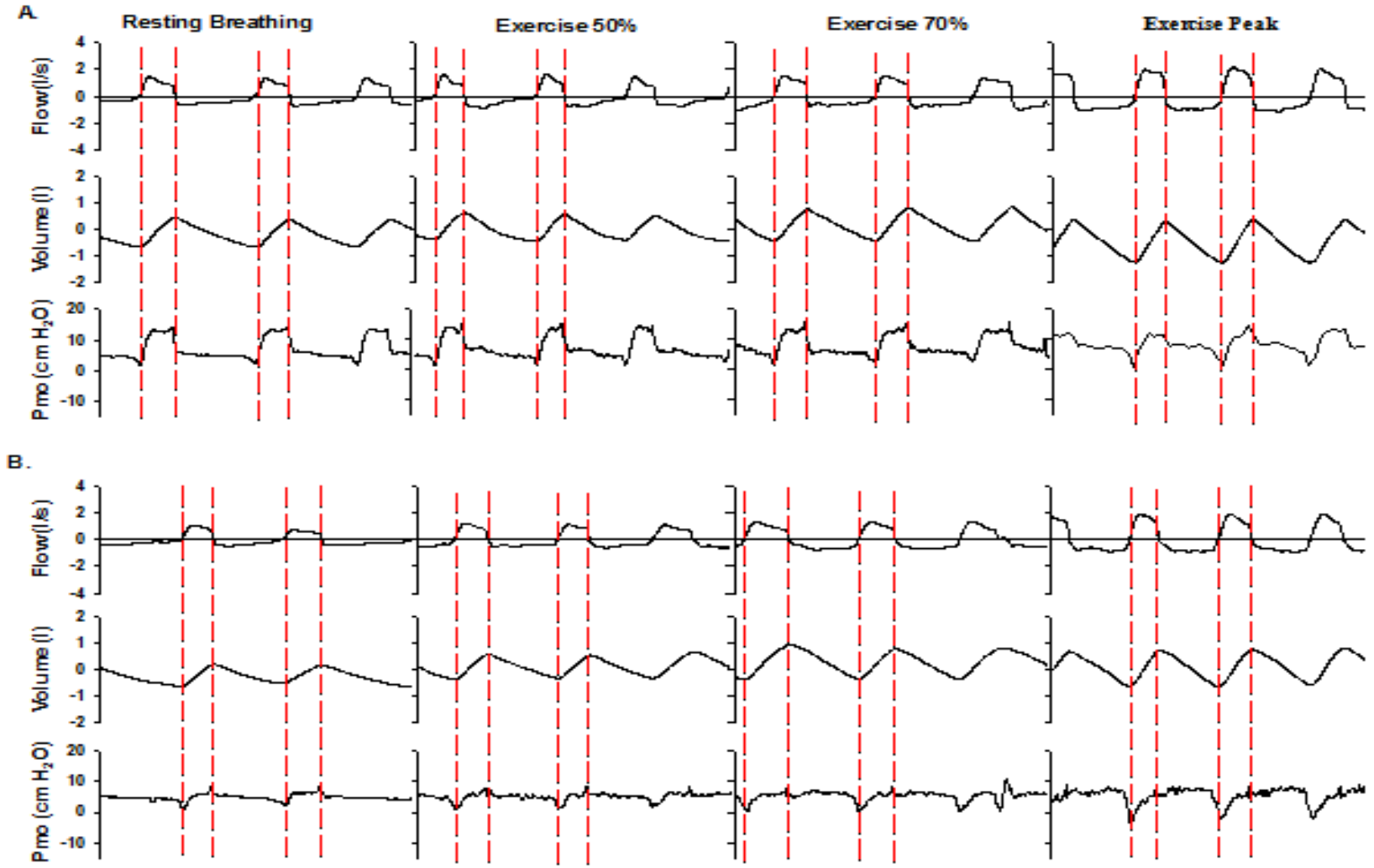

Figure 5.6: Flow, volume and mouth pressure signal at resting breathing, 50% exercise, 70% exercise and at peak exercise in Participant 9 during PSV10 (panel A) and lower titrated pressure of 3 cm H_2O (panel B)

PSV10 is pressure support ventilation of 10 cm H_2O. Pmo is mouth pressure.

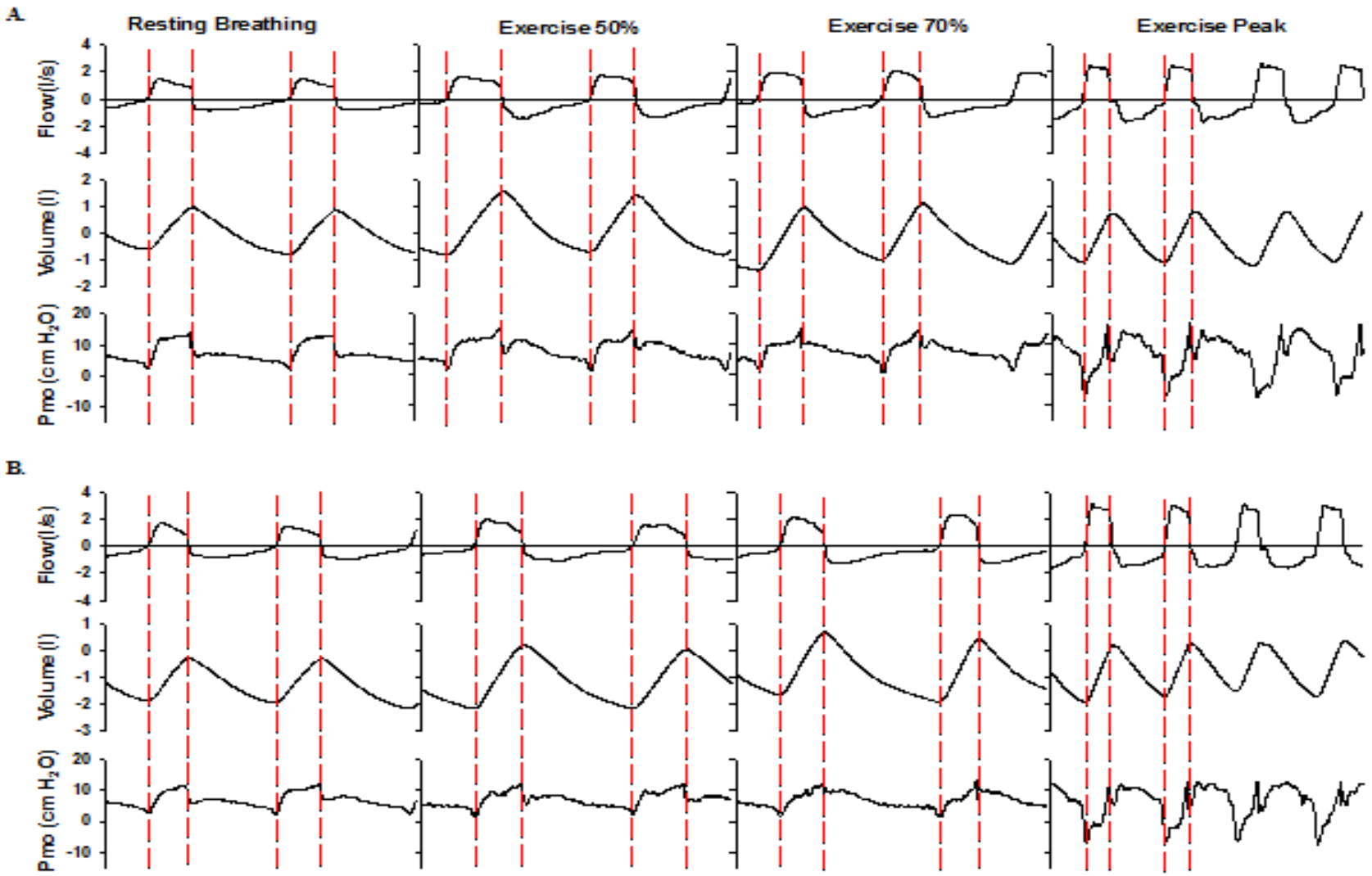

Figure 5.7: Flow, volume and mouth pressure signal at resting breathing, 50% exercise, 70% exercise and at peak exercise in participant 5 during PSV10 (panel A) and an average titrated pressure of 8 cm H_2O (panel B)

PSV10 is pressure support ventilation of 10 cm H_2O. Pmo is mouth pressure.

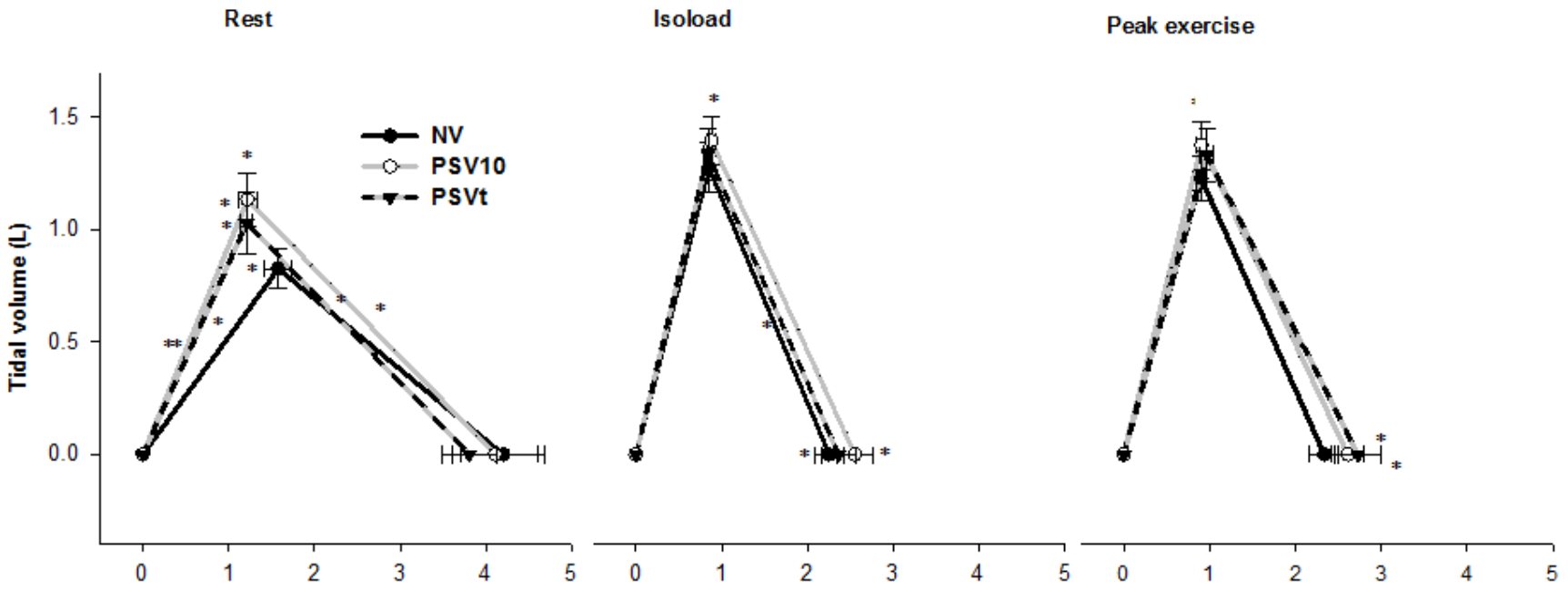

Figure 5.8: Spirograms depicting the breathing pattern at rest, isoload and peak exercise in conditions of NV, PSV10 and PSVt

*NV= no ventilator, PSV10= pressure support ventilation with assist of 10 cm H_2O, PSVt= pressure support ventilation titrated to comfort. Plots are average value ± SEM. For post-hoc contrasts: *p< 0.05, relative to without NV; **p< 0.001, relative to without NV; † p< 0.05, relative to PSV10; †† p< 0.001, relative to PS10*

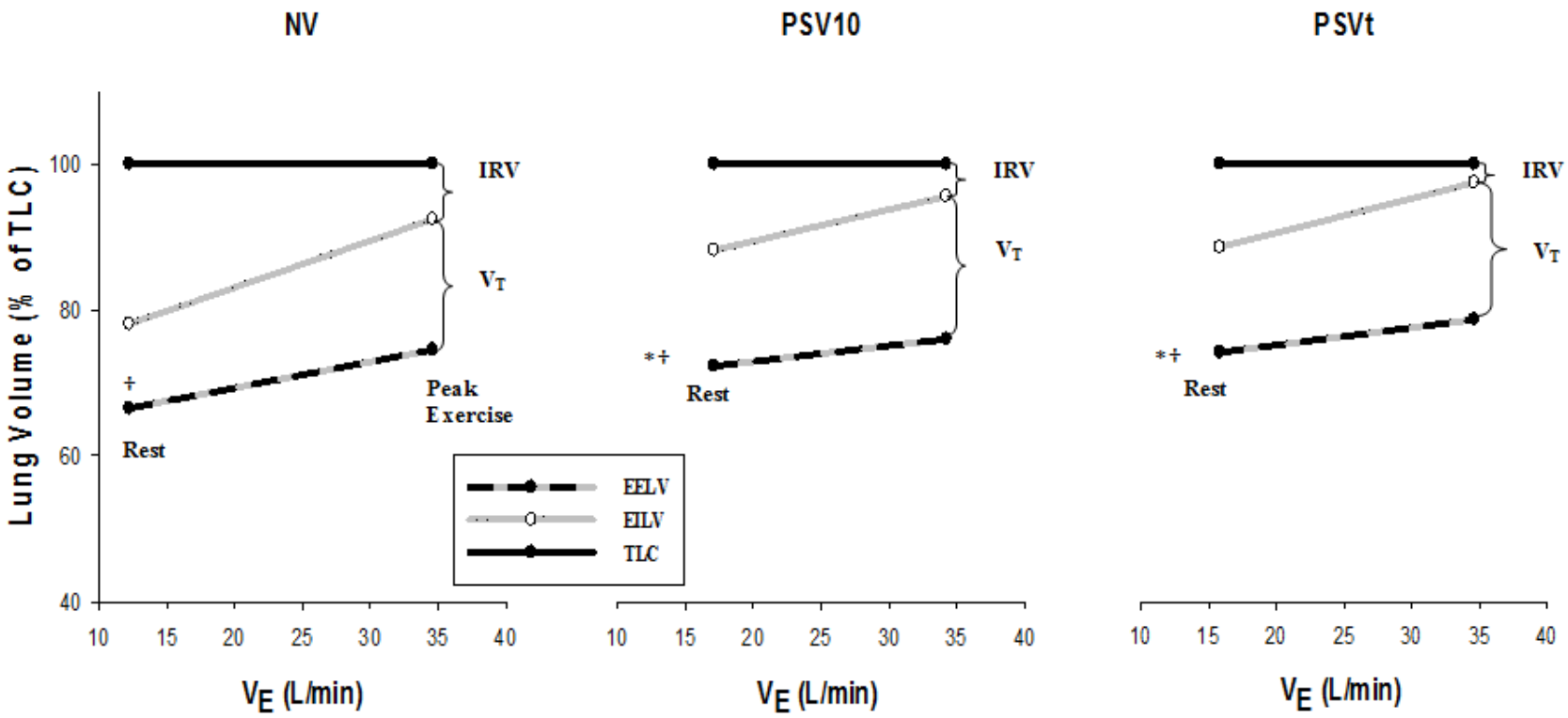

Figure 5.9: Plot of lung volumes vs ventilation at rest and peak exercise in conditions of NV, PSV10 and PSVt

*NV= no ventilator, PSV10= pressure support ventilation with assist of 10 cm H_2O, PSVt= pressure support ventilation titrated to comfort. ANOVA between the three conditions: † $p < 0.05$. For post-hoc contrasts: *$p< 0.05$, relative to without NV;*

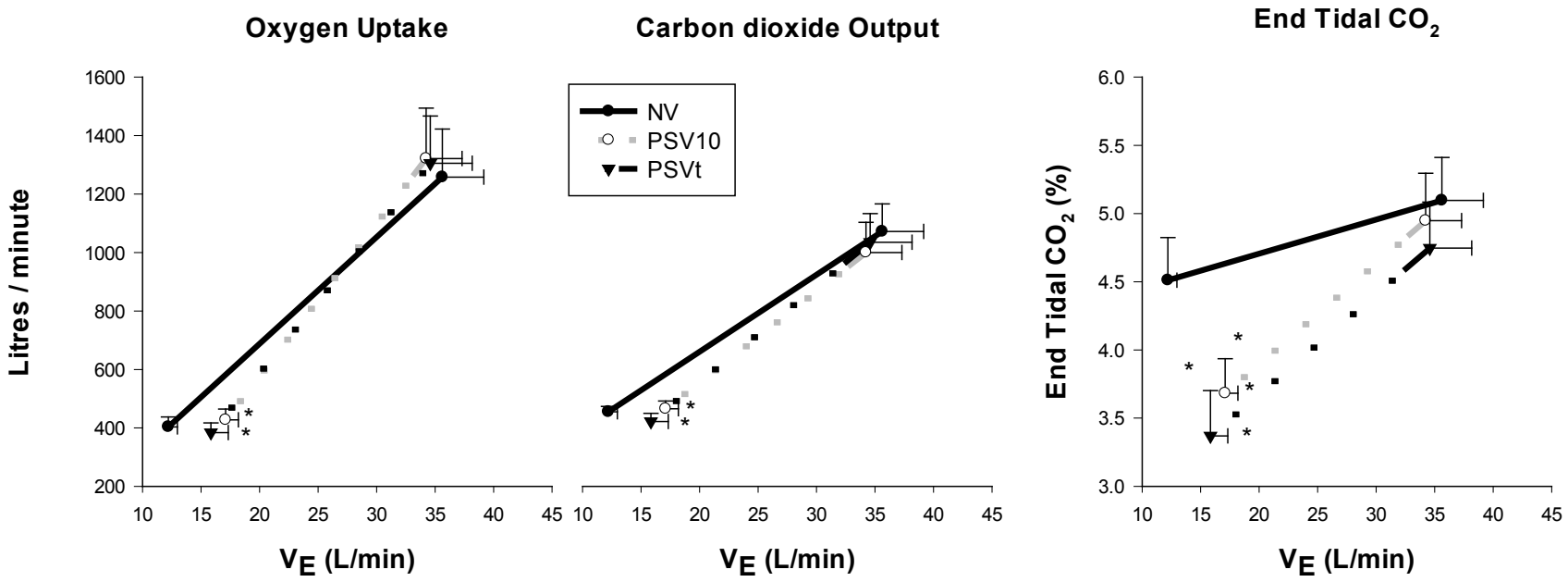

Figure 5.10: Plot of oxygen uptake, carbon dioxide output and end tidal CO2 vs minute ventilation at rest and peak exercise
*NV= no ventilator, PSV10= pressure support ventilation with assist of 10 cm H_2O, PSVt= pressure support ventilation titrated to comfort. For post-hoc contrasts: *p< 0.05, relative to without NV*

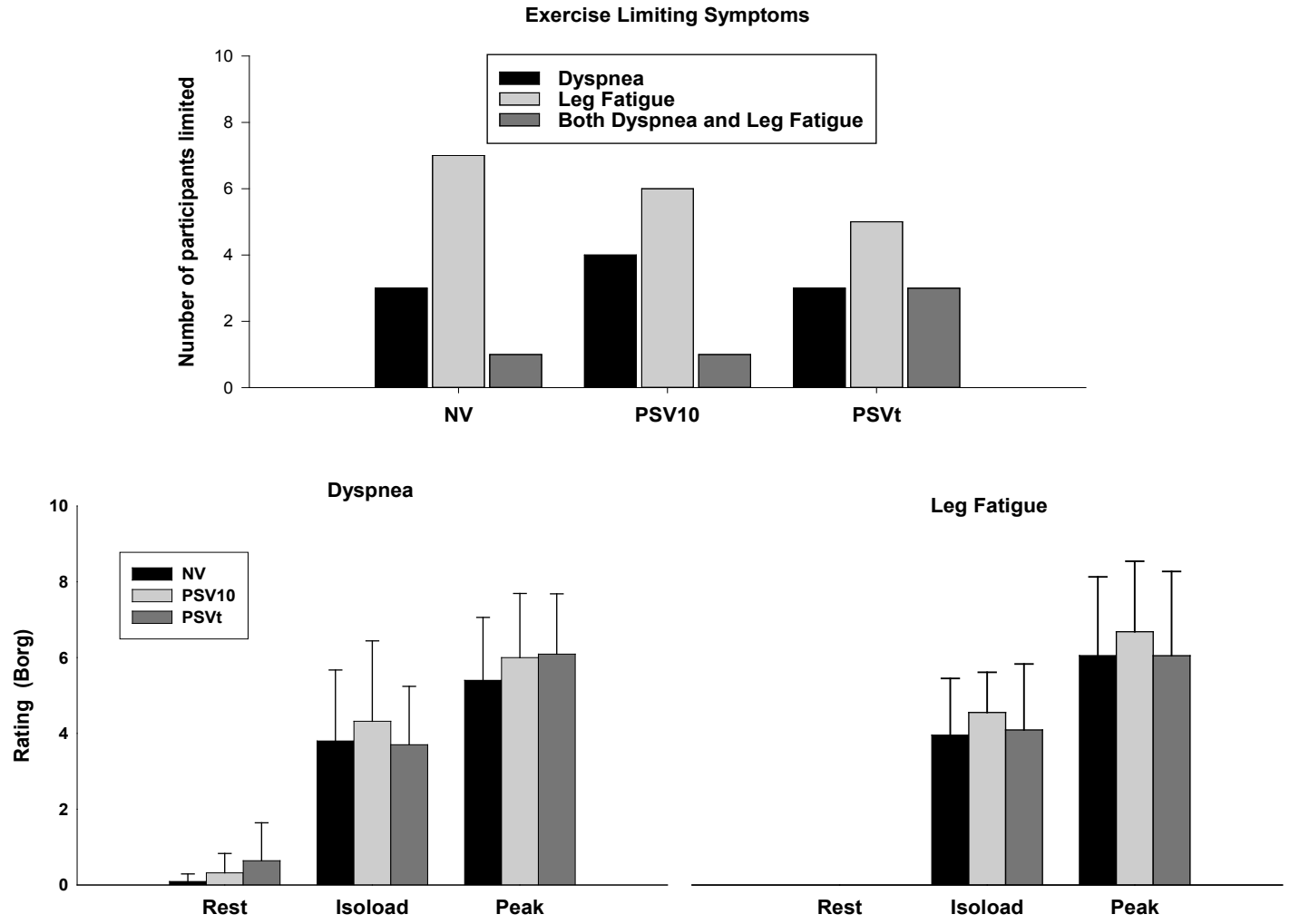

Figure 5.11:Exercising limiting symptoms in conditions of NV, PSV10 and PSVt (upper panel), dyspnea and leg fatigue rating at rest, isoload and peak exercise in the three ventilatory strategies (lower panel)

NV= no ventilator, PSV10= pressure support ventilation with assist of 10 cm H_2O, PSVt= pressure support ventilation titrated to comfort

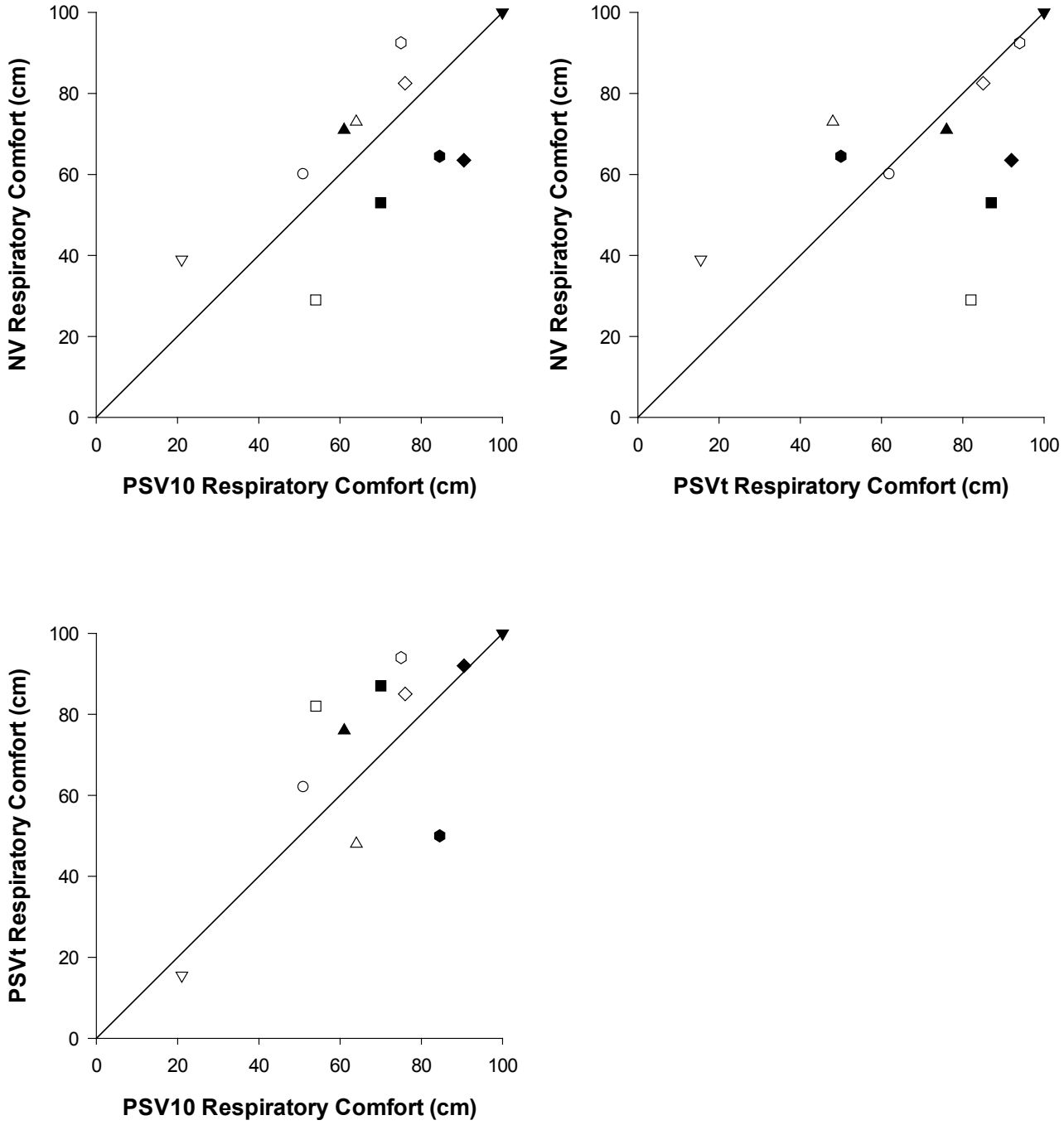

Figure 5.12: Identity plots of ratings of respiratory comfort during exercise

NV= no ventilator, PSV10= pressure support ventilation with assist of 10 cm H_2O, PSVt= pressure support ventilation titrated to comfort

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SAMPLE SIZE CALCULATION

The sample size was calculated based on our primary outcome (maximum exercise capacity). A previous study has given the minimal clinically important difference in maximum exercise capacity while using an incremental bicycle exercise test as 10watts [228]. Effect size of 0.625 was estimated from a standard deviation of 16 watts which we obtained from a previous study [12] which looked at the effect of BiPAP on symptom-limited maximum exercise in COPD patients. Using the software program G*Power (version 3.1.6) [229], sample size for ANOVA repeated measures within factor analysis was estimated. With an estimated effect size of 0.625, number of groups equal to 1, number of measurements for each outcome equal to 3, power of 90%, significance level of α=0.05, correlation among repeated measures of 0.2 and a non-sphericity correlation of 0.813 (estimated from the variances in the work of Moga et al [12]), we calculated that a minimum sample size of twelve subjects is needed for this study.

CHAPTER VI: CONCLUSION

Non-invasive mechanical ventilation has been used as adjunct to exercise in pulmonary rehabilitation but its acute effect during exercise on maximum exercise capacity remains to be fully explored. Findings from a recent study[12] which looked at the acute effect of non-invasive ventilatory support on maximum exercise capacity in patients with COPD revealed that BiPAP ventilation using a standard exhalation device resulted in a reduced maximum exercise capacity compared to no ventilatory assist. The BiPAP machine uses a single limb for inspiration and expiration which makes it prone to cause CO_2 re-breathing during ventilation with the standard exhalation device. Re-breathed CO_2 can result in increased work of breathing and decreased maximal exercise capacity. Comparatively the Maquet SERVO-i ventilator has a separate limb for inspiration and expiration and hence does not pose the risk of CO_2 re-breathing during ventilation. We therefore wondered if eliminating CO_2 rebreathing changes the effect of NIMV on maximum exercise capacity. Earlier studies which had examined the effect NIVM on exercise capacity had also used either a fixed level of support of about 10-12 cm H_2O or levels titrated to patient's comfort, but it remained unknown if titrating the level of support or using a fixed value was better in the use of NIMV as an adjunct to exercise. This study addressed these areas of knowledge that were lacking scientific evidence.

Eleven participants with moderate to severe COPD participated in this study, which used a crossover design to evaluate the effect of a fixed versus an individually optimized level of pressure support ventilation (PSV) delivered during symptom-limited incremental bicycle, on maximum exercise capacity, breathing pattern, metabolic parameters, EELV, exercise limiting symptoms and respiratory comfort in comparison to unassisted exercise.

The main findings of this study is that i) there was no difference in maximum exercise capacity between assisted and unassisted exercise; ii) titration of PSV level to comfort during resting breathing did not improve maximum exercise capacity and respiratory comfort during exercise. Our results indicate that the COPD patients in our study exercising with the Maquet SERVO-i ventilator were outdriving the ventilator as they approached peak exercise as shown by the mean inspiratory and expiratory Pmo values and Pmo tracings. This resulted in flow asynchrony,

trigger delays and expiratory muscles activation as exercise progressed towards peak which affected the efficiency of the Maquet SERVO-i ventilator at peak exercise.

The Maquet SERVO-i ventilator, to the best of our knowledge, has a strong capacity and capability in terms of flow, assist level, rate of rise etc. compared to other similar ventilators that have the pressure support mode. These results suggests that the conventional ventilators originally designed to assist breaths and unload inspiratory muscles in patients breathing at rest, may not be sufficient to effectively assist breath and unload inspiratory muscles during high intensity exercises. This underscores the need for manufacturers to consider this emerging area of need in pulmonary rehabilitation in the development of future non-invasive mechanical ventilators.

To the best of our knowledge this is the first study to show decreased effectiveness of a NIMV with progression in exercise intensity. This is also the first study to show that titration of pressure support level to comfort at rest does not seem to improve maximum exercise capacity and does not seem to improve respiratory comfort during exercise.

In conclusion, the study has contributed to the advancement of knowledge in this area by evaluating the acute effects of NIMV in individuals with COPD exercising with and without a ventilator. Since this study used the Maquet SERVO-i ventilator with a fixed inspiratory rise time of 0.2s, cycling at 50% and PEEP set to 4 cm H_2O, it would be interesting for future studies to determine if i) changing the type of ventilator used to deliver PSV, ii) titrating the inspiratory rise time, cycling criteria and external PEEP during resting breathing or exercise might alter outcomes and ventilator effectiveness in improving maximum exercise capacity achieved during a symptom-limited incremental exercise test.

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APPENDIX A: OUTCOME MEASUREMENTS

Maximum exercise capacity

Maximum exercise capacity was taken as the highest workload (WLmax) reached and maintained for at least 30 seconds on the incremental exercise test on the bicycle ergometer. Test-retest reliability of symptom-limited cycle ergometer tests has been shown to be as reliable in patients with chronic obstructive pulmonary disease as in apparently healthy subjects [184]. Isoload was operationally defined as the lowest of the three maximum exercise workloads achieved in the three symptom-limited incremental exercise tests.

Breathing pattern and ventilator pressure

Breathing pattern was assessed at rest and during exercise by measuring inspiratory and expiratory airflow using a pneumotach (Pneumotachograph, model 4813; Hans Rudolph, Kansas City, MO, USA) and a differential pressure transducer (TSD160A - Differential Pressure, 2.5 cm H20, DA100C, Biopac Systems, Santa Barbara, CA, USA). Volume was obtained by digital integration of the flow signal. Mouth pressure was recorded from a side port of the mouthpiece connected to a separate pressure transducer (TSD160E - Differential Pressure, 350 cm H20, DA100C, Systems, Santa Barbara, CA, USA). Calibration of the flow and pressure signals from the differential pressure transducers was done before each test using a 3 litre syringe and ....cm H_2O pressure from a U-tube manometer respectively. In all trials, the flow and pressure signals were acquired on line on a personal computer at a sampling rate of 125 Hz using a 16-bit A/D converter (MP 100A-CE, Biopac Systems, Santa Barbara, CA, USA), and was stored on a personal computer for offline analysis. The collected data was encoded and protected with by a password as it is being stored. Off-line breath by breath analysis was subsequently performed on the last 15-20 breaths of each minute at rest and during exercise in every participant and the group mean values was then be calculated from these breath-by-breath data. Mechanical timing parameters of breathing pattern including Ti, Te, Ttot and duty cycle (Ti/Ttot) was determined from the flow signal. The tidal volume (V_T) was used for the calculation of minute ventilation.

Metabolic Parameters

Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) [indicators of gas exchange] was measured at rest and during exercise with a COSMED system (COSMED K4b2, Rome, Italy). Calibration of the COSMED K4b2 system was performed, immediately before each test, by using a 3-liter syringe to calibrate the turbine and using a gas reference gas mixture (16% O_2 and 5% CO_2; balanced N_2) for its gas analyzers. Heart rate and oxygen saturation was also be measured continuously at rest and during exercise using a pulse oximeter (COSMED K4b2, Rome, Italy), while ECG was being monitored online during the test using. The validity, reliability and linearity of these instruments for use in the human respiratory system and COPD population has been shown in published studies [185-193].

Operational Lung Volume

End-expiratory lung volume (EELV) was obtained by subtracting the inspiratory capacity (IC) volume from measures of total lung capacity (TLC) previously obtained during pulmonary function testing. Changes in inspiratory capacity reflect changes in dynamic EELV [194]. Therefore, serial measurements of IC will mirror changes in operational lung volumes. O'Donnell et al [194], has shown that serial IC measurements during exercise are reproducible and responsive and to be well correlated with changes in exertional dyspnea. Individuals were asked to perform IC manoeuvres at rest, every minute during the exercise, and at peak exercise. To avoid possible effects of performing IC manoeuvres on dyspnea intensity, IC manoeuvres were always performed after completing the symptom intensity ratings.

Dyspnea and Leg Fatigue Symptoms

The modified 10-point Borg scale, was used to assess the perception of dyspnea and leg fatigue. Validity of the Borg Scale has been established by a high degree of correlation (r=0.98) and oxygen uptake (r=0.95) during incremental exercise [195, 196]. A very good reproducibility (r=0.96) for rating respiratory sensations at peak exercise has also been found in COPD patients [195, 196]. The modified 10-point visual analogue scale has been shown to be reproducible and to correlate closely with the Borg score when scaling the sense of effort to breathe during exercise in subjects with stable chronic obstructive pulmonary disease [197]. The modified 10-point Borg's scale of dyspnea have also been found to be highly reproducible and responsive

during cycle exercise in individuals with stable advanced COPD and the Borg's ratings of perceived leg discomfort scale is also reported to be highly reproducible [194].

The scale was explained to the participants before the start of the exercise and assessment was done at the last 15 seconds of every minute. On completion of the test, participants were also required to describe the main reason for stopping the exercise.

Comfort Assessment

A 10 cm visual analogue scale, with anchors of worst comfort and best comfort on either end, was used to assess patient`s level of respiratory comfort for each exercise test session [203, 230]. The scale was explained to the participants before the start of the exercise and assessment was done immediately after the exercise.