

**Effect of Inspiratory Pressure Support on Exercise Performance in Patients  
with Chronic Obstructive Pulmonary Disease**

By

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**Declaration**

I, the undersigned, declare that the project material, which I now submit, is my own work, that any data presented is accurate and was collected and analyzed by myself. Any assistance received by way of borrowing from the work of others has been cited and acknowledged within the work. I make this declaration in the knowledge that a breach of the rules pertaining to project submission may carry serious consequences. I am aware that the project will not be accepted unless this form has been handed in along with the project.

Signed: Anita Doggett Date: 4/10/06.

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## ABSTRACT

**Title:** Effect of inspiratory pressure support on exercise performance in patients with chronic obstructive pulmonary disease.

**Purpose:** This study examined the effects of a non-invasive ventilator on submaximal and maximal exercise performance in patients with chronic obstructive pulmonary disease (COPD).

**Methods:** Fourteen men ( $66.0 \pm 7.4$ yr) and six women ( $59.0 \pm 7.4$ yr) with a diagnosis of COPD, a forced expiratory volume<sub>1</sub> (FEV<sub>1</sub>) <40%, and the ability to tolerate 12 cmH<sub>2</sub>O of pressure on a non- invasive ventilator performed two maximal exercise tests on a cycle ergometer, with and without ventilatory assistance prior to exercise. Blood samples, respiratory metabolic measures, heart rate and rating of perceived exertion (RPE) were obtained throughout each exercise test.

### Results:

Peak work rate (W), total exercise time, and respiratory rate were higher ( $p < 0.05$ ) when exercise was preceded by ventilatory support compared to no support. There was no difference in peak oxygen uptake (VO<sub>2</sub>), carbon dioxide (VCO<sub>2</sub>), heart rate (HR), minute ventilation (V<sub>E</sub>), tidal volume (V<sub>T</sub>), blood lactate or RPE between the two experimental conditions. A total of 12 subjects completed at least 5 stages of the exercise protocol, and their physiological response during exercise with NIV and without NIV were compared. RPE was significantly lower during the first 3 min in the NIV condition than the no NIV condition. Circulating levels of blood lactate were lower ( $p < 0.01$ ) during stage 3 in the NIV than the than no NIV condition. There was no difference in RR, V<sub>T</sub>, HR, %HR, V<sub>E</sub>, VO<sub>2</sub> and %VO<sub>2</sub> between the two experimental conditions during sub maximal exercise.

**Conclusions:** Application of non-invasive ventilatory support prior to exercise improves maximal exercise performance, but has no effect on cardio-metabolic response during submaximal exercise in patients with COPD.

**Table of Contents:**

Title page	i
Declaration	ii
Acknowledgments	iii
Abstract	iv
Table of Contents	v
List of Tables	vi
<b>Chapters:</b>	
I: Introduction	7
II: Literature Review	9
III: Methodology	23
IV: Results	31
V: Discussion	37
VI: Conclusion	43
References	44
Appendices	48

**List of Tables:**

Table 1: Classification of COPD

Table 2: Patient demographics

Table 3: Patient clinical characteristics

Table 4: Hemodynamic and metabolic variables at peak exercise

Table 5: Demographic and physiological characteristics of patients who completed 5 stages and those who completed  $>5$  or  $\geq 6$  stages of the exercise protocol

Table 6: Peak exercise values for patients who completed 5 stages and those who completed  $>5$  or  $\geq 6$  stages of the exercise protocol

Table 7: Physiological responses at 1 min intervals in patients who completed the first 5 stages of the exercise protocol

## CHAPTER 1

### INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death worldwide, and is predicted to further increase in the coming decades (1). It is a group of disorders characterised by progressive limitation in predominantly expiratory airflow that is partially reversible by bronchodilator, or anti-inflammatory therapy (2). A post bronchodilator (salbutamol) FEV1 < 80% of predicted value in combination with an FEV1/FVC < 70% during spirometry, confirms expiratory airflow that is partially reversible by bronchodilator (1).

Treatment modalities in COPD include both invasive and non-invasive procedures. Invasive procedures include endotracheal tube, laryngeal mask, and tracheotomy. Non-invasive ventilation (NIV) refers to the provision of ventilatory support through the upper airway, with the use of a face mask. NIV ventilators increase the volume of air inhaled into the lungs. This augments alveolar ventilation ( $V_A$ ), by decreasing blood pH, arterial carbon dioxide content ( $\text{PaCO}_2$ ) and respiratory rate (RR) in patients with COPD (3). This procedure is currently used in patients with COPD who are in acute hypercapnic respiratory failure ( $\text{PaCO}_2 > 6\text{kPa}$ ) (3). A major advantage of NIV is that it delays and/or prevents the need for intubation.

Lung function does not appear to limit exercise performance in healthy individuals (4). In contrast, physical activity levels, particularly activities of daily living (ADL) are compromised in patients with COPD (5). Other co-morbidities such as cardiovascular disease (CVD), osteoporosis, myopathy, and anxiety, may also restrict physical activity in these patients. Therapies that are aimed to enhance physical activity levels have the potential to benefit this

patient group. The aim of the present study is to examine the effect of non-invasive ventilatory support on exercise performance in patients with COPD.

**Rationale:**

COPD patients have higher respiratory rates and reduced tidal volumes ( $V_T$ ) at rest due to major abnormalities in respiratory mechanics. This inability of the respiratory system to maintain adequate alveolar ventilation encroaches on the oxygen available to the non-respiratory muscles, which in turn may limit exercise capacity. NIV in the form of inspiratory pressure support (IPS) has been shown to augment  $V_A$  by delivering pressure support during inspiration. This is due primarily to an increase in  $V_T$  and decrease in RR. Improvements in pulmonary efficiency due to the provision of IPS prior to exercise may improve submaximal and maximal exercise performance.

**Aims of the Study**

The primary aim of the present study is to examine the effect of the administration of non-invasive ventilatory support prior to exercise on submaximal and maximal exercise performance in patients with COPD. The study will specifically examine the effect of the administration of non-invasive ventilatory support prior to exercise on  $V_T$ , RR, minute ventilation ( $V_E$ ),  $VO_2$ , carbon dioxide ( $VCO_2$ ), blood lactate and rating of perceived exertion (RPE).

It is hypothesized that the administration of NIV support prior to exercise will improve pulmonary efficiency and augment submaximal and maximal exercise performance in patients with COPD. Compared to no ventilatory support, the administration of NIV prior to exercise in patients with COPD will result in a lower  $V_T$ , RR,  $V_E$ ,  $VO_2$ ,  $VCO_2$ , blood lactate and RPE during each stage of a maximal exercise test.



## CHAPTER II:

### REVIEW OF LITERATURE

Non-invasive ventilation (NIV) refers to the provision of ventilatory support through the upper airway with the use of a facemask. Different types of ventilators have been used to provide NIV. These include inspiratory pressure support (IPS), bi-level pressure support (BIPAP), and proportional assisted ventilation (PAV). Patients with COPD who are in acute hypercapnic respiratory failure are routinely treated with NIV ventilators. This chapter will review previous studies that have examined the effect of ventilatory support on exercise performance, in patients with COPD.

#### **Structure and Function of the Lungs**

The primary purpose of the respiratory system is to provide oxygen ( $O_2$ ) to the tissues and to remove carbon dioxide ( $CO_2$ ). This exchange of gases occurs at two levels termed internal and external respiration. Internal respiration refers to the use of oxygen within the mitochondria to generate ATP by oxidative phosphorylation and the production of  $CO_2$  as a waste product. External respiration involves the movement of air into and out of the lungs (pulmonary ventilation), and the exchange of  $O_2$  and  $CO_2$  between the lungs and blood by diffusion.

The major organs of the respiratory system are the lungs, which are located in the thoracic cavity. Each lung is divided into lobes; the right lung has three lobes and the left lung has two lobes. Air moves into and out of the lungs by way of the upper airways, and a network of passageways called the respiratory tract. The exchange of  $O_2$  and  $CO_2$  occurs in small air sacs called alveoli. Millions of small pulmonary capillaries are wrapped around the alveoli, to provide an increased surface area for gas exchange.

The conducting zone of the airways consists of the trachea, bronchi, and the terminal bronchioles. The primary function of the conducting airways is to provide a passageway through which air can enter and exit the respiratory zone where gas exchange occurs. The conducting airways contain approximately 150 ml of air and are considered "dead space" because due to the fact that this air does not participate in gas exchange with blood. The terminal bronchioles divide into the respiratory bronchioles, which in turn terminate in the alveolar ducts. The alveoli ducts lead to the alveoli, where gas exchange occurs. The arrangement of the structures in the respiratory zone maximizes surface area and minimizes thickness in order to facilitate the diffusion of O<sub>2</sub> and CO<sub>2</sub> between the external environment and blood.

### **Chronic Obstructive Pulmonary Disease (COPD)**

COPD refers to a group of disorders characterised by progressive limitations in predominantly expiratory airflow that is partially reversible by bronchodilator or anti-inflammatory therapy (2). The term is often used to describe patients with advanced airflow limitation. Emphysema, chronic bronchitis, and asthmatic bronchitis are the three disorders categorized as COPD.

Emphysema is defined as a permanent, abnormal air-space enlargement that occurs distal to the terminal bronchiole, and includes destruction of the alveolar membrane. When the emphysema is limited to the respiratory bronchioles, the disease is categorized as centrilobular. When the air spaces are involved the disease is categorized as panlobular (7).

Chronic bronchitis is defined as the presence of chronic cough with sputum production for at least three months a year, for more than two consecutive years (7). Asthmatic bronchitis is a combination of asthma and bronchitis. Asthma is an inflammatory disease of the airways

that results in reversible airflow limitation (7). The severity of COPD can be classified into four stages (Table 1).

Table 1: Classification of COPD

Stage	COPD Disease Severity	Characteristics
I	At risk	Normal spirometry Chronic symptoms (cough, sputum production)
II	Mild	FEV1/FVC <70% FEV1 >80% predicted, with or without chronic Symptoms (cough and sputum)
III	Moderate	FEV1/FVC <70%, 30%<FEV1<80% predicted With or without chronic symptoms
IV	Severe	FEV1/FVC <70% FEV1<30% predicted or FEV1<50% + respiratory failure or clinical signs of right heart failure

Gold 2001 (1)

### Risk Factors for COPD

A number of host and environmental factors have been identified that contribute to COPD risk. The primary host factors are categorised as genetic, airway hyper responsiveness and lung growth development.

### Genetic Factors

The genetic risk factor contributing to COPD risk that is best characterized is a rare hereditary deficiency of the serum glycoprotein, alpha-1-antitrypsin (AAT) or alpha-1-protease inhibitor. A single gene on chromosome fourteen codes ATT. It is produced and released by the liver into the bloodstream, and inhibits the activity of neutrophil elastase and collagenase (7). These enzymes are produced by activated neutrophils in the fluid lining the alveolus. Elastase and collagenase destroy various components of the extracellular matrix when released into the interstitium or alveolus, and cause emphysema (7). Tobacco smoke stimulates excess release of these enzymes and subsequent increased lung degradation.

This hereditary deficiency of the blood component AAT occurs primarily in Caucasians (2), and accounts for <1% of patients with COPD (7).

### **Airway Hyper Responsiveness and Abnormal Lung Growth**

Airway hyper responsiveness and lung growth have recently been identified as host factors that may influence the development of COPD. Airway hyper responsiveness may occur when the lungs are exposed to irritants, dust and sensitising agents, especially in airways already damaged by other occupational exposures, such as cigarette smoke (1).

Abnormal lung growth may be related to processes occurring during gestation, and to birth weight (8). Abnormal spirometry defined as a postbronchodilator FEV<sub>1</sub> < 80% of the predicted value in combination with an FEV<sub>1</sub>/FVC < 70% may identify individuals who may be at risk of developing COPD (1).

### **Environmental Factors**

Cigarette smokers have a higher prevalence of pulmonary function abnormalities, and respiratory symptoms that lead to COPD. However, not all smokers develop COPD, which suggests that genetic and environmental factors may interact to modify individual risk (1). Passive exposure to cigarette smoke may contribute to respiratory symptoms that lead to COPD by increasing lung exposure to inhaled particles and gases (1). COPD may also result from prolonged or intense exposure to occupational dusts and chemicals (vapours, irritants, fumes). Few studies have examined the harmful effects of high levels of urban air pollution on the development of COPD.

## **Pathology and Pathophysiology of COPD**

COPD is characterised by pathological changes in the central airway and peripheral airways, lung parenchyma, and the pulmonary vasculature. The central airways are the site for excess mucus production due to the presence of enlarged mucus secreting glands and goblet cells (1). The peripheral airways have a smaller diameter size than the central airways.

Destruction of lung parenchyma occurs primarily in patients with COPD (1). It involves the dilation and destruction of the bronchioles in the peripheral airways. As the disease advances, destruction may spread to the pulmonary capillary bed. AAT deficiency is also thought to be a major mechanism in emphysematous lung destruction.

Morphological changes in pulmonary vascular structure are evident in patients with COPD. Thickening of the intima is one of the first structural changes that occur in the early stages of the disease. This is followed by an increase in smooth muscle proliferation, and infiltration of the vessel wall by inflammatory cells (9). Respiratory symptoms such as chronic cough and sputum production normally accompany these vascular changes. These symptoms may be present for many years before other symptoms or pathological changes become evident.

Airflow limitation due to destruction of bronchioles may alter the ability of the small airways to adequately transfer inspired air to the gas exchange regions of the lungs. In advanced COPD, peripheral airways obstruction, parenchyma destruction and vascular abnormalities may reduce the capacity for gas exchange (1), resulting in hypoxemia and hypercapnia (1). Patients with COPD may develop pulmonary hypertension, which in turn may lead to cardiovascular complications.

## **Clinical Evaluation of COPD**

A medical history, physical examination and pulmonary function test are commonly used to diagnosis COPD.

### **Medical History**

The medical history is used to assess exposure to risk factors and history of asthma, allergy, sinusitis, respiratory infections in childhood, and other respiratory diseases. Family history and any pattern of symptom development such as cough and sputum production is normally documented.

### **Physical Examination**

The physical examination is used to screen for the presence of increased respiratory rate, prolonged exhalation, bronchospasm, edema or corpulmonale, and involves an assessment of the accessory respiratory muscles and rib cage. Chest x-ray, arterial blood gas measurements, and  $\alpha$ 1-antitrypsin deficiency screening may also be undertaken during the physical examination.

### **Pulmonary Function Tests**

Standard pulmonary function tests including spirometry/bronchodilator response, lung volume assessment by nitrogen washout and diffusion are commonly used to assess for severity, predict prognosis, and monitor progression of COPD.

Spirometry involves measuring maximal inhalation (forced vital capacity, (FVC)), and the volume of air exhaled during the first second of exhalation ( $FEV_1$ ) during a forced manoeuvre. Patients with COPD have a decrease in both  $FEV_1$  and FVC.

A bronchodilator response test (BDR) involving the administration of salbutamol, followed by a repeated spirometry is commonly undertaken to evaluate the presence of airway reversibility. An improvement in  $FEV_1 \geq 15\%$  of the baseline value is indicative of airway reversibility. The presence of a post bronchodilator  $FEV_1 < 80\%$  of the predicted value in combination with an  $FEV_1/FVC < 70\%$  confirms the presence of airflow limitation that is not fully reversible (1).  $FEV_1/FVC < 70\%$  is considered an early sign of airflow limitation.

### **Lung Volumes**

Additional diagnostic and functional indices of lung capacity and volume can be obtained by assessing functional residual capacity (FRC), total lung capacity (TLC), tidal volume ( $V_t$ ), expiratory reserve volume (ERV) and residual volume (RV) using a nitrogen washout procedure. The test involves measuring the patient's baseline nitrogen level from tidal breathing. This is followed by breathing 100% oxygen on a closed system. RV, TLC, and FRC are usually increased in COPD (1). A high value for TLC indicates hyperinflation of the lungs, and a high RV indicates air trapping in the lower regions of the lung.

### **Single Breath Diffusing Capacity (DLCO):**

Ventilation is defined as the exchange of air between the atmosphere and alveoli by bulk flow. Diffusion is the exchange of  $O_2$  and  $CO_2$  between the alveolar air and blood in the lungs. In healthy individuals, ventilation and blood flow distribution are evenly distributed to each alveolus. This maintains equilibrium between gases in the alveoli and the blood flow in the capillaries. There is a mismatch between alveolar ventilation ( $V_A$ ) and blood flow ( $Q$ ) in patients with COPD.

Ventilation/perfusion ( $V_A/Q$ ) inequality is the term used to describe the mismatch between ventilation and blood flow in an alveoli. When  $V_A/Q$  inequality exists, not all alveoli in

the lung receive the same level of ventilation. Blood flow may also be unevenly distributed among the alveoli (10). This may alter the partial pressure gradients, and impair gas exchange in the lung. Partial pressure gradients facilitate the diffusion of  $O_2$  and  $CO_2$  during respiration. An inequality in VA/Q results in a decrease in arterial and venous  $PO_2$  and an increase in arterial and mixed venous  $PCO_2$ .

There is an uneven distribution of ventilation and perfusion in patients with emphysema due to emphysematous destruction of the terminal lung. The ability to redirect perfusion away from poorly ventilated areas is impaired in patients with bronchitis (7), due to airway inflammation. Minute ventilation ( $V_E$ ) in these patients becomes limited by airflow limitation.

The magnitude of diffusion depends on the surface area of the pulmonary capillary bed, and the matching between ventilation and perfusion within the lungs. The diffusing factor of the lung using carbon monoxide gas (DLCO) is a commonly used test to assess the gas exchange characteristics of the lung. Carbon monoxide (CO) is a highly soluble gas, which combines rapidly with haemoglobin in the capillaries. A 0.3% CO concentration is used during the test. The patient is instructed to inhale a maximum breath from FRC, and hold the breath for 10 sec to allow the CO gas to transfer across the alveolar beds. At the end of the 10 sec the patient exhales maximally and the exhaled breath is analysed to calculate the amount of diffusion that has taken place. DLCO decreases in proportion to the severity of emphysema, due to the loss of alveolar capillary bed (1). When DLCO is disproportionately low in comparison with changes in other pulmonary function tests, emphysema is likely to be the cause of the airflow limitation (1).

Some alveoli may not function adequately in gas exchange due to under perfusion of blood, or inadequate ventilation relative to alveolar surface area. Physiological dead space



(VD/VT) is the term used to describe that portion of the alveolar volume with poor regional perfusion (or ventilation) of tissues. In patients with COPD, VD/VT may be considered large compared to healthy individuals because of the inequality of blood flow and ventilation in the lungs (11).

### **Ventilatory Mechanics During Exercise**

In healthy individuals, ventilation increases during exercise due to an increase in tidal volume and respiratory rate. Tidal volume plateaus at 50-60% VC, and further increases in ventilation are achieved at higher exercise intensities by increasing respiratory rate. Increases in  $V_T$  are achieved by utilising both the ERV and IRV. End-expiratory lung volume (EELV) measures the amount of air remaining in the lung after a forced expiration. This volume decreases to allow  $V_T$  to increase.

Individuals with COPD have both inspiratory and expiratory flow limitations. This is evident as a reduced maximum expiratory flow rates (MEF) and maximum inspiratory flow rates (MIF) during spirometry testing. Airway narrowing causes a reduction in MEF. The reduction in MIF results from a combination of inspiratory flow resistance and reduced muscle strength (5). Reductions in MEF and MIF will greatly restrict an individual's ability to increase ventilation during exercise. Ventilation is limited by the boundaries of the maximal inspiratory and expiratory flow volume curves - the highest inspiratory and expiratory flow rates that can be generated during exercise (5). Patients with COPD can increase their ventilation during exercise by increasing EELV. This will increase MEF and MIF so that inspiratory time decreases, and the time available for expiration increases. This will result in an elevated VE response during exercise at the same relative workload in COPD compared to healthy individuals (5).

### **Respiratory Muscles**

Patients with COPD have skeletal muscle dysfunction due to low levels of physical activity. The respiratory muscles function during inspiration and expiration. In a healthy individual, the diaphragm, external intercostals, and the accessory muscles (scalenes and sternocleidomastoids) are active during exercise. The internal intercostals and the abdominals (rectus transverse, abdominus, abdominal obliques) are active during expiration. These respiratory muscles are active contributors to the respiratory movements of breathing, both at rest, and during exercise. The abnormal distribution of blood flow within the respiratory muscles (5) also impairs muscle perfusion and causes hypoxia in these patients. High/low doses of corticosteroids may cause profound myopathic changes, which may also impair respiratory muscle function (5).

### **Cardiovascular Function and Metabolic Acidosis**

There is a linear relation between heart rate and oxygen consumption  $VO_2$  during progressive incremental exercise in healthy individuals. In contrast, COPD patients have a higher heart rate at a given  $VO_2$  during exercise compared to a healthy individual (12,13,14,15). Heart rate and oxygen pulse ( $VO_2$ /heart rate) at peak exercise is usually lower in COPD than age and gender matched healthy individuals. There is also evidence that mixed venous  $PO_2$  may be higher than normal in some patients with COPD. This indicates impaired oxygen uptake by the working muscles, and/or impairment of the normal redistribution of blood flow to working muscles during exercise (5).

Metabolic acidosis is a respiratory stimulant and may further increase the ventilatory demands of exercise in patients with COPD (24). Acidosis may occur at a relatively low

exercise intensity in some patients with severe COPD (13) due to a) low  $VO_2\text{max}$ , b) cardiovascular dysfunction, and c) lactate production by the respiratory muscles (24).

### **Non-Invasive Ventilation (NIV)**

NIV refers to the technique of providing ventilatory support without a direct conduct to the airways (3). This form of ventilation is now used widely in patients with COPD. Two types of NIV ventilators are commonly used to treat patients with COPD. BIPAP ventilators provide pressure support on inspiration (IPAP) and during expiration (EPAP) and IPS ventilators provide pressure support only on inspiration. A number of studies have evaluated the benefits of NIV when administered during or prior to acute respiratory exacerbations. In contrast, few studies have evaluated the physiological effect of inspiratory pressure support ventilators during exercise in stable COPD patients.

### **Inspiratory pressure and exercise performance**

Van't Hul, et al., (16) evaluated the effect of inspiratory pressure support on exercise endurance performance during an acute bout of exercise. Forty-five patients with COPD performed three constant-load endurance tests on a cycle ergometer at 75% of maximal workload with no IPS, and with  $IPS5\text{cmH}_2\text{O}$ , and  $IPS10\text{cmH}_2\text{O}$ . Patients were attached to the ventilator via corrugated tubing and a mouthpiece. Spirometry, lung volumes, DLCO and mouth pressure assessments ( $PI_{\text{max}}$ ,  $PE_{\text{max}}$ ) were performed prior to each exercise test. Endurance times were similar in the control and  $IPS5\text{cmH}_2\text{O}$  condition ( $4.2 \pm 2.6$  versus  $4.4 \pm 2.9$  min). In contrast, endurance times were greater in the  $IPS10\text{cmH}_2\text{O}$  condition than the  $IPS5\text{cmH}_2\text{O}$  and control condition.

Polkey, et al., (6) investigated the effects of IPS administration in COPD patients when exercising above the lactate threshold. Patients performed two separate treadmill walks, separated by an interval of at least 30 min, with and without IPS. The IPS pressure was individually titrated to maximise patient comfort. Arterialised blood was drawn from a hand vein at baseline and at the end of exercises. Mean time was higher during the IPS assisted walk than the IPS unassisted walk. Plasma lactate levels increased significantly above baseline during both the assisted and non-assisted walk. Peak lactate was significantly higher at the end of the unassisted walk than the assisted walk. It was concluded that the difference in peak lactate levels between unassisted and assisted walk could be attributed to a decreased workload in the respiratory muscles. It was further hypothesised that IPS during exercise may increase the training benefit of pulmonary rehabilitation.

Using a similar study design, Keilty, et al., (17) investigated the effect of IPS, CPAP (Continuous Positive Airway Pressure) and supplemental oxygen during sub maximal treadmill exercise in eight COPD patients. IPS (12-15cmH<sub>2</sub>O), CPAP (6 cmH<sub>2</sub>O), and oxygen (2.0 l/min) were administered during a treadmill test on 3 separate days. Each treadmill test was compared to a control walk using a sham circuit (breathing air via an oxygen mask) and with a baseline walk in which patients walked freely on the treadmill. Walking distance increased 62% in the IPS condition compared to the control walk (sham circuit). There was no change in walking distance following administration with either CPAP or oxygen. The provision of IPS also reduced breathlessness and increased exercise duration during sub maximal treadmill.

Polkey, et al., (18) examined the possibility that IPS could improve inspiratory muscle relaxation rate (MRR) during exhaustive treadmill walking in severe COPD. The inspiratory MRR was measured from esophageal pressure during a sniff manoeuvre. Six men with COPD underwent a treadmill walk, unassisted and assisted with IPS. There was a 41%

slowing of the inspiratory MRR ( $p < 0.03$ ) following the assisted walk representing a considerable unloading of the inspiratory muscles.

Two published studies that have shown a negative effect of NIV on exercise performance. Revill, et al., (19) examined the effects of ambulatory oxygen and IPS at 14cmH<sub>2</sub>O administered during an endurance shuttle walk test (ESWT). Ten COPD patients underwent ESWT under five test conditions: IPS at 14cmH<sub>2</sub>O, sham IPS <8cmH<sub>2</sub>O, baseline walk, oxygen at 2.0 l/min, sham oxygen. Ambulatory oxygen supplementation resulted in improved performance time in the ESWT. In contrast, IPS administration decreased performance time.

Highcock, et al., (20) evaluated the effect of three bilevel pressure support (BiPAP) ventilators (BiPAP S/T 30, Nippy 2 and Vpap II ST) during submaximal treadmill exercise. Eight patients with COPD walked to exhaustion while using each ventilator, and a mouthpiece only condition. The test order was randomly assigned. Patients also performed four unencumbered walks (no mouthpiece/ventilator). The total distance covered during the unencumbered walks was  $259 \pm 123$ m. With the mouthpiece alone this decreased to  $211 \pm 96$ m and decreased to  $145 \pm 76$ m when using the ventilators. There was no difference between the various ventilators.

Hawkins, et al., (21) examined the effect of PAV (proportional assisted ventilation) on  $V_E$ , heart rate and arterialised venous plasma lactate concentration (La) during exercise in COPD patients. Patients underwent a 6 wk supervised outpatient cycle exercise programme. Heart rate,  $V_E$  and blood lactate levels were assessed before and after each test. Ten patients received PAV during exercise, and 9 exercised unaided. Exercise capacity at 6 weeks was 15.2% and 18.4% higher in the group that used ventilatory assistance and unaided group respectively. Plasma lactate was reduced by 30% in the assisted group. The study findings

suggest that maximum exercise capacity can be significantly improved in COPD patients when PAV is provided.

A similar study by Dolmage, et al., (22) assessed the impact of PAV and CPAP on exercise performance. Ten subjects completed five sessions (1) baseline (2) PAV (3) CPAP 5 cmH<sub>2</sub>O (4) PAV + CPAP and (5) sham. Dyspnea was measured using the Borg Scale. Subjects reached the same level of dyspnea during all experimental conditions. Total exercise time was greater during the PAV + CPAP ( $p < 0.05$ ) (12.88(8.74) min) compared to the sham session.

Garrod, et al., (23), examined the benefit of BIPAP incorporated into an exercise training (ET) program. Forty-five patients underwent a shuttle walk test (SWT) at baseline followed by an eight-week training program. Twenty-three patients were instructed to use a BIPAP (16cmH<sub>2</sub>O/ 4cmH<sub>2</sub>O) overnight, or for at least 8 h/d throughout the study period. Twenty-two patients underwent the ET only. In the BIPAP+ET exercise time increased group from 169(112) to 269(124) min ( $p = 0.001$ ) compared with the ET group: 205(100) to 233(123) min ( $p = 0.19$ ); mean difference (95% confidence interval: 72(12.9 to 131) min. BIPAP + ET also showed a significant improvement in arterial oxygenation; mean difference: 3.70 mmHg (0.37 to 7.27 mmHg). These findings suggest that NIV may be used to augment the effect of rehabilitation in severe COPD.

There is accumulating evidence to suggest that exercise performance is enhanced in COPD patients following the administration of IPS during exercise. Additional research into the potential benefits of IPS administration prior to exercise in patients with COPD, is warranted.

## CHAPTER III

### METHODOLOGY

#### **Patients**

Patients [(14 men ( $66.0 \pm 7.7$  yr) and 6 women ( $59.0 \pm 7.4$  yr)] with a diagnosis of chronic obstructive pulmonary disease (COPD) were recruited. Inclusion criteria included a forced expiratory volume<sub>1</sub> (FEV<sub>1</sub>) <40%, and the ability to tolerate 12 cmH<sub>2</sub>O of pressure on a non-invasive ventilator (Nippy 1, Respironics). Patients were excluded if they had an exacerbation within the past month, and had been treated previously with non-invasive ventilation (NIV). Written consent was obtained in accordance with St. James's Hospital Ethics Review Board.

#### **Experimental Design**

Patients visited the Respiratory Laboratory at St. James's hospital on 3 separate occasions. The first visit was used to screen potential patients. A graded maximal exercise test with and without the use of the ventilator prior to exercise was performed during the second and third visit. Patients did not exercise for 24 h before testing, and fasted for 1 h before each testing session. The testing sessions were separated by 48 h. On arrival to the laboratory, a 21G indwelling catheter was inserted into a prominent forearm vein to facilitate the collection of blood samples. Spirometry was performed followed by a resting period of 10 min. The patients then undertook a maximal exercise test on a cycle ergometer. Respiratory metabolic measures, heart rate, blood samples and RPE were obtained throughout each exercise test.

## **Experimental Procedures:**

### **Anthropometrics**

Height and weight were measured using a stadiometer (Seca 797, USA). Footwear was removed prior to the measurement. Height was measured to the nearest cm, and weight was measured to the nearest 0.1 kg.

### **Spirometry**

Spirometry was performed using a metabolic cart (Sensormedics Vmax. 229, Loma Linda, CA, USA). The Vmax 229 consists of an analyser module, pneumatics module, peripheral device input/output, and operating software. Each manoeuvre consisted of a maximal inhalation to total lung capacity (TLC) followed by a quick exhalation that was maintained for as long as possible. Patients then re-inhaled to TLC and finally returned to normal tidal breathing. Patients were instructed to keep a tight seal around the mouthpiece during the manoeuvre. The same investigator offered verbal encouragement during each test. Three successful manoeuvres were recorded.

### **Ventilatory Support Tolerance Test**

A tolerance test was performed to insure that subjects were comfortable wearing the facemask (Comfort Full, Respirationics), and that they were able to tolerate an inspiratory pressure of 12 cmH<sub>2</sub>O. The pressure on the ventilator was slowly ramped to 12 cmH<sub>2</sub>O.

### **Ventilatory Support**

A facemask was positioned comfortably on each patient, and the ventilator was set at 12 cmH<sub>2</sub>O of inspiratory pressure support (IPS). Patients were encouraged to relax and breathe



normally through the mask. They remained seated for 2 h while wearing the ventilator. Blood samples were taken before and after IPS.

### **Exercise Test**

The exercise tests were performed on an electrically braked cycle ergometer (Sensormedics er900, USA). Work rate was independent of the pedalling rate. A peripheral device interfaced the work rate of the cycle ergometer with the Vmax 229 system at a sampled rate of 125Hz.

Following a 2 min warm-up at zero Watts the work rate was increased  $5 \text{ Wmin}^{-1}$  for women and  $10 \text{ Wmin}^{-1}$  for men, using a ramp protocol. The controlled ramp signal was delivered to the ergometer via a computer (Dell Pentium II processor, Dell Computer Corporation, Texas, USA). Patients were encouraged to give their best effort throughout the test by the same investigator.

### **Mass Flow Sensor Heated wire Anemometer- Mode of operation**

A mass flow sensor (Sensormedics, Loma Linda, CA, USA) was used to collect breath-by-breath measurements of ventilation. The mass flow sensor is a low resistance tube with a tapered internal diameter extending from both ends of a laminar flow throat. A cold and hot stainless steel wire electrically heated to  $-180^{\circ} \text{C}$  and  $-240^{\circ} \text{C}$  respectively, are centred in the flow stream. These wires are elements in a servo-controller bridge circuit that maintains the resistance ratio of the two wires at a constant value. If only the temperature of the inspired gases change, then both wires lose heat at the same rate, and no current change is required to keep the bridge balanced. As air flows across the wires, the hot wire loses heat more rapidly than the cold wire and current is added to keep the bridges balanced at a 3:4 ratio. The amount of current required is proportional to the mass flow of the gas. This method ensures that the sensor measures only the heat loss from the molecular convection of the

moving gas stream, and not the artefact due to cooling of the gas as it passes through a breathing assembly. The mass flow meter responds to instantaneous flow rates between 0-16 L·sec<sup>-1</sup> and integrated flow between 0-350 L·min<sup>-1</sup> with flow resistance <1.5 cmH<sub>2</sub>O/litre/sec. The mass flow sensor was outputted to the analyser module of the Vmax 229 and sampled at a rate of 125 Hz.

### **Calibration**

A 3-litre volume syringe (Sensormedics, Loma Linda, CA, USA) was used to calibrate the mass flow sensor prior to each test. The syringe was connected to the mass flow sensor, and stroked 4 times in order to measure inspired and expired volumes. The volumes were calculated by expressing 3 litres as a fraction of each measured inspired and expired volume achieved during calibration. An average correction factor was calculated for inspired and expired volumes, and used to fine-tune the volume measurement. A verification procedure was performed. This involved stroking the 3-litre volume syringe four times. Inspired and expired volumes were measured using the newly calculated correction factors. In order to pass the calibration procedure one of the four strokes had to have an average flow rate <0.5 l·sec<sup>-1</sup>, and at least one of the four strokes had to have an average flow >3.0 l·sec<sup>-1</sup>.

### **Blood Pressure**

Blood pressure was assessed automatically using a Sensormedics er900 blood pressure cuff (Sensormedics Corp., Yorba Linda C, USA).

### **Pulse Oximetry**

A finger oximeter probe (Sat-Trak Pulse, USA) was placed on the middle index finger to monitor S<sub>a</sub>O<sub>2</sub>. The pulse oximeter transmits light through body tissue at two or more

wavelengths. The intensities of the emerging light is measured and converted into an electronic signal for processing.

### **Respiratory Metabolic Measures**

Respiratory metabolic responses were determined using standard open-circuit spirometry techniques. Prior to testing, the gas analysers were calibrated with standard gases of known concentration.

### **Gas Analysers**

A Vmax 229 Metabolic cart (Sensormedics, Loma Linda, CA, USA) was used to assess the respiratory metabolic responses during the exercise test. The Vmax 229 utilizes a rapid response non-dispersive infrared measurement technique. An O<sub>2</sub> and CO<sub>2</sub> analyser is integrated within the Vmax 229.

A small sample of inspired air is drawn through a sample cell, and exposed to an infrared light through an optical that is passed through a band-pass filter and the sample cell. An infrared detector responds to the amount of infrared light that passes through the sample cell. Carbon dioxide absorbs infrared light over wavelengths ranging from 0.7 $\mu$ m to 15.0  $\mu$ m. The amount of light passing through the sample cell varies according to the concentration of CO<sub>2</sub> in the sample cell. Based on measured levels of infrared light intensity, the analyser computes the PCO<sub>2</sub> in the gas sample. The CO<sub>2</sub> analyser is linearly scaled across the 0-100% range with a resolution of 0.01 %CO<sub>2</sub>, and a response time of <130ms (10-90%) at 500 ml·min<sup>-1</sup> flow.

The O<sub>2</sub> analyser is based on the high paramagnetic susceptibility of O<sub>2</sub>. A diamagnetic glass dumbbell suspended in a magnetic field rotates in proportion to the PO<sub>2</sub>.

The analyser is linearly scaled across the 0-100 % range with a resolution of 0.01%O<sub>2</sub> and a response time of <math>130 \text{ m sec}^{-1}</math> (10-90%) at 500 ml·min<sup>-1</sup> flow.

### **Calibration of Gas Analysers**

The gas analysers were calibrated using gases of known concentration (BOC gases, Dublin, Ireland). The gas composition in tank 1 was  $26.00 \pm 0.02$  %O<sub>2</sub> and the balance N<sub>2</sub>. The gas composition in tank 2 was  $4.00 \pm 0.02$  %CO<sub>2</sub>,  $16.00 \pm 0.02$  %O<sub>2</sub> and the balance N<sub>2</sub>. A small bore drying tube connected to the CO<sub>2</sub> and O<sub>2</sub> analysers samples the calibration gases and inhaled/exhaled air by the subjects. The absorption and evaporative properties of the drying tube ensured that the relative humidity in the inhaled/exhaled gas and the calibration gas was equilibrated to ambient conditions before being sampled by the analysers. Samples of the calibration gas and the gas inhaled by subjects were taken at a rate of 125 Hz. The response time of the CO<sub>2</sub> analyser was synchronised with that of the O<sub>2</sub> analyser.

### **Heart rate Monitoring**

Heart rate was measured continuously during each test using a 3 lead electrocardiogram (ECG) module. A peripheral device input interfaced the ECG module between the ECG and the Vmax 229. An ECG signal was displayed on the desktop computer (Dell Pentium II processor, Dell Computer Corporation, Texas, USA) throughout the exercise. The computer calibrated the heart rate signal using a set signal of one volt (250 beats·min<sup>-1</sup>) generated by the heart rate monitor and was sampled at a rate of 125 Hz. The ECG signal was set at a high pass filter of 20 Hz and a line filter of 50 Hz.

### **NIPPY 1 (Respironics) Ventilator**

The Nippy 1 (B & D Electromedical, Respironics) is a pressure controlled, intermittent positive ventilator. Ambient air is drawn through a dust filter and compressed by a centrifugal fan. An electronically controlled valve controls output airflow. Air is delivered to the patient through a close fitting full facemask. The output pressure, timing and alarms are adjusted by controls on the panel. As the airflow is servo controlled, the ventilator is able to compensate for leaks around the mask. If leaks become too great, the pressure will fall below the pre-set low-pressure alarm level.

Air is delivered to the mask during inspiration. This may be triggered by the subject's own inspiratory effort or by the ventilator expiratory timer if there was insufficient inspiratory effort. The inspiratory pressure was adjusted with the set pressure control. The inspiratory time was set by the inspiratory time control. At the end of the inspiratory time, the exhalation valve opened. The subject exhaled through the exhalation valve. If the ventilator did not detect an inspiratory effort, the next breath was initiated by the end of the expiratory time, as set by the expiratory time control. The trigger was activated when the inspiratory pressure in the mask dropped below the level set by the trigger control.

### **Blood Lactate Analyser**

Whole blood lactate levels were determined using a YSI 2300 STAT PLUS analyser and expressed in mmol L<sup>-1</sup>. The 2300 STAT PLUS was calibrated prior to each run. Blood samples were analysed in duplicate. Each test tube was positioned in the analyser holder to prepare for sampling. A sipper pump piston moved to the sample test tube and travelled 3 mm below the surface of the fluid. A sipper pump piston retracted and aspirated 25 µL sample. The sipper then moved back to a sample chamber, extended and the sample was dispensed. Values were displayed and printed.

### **Statistical Analysis**

A paired sample student's t-test was used to compare peak data between the two experimental conditions. A total of 12 patients completed 6 min of the maximal exercise test. A two way (condition x time) repeated measures ANOVA was used to compare differences between the two experimental conditions for the first 6 min of the test. Significant main and interaction effects were analyzed using paired t-tests with Bonferroni adjustment for multiple comparisons. The significance was set at an  $\alpha$ -level of  $p < 0.05$ . Data are presented as mean  $\pm$  standard deviation.

## CHAPTER IV

### RESULTS

Patient demographic and clinical characteristics are presented in table 2 and 3 respectively. Peak workrate, total exercise time and respiratory rate were higher ( $p < 0.05$ ) when exercise was preceded by ventilatory support compared to no support (Table 4). There was no difference in peak  $VO_2$ ,  $VCO_2$ , heart rate, minute ventilation, tidal volume, RPE or blood lactate between the two experimental conditions.

Since the total number of completed stages ranged from 3 to 11 it was not possible to compare the submaximal physiological responses each min in all subjects. A total of 12 subjects completed at least 5 stages of the exercise protocol. A repeated measures ANOVA was used to compare differences in physiological responses between the two experimental conditions in these 12 subjects. There was no difference in demographic data or peak exercise data between the 12 patients who completed 5 stages of the maximal exercise test and the other 8 patients (x completed less than five and y completed y 5 stages) (Table 5 and Table 6). RPE was significantly lower in during the first 3 min in the NIV condition than the placebo (Table 7). Circulating levels of blood lactate were lower ( $p < 0.01$ ) during stage 3 in the NIV than the placebo group (Table 7). There was no difference in RR,  $V_T$ , HR, %HR,  $V_E$ ,  $VO_2$  and % $VO_2$  between the two experimental conditions during sub maximal performance (Table 7).

**Table 2: Patient demographics**

<b>Variable</b>	<b>Mean ± SD</b>
Age (y)	63.4 ± 8.2
Weight (kg)	62.3 ± 12.3
Height (cm)	164.6 ± 8.0
BMI (kg·m <sup>2</sup> )	23.0 ± 4.1
Systolic blood pressure (mmHg)	84.5 ± 12.3
Diastolic blood pressure (mmHg)	136.1 ± 17.1



**Table 3: Patient clinical characteristics**

<b>Variable</b>	<b>N (%)</b>
<b><u>Patient History</u></b>	
Cardiopulmonary disease	0
Pulmonary disease	20(100)
Metabolic disease	0
Cancer	1(5)
Bleeding problems	1(5)
Orthopedic problems	0
Vegetarian	1(5)
<b><u>Family History n (%)</u></b>	
Hypertension	4(20)
Diabetes mellitus	5(25)
Cerebrovascular accident*	0
Total cholesterol†	2(10)
BMI > 30 kg m <sup>-2</sup>	1(5)
Cancer	8(40)
Asthma	20(100)
Angina	2(10)
Prior MI	1(5)
Prior CABG	0
<b><u>Allergies</u></b>	
Food	1(5)
Medication	2(10)
<b><u>Smoking status</u></b>	
Former (past history of smoking)	20(100)
Current (present smoker)	11(55)
<b><u>Current alcohol use</u></b>	
	11(55)
<b><u>Medications</u></b>	
Atrovent	2(10)
Seretide	8(40)
Serevent	3(15)
Combivent	11(55)
Beclazone	2(10)
Salbutamol	6(30)
Pulmicort	3(15)
Becotide	6(30)
Intel	1(5)
Oxivent	2(10)
Duovent	1(5)
Steroids	2(10)
Bricanyl	1(5)

\*Cerebrovascular accident (CVA): encompass problems such as stroke (damage to a group of nerve cells in the brain) and cerebral haemorrhage (sudden and abrupt bleed into the tissue of the brain).

† Total cholesterol > 5.2 mg/l

**Table 4:** Hemodynamic and metabolic variables at peak exercise

Variable	Experimental Condition		
	NIV	No NIV	P Value
Workrate (W)	50.20 ± 18.58	44.30 ± 20.90	0.04
VO <sub>2</sub> (l min <sup>-1</sup> )	0.60 ± 0.23	0.59 ± 0.25	0.74
VCO <sub>2</sub> (l min <sup>-1</sup> )	0.56 ± 0.22	0.56 ± 0.25	0.86
HRM	121.45 ± 20.60	115.90 ± 13.10	0.21
V <sub>E</sub> (l min <sup>-1</sup> )	23.43 ± 7.72	22.57 ± 6.92	0.33
RR (breaths min <sup>-1</sup> )	31.40 ± 6.10	29.30 ± 5.14	0.03
V <sub>T</sub> (l min <sup>-1</sup> )	0.92 ± 0.26	0.95 ± 0.28	0.41
La (mmol l <sup>-1</sup> )	1.50 ± 0.58	1.45 ± 0.60	0.74
RPE	19.55 ± 1.23	18.85 ± 1.87	0.09
Total time (sec)	308.70 ± 114.90	258.10 ± 124.50	0.02

Values are mean ± SD

**Table 5:** Demographic and physiological characteristics of patients who completed 5 stages and those who completed >5 or ≥ 6 stages of the exercise protocol

Variable	Experimental Condition		P Value
	>5 and ≥6 stages (n=8)	5 stages (n=12)	
Age (y)	62.8 ± 7.7	63.7 ± 8.8	0.04
Weight (kg)	66.7 ± 14.4	59.3 ± 10.1	0.74
Height (cm)	162.5 ± 7.3	166.0 ± 8.4	0.86
BMI (kg m <sup>2</sup> )	25.01 ± 4.2	21.5 ± 3.4	0.21
Diastolic blood pressure (mmHg)	147.0 ± 17.3	132.0 ± 15.0	0.33
Systolic blood pressure (mmHg)	91.2 ± 12.4	79.1 ± 11.9	0.03

Values are mean ± SD

**Table 6:** Peak exercise values for patients who completed 5 stages and those who completed >5 or ≥ 6 stages of the exercise protocol

Variable	Experimental Condition		P value
	> 5 and ≥6 stages (n=8)	5 stages (n=12)	
Workrate (W)	41.87 ± 30.8	45.92 ± 12.06	0.73
VO <sub>2</sub> (l·min <sup>-1</sup> )	0.58 ± 0.35	0.59 ± 0.17	0.90
VCO <sub>2</sub> (l·min <sup>-1</sup> )	0.53 ± 0.34	0.57 ± 0.17	0.80
Heart rate (bpm)	122.2 ± 14.0	111.7 ± 11.11	0.08
V <sub>E</sub> (l·min <sup>-1</sup> )	21.35 ± 8.57	23.3 ± 5.8	0.53
RR (breaths·min <sup>-1</sup> )	29.12 ± 2.41	29.42 ± 6.4	0.90
V <sub>T</sub> (l·min <sup>-1</sup> )	0.88 ± 0.32	0.98 ± 0.24	0.43
La (mmol·l <sup>-1</sup> )	1.33 ± 0.85	1.52 ± 0.38	0.50
RPE	18.25 ± 2.25	19.25 ± 1.54	0.25
Total time (sec)	254.5 ± 191.5	260.5 ± 58.4	0.93

Values are mean ± SD

**Table 7:** Physiological responses at 1 min intervals in patients who completed the first 5 stages of the exercise protocol

Condition	Time				
	1 min	2 min	3 min	4 min	5 min
Respiratory rate (breaths min <sup>-1</sup> )					
No NIV	24.1 ± 6.0	25.3 ± 6.5	24.6 ± 4.1	26.4 ± 3.9	28.3 ± 4.9
NIV	23.5 ± 6.0	24.7 ± 5.5	25.8 ± 7.5	26.6 ± 8.6	29.9 ± 9.4
Tidal volume (l min <sup>-1</sup> )					
No NIV	0.71±0.1	0.75±0.17	0.82±0.15	0.87±0.15	0.90±0.20
NIV	0.68±0.2	0.70±0.14	0.76±0.18	0.82±0.18	0.85±0.26
Heart rate (beats min <sup>-1</sup> )					
No NIV	87.30±12.0	89.10±14.8	93.4±11.0	99.8±12.4	104.0±13.0
NIV	90.50± 18.1	87.80±13.9	93.0±17.0	100.0±25.3	105.0±20.4
%HR					
No NIV	78.10±6.40	79.68±9.98	83.65±6.14	89.31±7.1	92.96±6.94
NIV	76.10±10.4	74.62±11.7	80.59±17.4	85.07±16.6	88.75±12.5
Minute ventilation (l min <sup>-1</sup> )					
No NIV	13.53±2.6	14.76±2.9	16.04±2.5	18.54±3.50	20.27±3.60
NIV	12.71±3.44	13.80±3.47	15.45±3.59	17.41±4.18	19.71±4.56
RPE					
No NIV	8.42±1.16 <sup>‡</sup>	8.58±1.10 <sup>*</sup>	10.58±1.08 <sup>*</sup>	12.05±1.6	16.08±2.91
NIV	6.83±0.94 <sup>‡</sup>	7.58±1.1 <sup>*</sup>	9.58±1.24 <sup>*</sup>	12.10±1.8	15.0±2.34
Lactate (mmol l <sup>-1</sup> )					
No NIV	1.27±0.42	1.11±0.30 <sup>†</sup>	1.05±0.19	1.22±0.31	1.34±0.36
NIV	1.48±0.66	0.80±0.22 <sup>†</sup>	0.91±0.32	0.94±0.35	1.05±0.36
VO <sub>2</sub> (l min <sup>-1</sup> )					
No NIV	0.26±0.07	0.30±0.06	0.35±0.07	0.43±0.08	0.49±0.11
NIV	0.24±0.08	0.28±0.06	0.32±0.07	0.39±0.08	0.47±0.15
%VO <sub>2</sub>					
No NIV	44.86±12.4	51.50±10.9	60.28±11.1	74.38±13.1	84.48±15.8
NIV	40.28±9.75	49.22±10.2	56.47±15.7	69.43±18.8	79.41±16.9

Values are Mean±SD n=12; \* p< 0.05 vs Nippy, †p<0.01 vs Nippy, ‡ p<0.001 vs Nippy.

## **Chapter V:**

### **Discussion**

NIV is an established treatment modality in the management of acute respiratory failure in patients with COPD (3). The application of NIV during exercise has been found to improve exertional dyspnoea and endurance performance (26). To my knowledge, this is the first study to examine the effects of administering ventilatory support prior to exercise in patients with COPD. The major findings of the present study is that the application of inspiratory pressure support (IPS) prior to exercise increased exercise duration, RR and maximal workload in patients with COPD. There was no effect of pre-exercise ventilatory support on  $VO_2$ ,  $\%VO_2$ ,  $VCO_2$ , HR,  $\%HR$ ,  $V_E$ , and RPE during submaximal and maximal exercise. The  $\%VO_2$  and  $\%HR$  corresponding to the VT and LT were similar in both experimental conditions.

Intrinsic positive end expiratory pressure (PEEP) reflects the recoil pressure of over inflated lung (3), and contributes to a positive intrathoracic pressure at end expiration. At rest, the inspiratory muscles need to generate an inspiratory pressure to overcome PEEP before airflow can begin. PEEP is increased at rest and during exercise in COPD patients (17). This may limit exercise performance in these patients.

We did not assess if IPS unloaded the inspiratory muscles prior to exercise. However, a study by Polkey, et al., (18) reported that the maximum relaxation rate (MRR) of the inspiratory muscles was slowed following the administration of IPS. Six men with severe COPD performed two treadmill walks separated by 30 min, to an intolerable dyspnea; with and without IPS. IPS was adjusted to optimize patient comfort. A Sniff (Sn Pes MRR) manoeuvre involving a deep inhalation through the nostril was performed over a 10 min following each

walk. During the sniff manoeuvre, esophageal and gastric pressures (Pes and Pgas) were recorded with a balloon catheter. Transdiaphragmatic pressure (Pdi) was obtained as the difference between Pes from Pgas. Pes MRR was calculated as the maximal rate of decay of pressure divided by peak pressure over 50 ms, and was reported as % pressure loss/10 ms. Sn Pes MRR had slowed by 41% when exercise was performed without with no IPS compared to 20% with IPS. This represents a considerable unloading of the inspiratory muscles.

IPS may improve exercise performance by allowing patients to adopt a more effective breathing pattern, by lowering RR and increasing VT. Previous studies have reported increases in VT and decreases in RR during exercise with IPS, due to improved alveolar ventilation (25, 27). In the present study, peak RR was 7% higher during exercise with IPS compared to no IPS. There was no difference in submaximal or peak VT between the two experimental conditions. This is consistent with breathing patterns observed in patients with COPD when exercising without any NIV. The higher RR may be due to the fact that these patients were exercising at higher workloads when IPS was given prior to exercise compared to no IPS.

At low exercise intensities oxygen supply equals the oxygen demand. As the exercise intensity increases, the oxygen delivery system may be unable to keep up with the demand resulting in a greater reliance on anaerobic glycolysis, and accumulation of lactic acid. The resultant dissociation of H<sup>+</sup> from lactic acid will result in a decrease in intracellular pH. High Low pH levels will have a deleterious effect on muscle function, and limit exercise performance. In some COPD patients, decreased oxygen delivery due to increased pulmonary vascular resistance, arterial hypoxemia, and abnormalities in the skeletal muscles may also limiting aerobic energy production resulting in early onset of lactic acidosis (31).

The exercise intensity at which lactate production begins to exceed the rate of removal is termed the lactate threshold (LT). Most ADL are performed at intensities at or below the LT. Polkey, et al., (6) suggest that the physiological benefit resulting from participation in pulmonary rehabilitation is more likely if exercise is performed above LT. In the present study we were unable to detect the LT in any of our COPD patients. The inability to detect the LT may be due to the fact that these patients having difficulty in achieving adequate levels of ventilation needed to eliminate the additional CO<sub>2</sub> generated during exercise. In addition, severe deconditioning related to inactivity (28), malnutrition, low anabolic hormone levels and myopathy related to corticosteroid use (31), may also limit exercise performance in patients with COPD. This is in contrast to others (29, 30), who found that the LT occurred at a low relative workload in a small number of patients with COPD.

There was no difference in submaximal or peak blood lactate between the two experimental conditions. To my knowledge, this is the first study to investigate peak blood lactate following the administration of ventilatory support prior to exercise in patients with COPD.

Polkey et al., (6) found that the administration of IPS had an effect on exercise duration during treadmill walking to severe dyspnoea in 8 men (70 ± 8 yr) with severe COPD. Limited information was provided with regard to the exercise protocol and treatment modality used in this study. IPS was set individually and was administered during one of the treadmill walks. Walking time was increased by 5.5 min and 13.6 min in the control and IPS condition respectively. The recovery time of 30 min between two maximal exercise tests may have been too short for elderly patients with severe COPD.

The  $V_T$  is commonly used as a non-invasive method to determine LT. We were unable to detect  $V_T$  in any patient using the ventilatory equivalent or V-slope method. It is

possible that the patients were unable to exercise sufficiently to reach  $V_T$  possibility due to decreased ventilatory capacity and increased ventilation requirement. Decreased ventilatory capacity is due to airflow limitation combined with increased airway resistance (31). Increased ventilatory requirement is primarily due to inefficient ventilation of the lungs consequent to the mismatching of ventilation- perfusion (certain regions of the lungs are hypoventilated, whereas other are hyperventilated) (31). These factors contribute to reduced exercise tolerance and make detection of  $V_T$  difficult in patients with COPD. Irregular breathing patterns may have also contributed to the difficulty of determining  $V_T$  in the present study. The detection of  $V_T$  may not be possible in many patients with COPD who fail to show a disproportionate increase in  $V_E$  in response to metabolic acidosis.

Although the increments in workload were relatively small (5 W women, and 10 W men), the exercise protocol may still have been too aggressive to detect  $V_T$ . A less aggressive protocol may facilitate the detection of  $V_T$ . Debigaré, et al., (32), examined the effect of work rate on exercise responses in patients with COPD. Nine men and one woman ( $65 \pm 5$  yr) with severe COPD underwent three ergometer exercise tests. Exercise testing was conducted over three consecutive days and the testing was randomized. Work rate was increased every min by  $5 \text{ W}\cdot\text{min}^{-1}$ ,  $10 \text{ W}\cdot\text{min}^{-1}$ , or  $20 \text{ W}\cdot\text{min}^{-1}$  increments. Peak workrate was 65% higher when the work rate increment was increased from from  $5 \text{ W}\cdot\text{min}^{-1}$  to  $20 \text{ W}\cdot\text{min}^{-1}$ . In contract, peak values for  $\text{VO}_2$ ,  $V_E$ , and HR were independent of the exercise protocol. These findings show that for a given work rate,  $\text{VO}_2$ ,  $V_E$ , and HR were lower with higher work rate increments ( $20 \text{ W}\cdot\text{min}^{-1}$ ) during exercise in patients with COPD. It was suggested that peak  $\text{VO}_2$  rather than  $W_{\text{peak}}$  should be used to quantify exercise tolerance in patients with COPD (32). Patients with COPD have slower  $\text{VO}_2$ ,  $V_E$ , and HR responses during ergometer testing compared to healthy individuals (33).



In the present study, the administration of IPS prior to exercise had no effect on  $VO_2$  and  $VCO_2$  at peak exercise or during submaximal exercise. This finding suggests that IPS may not have unloaded the inspiratory muscles prior to exercise. However, a previous study (16) reported that  $VO_2$  and  $VCO_2$  were significantly reduced during an acute bout of exercise. Forty-five patients with COPD performed three constant-load endurance tests on a cycle ergometer at 75% of maximal workload with no IPS, and with IPS5cmH<sub>2</sub>O, and IPS10cmH<sub>2</sub>O. Endurance times were greater in the IPS10cmH<sub>2</sub>O condition than the IPS5cmH<sub>2</sub>O and control condition. A reduction in  $VO_2$  (5%) and  $VCO_2$  (4%) was found at the iso-time (peak exercise time with IPS5cmH<sub>2</sub>O) with IPS10cmH<sub>2</sub>O. This suggests that the inspiratory muscles were unloaded during exercise with IPS.

Perceived exertion is defined as perception of effort, stress or discomfort during exercise (34). Central (respiratory-metabolic) and peripheral /non- specific factors regulate perception of effort (34). Respiratory-metabolic mediators such as  $V_E$ ,  $VO_2$ ,  $VCO_2$ , HR and blood pressure influence ventilatory drive during exercise (34). Peripheral physiological mediators are localized to the limbs, trunk, and upper trunk (34). The physiological processes that are thought to mediate the intensity of peripheral exertional perceptions are; metabolic acidosis, fast-slow contractile properties of skeletal muscle fibres, muscle blood flow and blood borne energy substrates (34). Non-specific mediators such as hormonal, temperature regulations and pain reactivity are not directly linked to peripheral or respiratory metabolic signals, but do continue to effort sensations during exercise.

RPE is used for both the prescription and regulation of exercise in sport, clinical and recreational applications. In the present study, there was no difference in RPE between the two experimental conditions. It had been hypothesised IPS would improve pulmonary

efficiency by adopting a more efficient breathing pattern, therefore, decrease the stress or discomfort that is felt during exercise.

In the present study, we were unable to assess submaximal exercise, due to the nature ramp protocol used. The large interindividual variations in fitness levels also made it difficult to compare the physiological responses at relative workloads. Future studies should exercise patients at the same relative workloads. This workload should be compatible with the intensities associated with the ADL. This would be particularly beneficial to patients with COPD, as they perform ADL at submaximal intensities.

The ventilator used in the present study could only provide pressure support on inspiration, with only one intensity level selected. There is a large selection of NIV ventilators on the market with improved technical performances that provide pressure support both on inspiration and expiration (BiPAP) that may show greater improvements compared to the ventilator used in the study. Future studies should focus on comparing different intensity levels of NIV support, and possibly examine the benefits of wearing the ventilator for longer period of time prior to exercise. In particular, research should examine P<sub>sniff</sub> MRR during exercise when IPS has been administered prior to exercise.

IPS has been shown to be a safe and effective aid if administered during exercise in patients with COPD (6, 17,18). The present findings indicate that IPS administered prior to exercise will enhance exercise performance by increasing exercise duration and maximal workload. It has been suggested that IPS used during exercise may increase the benefit of pulmonary rehabilitation (6). This hypothesis warrants further experimental research to evaluate not only any ergogenic properties of IPS but also any ventilation improvements in patients with COPD.

## Chapter VI:

### **Conclusions and Recommendations**

#### **Conclusions**

The findings of this investigation warrant the following conclusions:

- 1) Work rate, RR, exercise stage and duration was greater with ventilatory support prior to exercise. This is the first study to show these findings.
- 2) IPS was not effective in reaching AT or LT when administered prior to exercise.  $VO_2$ ,  $V_E$ ,  $V_T$ ,  $VCO_2$  were not significantly higher with ventilatory support prior to exercise.

#### **Recommendations**

Based on the present experimental findings, the following suggestions are proposed for future research regarding the ergogenic effect and health benefits of IPS:

- 1) Future studies should exercise patients at the same relative workloads. The workloads should be compatible with the intensities associated with the ADL.
- 2) Future investigations should compare different intensity levels of NIV support, and possible examine the benefits of wearing the ventilator for longer period of time prior to exercise.
- 3) Determine the effects of other modes of NIV (BiPAP, PAV) in patients with COPD when administered prior to exercise.

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## **Appendices**

### **Subject Informed Consent Form**

#### **St. James's Hospital**

**Title of Project:**

Effects of inspiratory pressure support on exercise performance in patients with chronic obstructive pulmonary disease

**Principal Investigator:** Ms. Anita Doggett, Snr. Respiratory Technician, St. James's Hospital.

**Other Investigators:** Prof. Niall Moyna, Dublin City University.

**Study Physician:** Dr. Finbarr O' Connell, Respiratory Consultant, St. James's Hospital.

**Introduction:**

Chronic Obstructive Pulmonary Disease (COPD) is a common disease of the lung. It is a progressive illness affecting people in different ways. Depending on the severity of the disease, it can limit your daily activity. Exercise intolerance is the most common consequence of this disease. Therefore, regular exercise activity is one of the main approaches suggested in the treatment of this illness. It has a beneficial effect on improving your fitness level.

This study will examine the benefits of a breathing ventilator given prior to exercising on a bicycle. This research study will take place at St. James's Hospital Respiratory Laboratory and will last approximately three days.

**Procedure:**

This is what will happen during the research study

**Study day 1 (pre screening day)**

This visit to the Respiratory Laboratory will last approximately two hours. On arrival I will have my weight and height measured for a breathing test.



I will then complete the short breathing test called a Spirometry. This involves a blowing manoeuvre into a plastic mouthpiece attached to a computer. This test measures the amount of air I can take in on inspiration and blow out on expiration.

The level of oxygen in my blood (%Sao<sub>2</sub>) will be measured using a finger probe (Novametric oximeter). Following this, I will complete a "pressure tolerance test" using the ventilator. This device will make it easier for me to breathe.

**Study day 2:**

On the morning of study day two, I will undergo a repeated breathing test. I will then complete an exercise stress test to determine my fitness level. A polyethylene cannula/line will be inserted into my vein in my forearm to allow blood samples to be taken. A blood sample will be taken at rest and every minute throughout the duration of the exercise test. During the exercise, a nose clip will be attached to my nose and a rubber mouthpiece attached to a headset, which then will be placed in my mouth. This will remain in position for the duration of the test. During the test, I will be closely monitored with an electrocardiogram (ECG) and by medical personnel.

**Study day 3:**

The morning of study day 3 (a minimum of 48hrs after study day 2), I will have a repeated breathing test. I will then wear the ventilator for two hours, throughout which I will have my blood pressure monitored. Before wearing the ventilator, a cannula/ line will be inserted into a vein in my forearm and blood samples taken before and after the ventilator. Immediately after this, I will undergo my second exercise stress test which will be under the same conditions as my previous exercise test in the laboratory.

**Benefits:**

I will receive a copy of my personal spirometry and exercise fitness test after the study as well as a summary of the overall results. There are no other direct benefits to me.

**Discomforts and Risks:**

1. Exercise testing carries with it a very small risk of abnormal heart rhythms, heart attack, or death in less than one in 30,000 patients. As I will be asked to give a maximum effort, I may experience some muscle soreness in my arms and legs following each maximal exercise test.
2. Drawing blood causes pain where the needle is inserted and can leave a bruise. A person trained to take blood will be used to decrease these risks.
3. The amount of blood drawn is not harmful, however, if I have a history of anemia, I should inform the investigator.
4. There is a small possibility of eye irritation if there is a leak from the full face mask, and of a blocked nose sensation. Blood pressure may fall initially when put on the ventilator.
5. Spirometry can cause light-headedness and dizziness.

**Exclusion from participation:**

You cannot be in this study if any of the following are true:

- Not diagnosed with Chronic Obstructive Pulmonary Disease.
- Not within the age requirements: 40-75yrs.
- No recent exacerbations within one month

**Alternative treatments:**

You do not have to be a part of this study to be treated. There are other medications available that can be used to treat your complaint and your doctor has discussed this with you.

**Confidentiality :**

All records associated with my participation in this study will be subject to usual confidentiality standards applicable to medical records, and in the event of any publication resulting from the research no personally identifiable information will be disclosed.

**Compensation:**

The Doctors are covered by standard medical malpractice insurance. Nothing in this document restricts or curtails your rights.

**Voluntary Participation:**

You have volunteered to participate in this study. You may quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits, which you had before entering the study.

**Stopping the study:**

I understand that my participation in this research may be terminated by the investigator without regard to my consent if I am unable or unwilling to comply with the guidelines and procedures explained to me.

Permission: granted 19<sup>th</sup> February 2002.

**Further information:**

You can get more information or answers to your questions about the study, your participation in the study, and your rights, from Ms Anita Doggett who can be telephoned at 4162794. If Dr Finbarr O'Connell learns of important new information that might affect your desire to remain in the study, he will tell you.

This is to certify that I consent to and give permission for my participation as a volunteer in this program of investigation. I understand that I will receive a signed copy of this consent form. I have read this form and understand the content of this consent form.

.....

**Volunteer's Signature                      Date**

I, the undersigned, have defined and explained the studies involved to the above volunteer.

.....

**Investigator's Signature                      Date**

.....

**Witness's Signature                      Date**