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**EFFECTS OF PORTABLE  
NON-INVASIVE VENTILATION ON  
EXERCISE TOLERANCE IN  
PATIENTS WITH COPD**

**NIKOLAOS CHYNKIAMIS**

A thesis submitted in partial fulfilment of  
the requirements of the University of  
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## **Abstract**

Breathlessness is the dominant symptom that limits exercise tolerance in patients with COPD. Several ergogenic approaches have been employed to improve exercise tolerance in this population including bronchodilators, oxygen and heliox supplementation, intermittent exercise and non-invasive ventilation (NIV). Although application of NIV during exercise is beneficial for increasing exercise capacity in patients with COPD, there are several disadvantages that limit its wider application during exercise, including lack of compliance with the equipment, and the time required to set up and supervise the equipment in the setting of pulmonary rehabilitation.

Recent advances in technology have facilitated the development of portable non-invasive ventilation (pNIV) devices aiming to alleviate breathlessness during activities of daily living. The VitaBreath (Philips, Respironics) was developed in 2016 as a portable, handheld, battery powered, bi-level, NIV device, providing fixed positive inspiratory and expiratory airway pressure support (IPAP:18 and EPAP: 8 cmH<sub>2</sub>O, respectively). Accordingly, this dissertation aimed to investigate the physiological effects of pNIV application during controlled laboratory exercise conditions and activities of daily living, in patients with advanced COPD. As the VitaBreath device is no longer commercially available, but similar devices may come to market, the present dissertation provides proof of concept on how pNIV can be applied intermittently during exercise in patients with COPD, and how to select patients most likely to respond to pNIV. This in turn may encourage the development of more suitable devices.

Intermittent exercise was chosen to evaluate the effects of pNIV in comparison to the commonly adopted pursed lip breathing (PLB) technique, as this type of exercise allowed regular application of the pNIV device or the PLB technique during recovery periods. Patients retained the device for 3 months to investigate the acceptability, comfort and usability of the device during activities of daily living.

Twenty-four COPD patients were randomised to perform two intermittent exercise protocols sustained at different work intensities (60% WR<sub>peak</sub> for 6-min and 80% WR<sub>peak</sub> for 2-min) alternated with 2-min rest periods. Within each intermittent exercise modality, patients performed two identical exercise tests using either pNIV or the PLB technique in a balanced order sequence, during the recovery phases of intermittent exercise. The findings of this study showed that with both intermittent protocols average endurance time was greater when pNIV was applied compared to PLB. Improvements

in exercise tolerance were due to lower degrees of dynamic hyperinflation (DH) and breathlessness with pNIV compared to PLB.

An important finding of the aforementioned study was that a subgroup of patients (8/24) failed to show a clinically important improvement in DH with pNIV compared to PLB and did not improve exercise tolerance. Analysis identified that these 8 patients experienced greater resting lung hyperinflation, greater exercise-induced DH and breathlessness, secondary to the adoption of a tachypnoeic breathing pattern with pNIV compared to PLB. Interestingly, these patients also reported less benefit from using the device at home, in terms of anxiety around breathlessness and recovery time from breathlessness. Considering the variation of response reported in the present thesis it is important that clinicians assess the response to pNIV on an individual basis.

As with any new method, it was important to appreciate the physiological consequences of the acute application of pNIV on thoracoabdominal volume regulation and respiratory muscle recruitment (assessed by optoelectronic plethysmography), and central hemodynamic responses. Compared to PLB, acute application of pNIV was associated, in the majority of patients, with increased end-inspiratory and end-expiratory rib cage volumes and greater rib cage muscle recruitment, as well as decreased end-expiratory abdominal volumes reflecting reduced expiratory abdominal recruitment. Measurement of cardiac output revealed no adverse circulatory responses with the application of positive airway pressures provided by pNIV during the recovery periods. However, the pattern of thoracoabdominal volume regulation and respiratory muscle kinematics confirmed the findings of the original studies, thereby identifying responders and non-responders to pNIV. Interestingly, responders to pNIV exhibited greater recruitment of the expiratory abdominal muscles compared to non-responders, thereby facilitating them to combat end-expiratory rib cage dynamic hyperinflation effectively.

When patients used the VitaBreath device during their daily physical activities, the majority of patients felt less anxious about becoming breathless and felt that their breathlessness recovered faster when using the device at home for 3 months. Moreover, almost all patients used the device at least weekly and all patients rated the ease of VitaBreath use to be between good and excellent. Additionally, most patients felt that using the device had benefited them and that they would recommend the device to other patients. The main disadvantage of the device was reported to be the high cost and its portability.

The pNIV method provided fixed IPAP and EPAP. This represents a very important disadvantage of this particular pNIV device, which clearly mitigated the beneficial impact it had on some patients. Future research into pNIV devices should examine how best to identify patients who benefit from a pNIV method in everyday life. On-going development of auto-adjusted ventilators would facilitate a larger fraction of COPD patients to be physically active and experience a better quality of life.

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**Figure 6.6.** Effect of 1-min application of pNIV (closed symbols) compared to pursed lip breathing (open symbols) on: a) thoracoabdominal, b) rib cage and c) abdominal end-expiratory volume (circles) and end-inspiratory volume (triangles) of the total thoracoabdominal volume and d) stroke volume (circles) and heart rate (triangles)..... 150

**Figure 6.7.** Effect of 1-min application of pNIV (closed symbols) compared to pursed lip breathing (open symbols) on: a) thoracoabdominal, b) rib cage and c) abdominal end-expiratory volume (circles) and end-inspiratory volume (triangles) of the total thoracoabdominal volume and d) stroke volume (circles) and heart rate (triangles)..... 152

## List of published manuscripts and abstracts presented at national and international conferences containing the results presented in the present thesis

### Published manuscripts

1. Vogiatzis, I.; **Chynkiamis, N.**;Armstrong, M.;Lane, N.D.;Hartley, T.;Gray, W.K., and Bourke, S.C. 2019. Intermittent Use of Portable NIV Increases Exercise Tolerance in COPD: A Randomised, Cross-Over Trial. **J Clin Med. 2019 Jan 15;8(1):94.** doi: 10.3390/jcm8010094.
2. **Chynkiamis N**, Armstrong M, Hume E, Alexiou C, Snow L, Lane ND, Hartley T, Bourke SC, Vogiatzis I. 2020. Effect of portable non-invasive ventilation on exercise tolerance in COPD: One size does not fit all. **Respir Physiol Neurobiol. 2020 Jun;277:103436.** doi: 10.1016/j.resp.2020.103436.

### National and international conferences presentations

1. **Nikolaos Chykiamis**, Matthew Armstrong, Vivien Spencer, Nick Lane, Tom Hartley, William Gray, Stephen Bourke, Ioannis Vogiatzis. Influence of the VitaBreath on Exercise Tolerance in Patients with COPD. **European Respiratory Society congress 2018, Paris, Abstract number: PA3361**
2. **N. Chynkiamis**, M. Armstrong, N. Lane, T. Hartley, S. Bourke, I. Vogiatzis. Effect of the VitaBreath device on exercise capacity and symptoms in COPD. **British Thoracic Society winter meeting 2018, London, Abstract number: S8**
3. **N. Chynkiamis**, M. Armstrong, E. Hume, C. Alexiou, L. Snow, N. D. Lane, T. Hartley, S. C. Bourke, I. Vogiatzis. Effect of portable non-invasive ventilation on exercise tolerance in COPD: one size does not fit all. **European Respiratory Society congress 2020, Abstract number: 3846**
4. **N. Chynkiamis**, J. Manifield, D. Megaritis, C. Alexiou, I. Loizou, N. D. Lane, S. C. Bourke, I. Vogiatzis. Interim analysis of the effect of portable NIV (pNIV) on thoracoabdominal volumes during intermittent exercise in COPD. **European Respiratory Society congress 2020, Abstract number: 4001**



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## **Declaration**

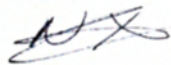
I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas and contributions from the work of others. The work was done in collaboration with Northumbria Healthcare NHS Foundation Trust.

Any ethical clearance for the research presented in this thesis has been approved. Approval has been sought and granted by the Faculty Ethics Committee / University Ethics Committee / external committee [HRA Health Research Authority] on [27<sup>th</sup> of April 2017 and 21<sup>st</sup> of May 2019, respectively].

**I declare that the Word Count of this Thesis is 35,660 words**

Name: Nikolaos Chynkiamis

Signature:



Date: 10/06/2020

# 1. General introduction

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## 1.1. Exercise intolerance in COPD

Chronic Obstructive Pulmonary Disease (COPD) is characterized by a progressive reduction in pulmonary function ( $FEV_1$ ,  $FEV_1/FVC$ ), partially or not reversible ( $<12\%$ ) following bronchodilator medication and progressively deteriorating over time [1]. It includes two key components: chronic bronchitis which is partially reversible, and pulmonary emphysema which is irreversible [1]. According to the World Health Organisation (WHO) COPD is currently the fifth leading cause of death worldwide and will become the third leading cause of death by 2030 [2]. COPD may be asymptomatic in its early stages but causes severe symptoms such as dyspnoea, cough and sputum overproduction in later stages. As the disease severity progresses, a decline in forced expiratory flow at the first second ( $FEV_1$ ) occurs, due to decreased elastic properties of the lung and increased airway resistance, usually accompanied by reduced arterial oxygen saturation indicating respiratory insufficiency [3].

Regarding the prevalence of COPD, a number of studies in Europe showed that 4% to 10% of the adult population suffers from COPD [4]. A recent systematic review and meta-analysis suggested that 66 million people in Europe live with COPD [5], whilst 4.8% of people in the entire world are diagnosed with COPD [6]. However, this finding may only partially represent the burden of the disease as a significant proportion of patients are undiagnosed or misdiagnosed [7, 8].

The major risk factor for COPD is tobacco smoke, as 85% of all cases are attributed to smoking [9, 10], whilst air pollution is also an important risk factor especially in the developing world [1, 11]. Although smokers are 5 times more likely to develop COPD [10], less than 50% of smokers develop COPD during their life [12, 13]. Furthermore,

passive smoking can also contribute to the development of COPD due to the inhalation of toxic gases and particles [14]. Finally, COPD can develop due to genetic disorders, abnormal lung development and aging [1]. In fact, low levels of a protein called alpha-1 antitrypsin caused by a genetic abnormality and respiratory infections during childhood are responsible for 1-5% of COPD development [15, 16].

Patients with COPD across different disease severity exhibit lower exercise tolerance compared to age matched individuals due to expiratory flow limitation (EFL) [17, 18]. EFL caused by airway collapsing leads to air trapping in the lungs resulting in a phenomenon known as dynamic hyperinflation (DH). Dynamic hyperinflation during exercise limits the normal increase in tidal volume, worsening breathlessness and reducing exercise capacity [19, 20]. In addition, DH and the concomitant high mean intrathoracic pressure swings are associated with adverse effects on central hemodynamic regulation, reducing the supply of oxygenated blood to deconditioned peripheral muscles [18, 20, 21]. This increases leg discomfort and further limits exercise tolerance.

Different ergogenic strategies have been successfully employed to reduce exercise-induced DH, breathlessness and leg discomfort, as well as increase exercise tolerance [20]. Bronchodilators, oxygen and heliox supplementation, non-invasive ventilation (NIV) and various intermittent exercise modalities have all been shown to induce clinically meaningful improvements in exercise tolerance in patients with COPD [20, 22-25]. Bronchodilators and oxygen supplementation are commonly used during exercise in this population and increase exercise tolerance by an average of >100 seconds, that represents the minimal clinical important difference (MCID) [26, 27]. Heliox supplementation is beneficial for increasing exercise tolerance by an average of approximately 200 seconds but is also impractical and expensive; therefore it has

primarily been used for research purposes [28]. Finally, intermittent exercise has been found to triple exercise endurance time in patients with COPD mainly due to lower ventilatory requirement and metabolic acidosis, thereby resulting in lower symptoms of breathlessness and leg discomfort [29].

Non-invasive ventilation (NIV), developed as a surrogate of invasive ventilation, is one of the most important developments in respiratory medicine over the past two decades [30, 31] and includes a variety of different ventilatory modes and settings to support ventilation [32]. The primary objective of NIV includes the support of ventilation in Intensive Care Units (ICU) and nocturnal application at home mainly in patients with lung diseases [32]. However, during the last two decades technological advances have led to the availability of high-performance ventilators, allowing application of NIV during exercise [33] in patients with lung and heart diseases.

Different ventilatory modes have been used during exercise to increase exercise tolerance. Application of Continuous Positive Airway Pressure (CPAP) reduces dyspnoea and increases exercise tolerance in patients with COPD [34-36]. In addition, when Inspiratory Pressure Support (IPS) was applied during exercise, work of breathing (WoB) was reduced resulting in lower dyspnoea and increased exercise capacity [37-43]. Finally, application of Proportional Assist Ventilation (PAV) during exercise has been found to increase exercise tolerance in patients with COPD [44-48].

Although the application of NIV during exercise is beneficial for increasing exercise capacity, there are the following potential problems with the application of NIV during exercise:

- i) Non-invasive ventilation is provided by either full-face/nasal masks or a mouthpiece. However, breathing through a mask or a mouthpiece during

exercise may not be fully tolerable by the patients and can potentially reduce the compliance to the application of NIV [49].

- ii) Presence of comorbidities, including ischaemic cardiac disease, is very common in patients with COPD. Although application of NIV might allow greater exercise loads, it is also associated with reduced cardiac output due to impaired venous return, secondary to increased intrathoracic pressures both in healthy and disease [50, 51], thus could potentially cause adverse central haemodynamic effects [49].
- iii) Application of standard NIV methods is associated with practical problems such as lack of compliance with the equipment, time required to set up and supervise the use of the equipment during exercise sessions [49].

Recent advances in technology have promoted the development of portable non-invasive ventilation (pNIV) devices aiming to alleviate breathlessness during daily life physical activities. The VitaBreath (Philips, Respironics) is a portable, handheld, battery powered, non-invasive ventilation device (pNIV), intended to reduce activity-related shortness of breath. It delivers 18 cmH<sub>2</sub>O inspiratory and 8 cmH<sub>2</sub>O expiratory pressures (IPAP and EPAP, respectively) (Figure 1.1) [52]. However, when this dissertation began, there was a lack of studies investigating the physiological effects of the application of pNIV either during controlled laboratory exercise conditions or during daily life physical activities.



**Figure 1.1.** The VitaBreath device

### **1.2. Importance of the study**

The VitaBreath device was introduced by Philips in 2016 as a non-invasive support ventilation device intended to reduce activity-related shortness of breath in patients with COPD. However, at that time there was not any available evidence to support this intention. Accordingly, the original objective of this dissertation was to investigate the effect of application of the VitaBreath device on exercise tolerance, dynamic hyperinflation, and breathlessness during well-controlled laboratory conditions in patients with COPD. Furthermore, use of, and perceived benefit from the VitaBreath device was examined during daily life activities in patients with COPD. In addition, the acute physiological effect of pNIV application on thoracoabdominal volume regulation and central hemodynamic function was investigated in both healthy individuals (not presenting confounding factors due to lung disease) and in patients with COPD. As the VitaBreath device is no longer available in the market the present dissertation provides proof of concept on how pNIV can be applied intermittently during exercise and how to select patients most likely to respond.

### **1.3.Objectives**

These were the following:

- i) To investigate whether compared to the commonly adopted pursed lip breathing (PLB) technique, application of portable non-invasive ventilation (pNIV) support was more effective in terms of reducing breathlessness and enhancing exercise tolerance in patients with COPD.
- ii) To determine use of, and benefit from the pNIV device during activities of daily living in patients with COPD.
- iii) To appreciate the acute physiological effect of application of pNIV on thoracoabdominal volume and circulatory regulation during intermittent exercise in patients with COPD.

### **1.4. Hypotheses**

- i) Use of pNIV compared to PLB would increase exercise tolerance by reducing the magnitude of exercise-induced dynamic hyperinflation and thus the intensity of breathlessness during exercise in patients with COPD.
- ii) Use of pNIV during activities of daily life would reduce activity-related breathlessness, thereby increasing self-reported patient's confidence to perform tasks of daily life in patients with COPD.
- iii) Acute application of fixed inspiratory and expiratory positive airway pressures by pNIV would be associated with increased end-inspiratory and end-expiratory thoracoabdominal volumes potentially causing adverse circulatory effects in patients with COPD.



### **1.5. Experimental approach**

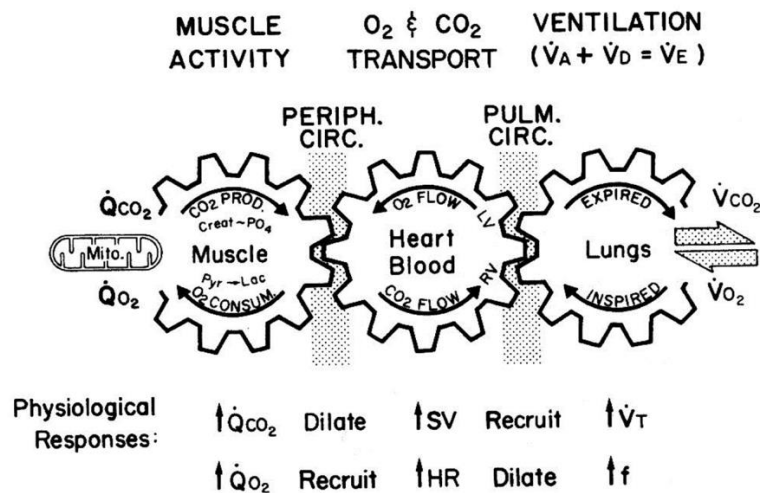
The objectives of this dissertation were addressed by the following studies:

- 1) A cross sectional study to identify patients experiencing profound exercise-induced dynamic hyperinflation and breathlessness as the primary symptom limiting exercise tolerance (Chapter 4) in order to subsequently investigate the effect of pNIV on exercise-induced dynamic hyperinflation on these patients.
- 2) A randomised, open label, cross over study comparing the effect of PNIV to PLB during recovery periods on exercise tolerance and dynamic hyperinflation across two different intermittent exercise protocols in patients with COPD (Chapter 5).
- 3) An observational cross over study investigating the effect of pNIV on thoracoabdominal volumes and central hemodynamic responses during intermittent exercise in patients with COPD (Chapter 6).
- 4) A survey research study to assess patient adherence with pNIV as well as the effects of pNIV on anxiety, symptom burden and ability to perform activities of daily living in patients with COPD (Chapter 7).

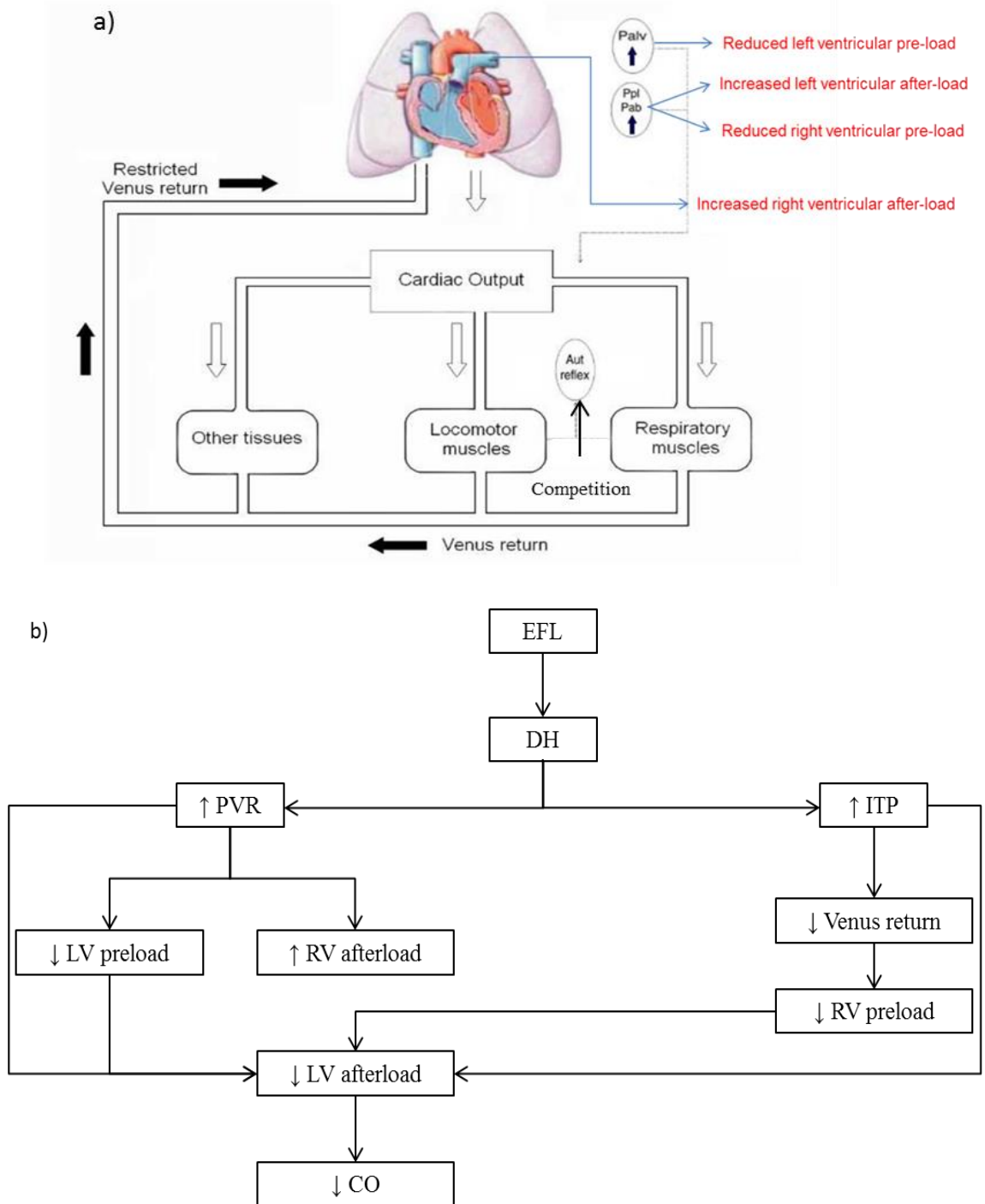
## 2. Literature review

### 2.1. Factors limiting exercise tolerance in patients with COPD

Exercise intolerance is defined as “a condition where the patient is unable to undertake physical activity at the level or for the duration that would be expected of someone in his or her age and general physical condition” [18]. Exercise capacity depends on the ability of in-series systems, including ventilation, gas exchange, circulation, O<sub>2</sub> transport and utilisation to the locomotor muscles and CO<sub>2</sub> elimination [18, 53] (Figure 2.1).



**Figure 2.1.** In-series physiological systems participating in oxygen transport and utilisation [53].



**Figure 2.2.** a) Limitation of energy supply [18], b) Effect of expiratory flow limitation (EFL) on cardiac function. DH: dynamic hyperinflation; ITP: intra-thoracic pressure; PVR: pulmonary vascular resistance; LV: left ventricular; RV: right ventricular; CO: cardiac output.

The lower exercise capacity in patients with COPD compared to aged matched healthy individuals has multifactorial background [54] including not only ventilatory constraints leading to excessive breathlessness [55], but also gas exchange abnormalities [56], central haemodynamic [57] and peripheral muscle dysfunction [58]. The aforementioned abnormalities collectively impede oxygen transport and utilisation, thus reducing exercise capacity (Figure 2.2a) [18]. In COPD exercise intolerance occurs due to the following mechanisms: a) mismatch between ventilatory capacity and ventilatory demand, b) mismatch between oxygen requirement and oxygen availability, secondary to impaired venous return and c) low aerobic capacity at the level of the peripheral muscles [18].

### **2.2.Imbalance between ventilatory capacity and demand**

Ventilatory capacity is reduced in patients with COPD mainly due to dynamic hyperinflation [55], secondary to expiratory flow limitation [18, 55]. Dynamic hyperinflation limits tidal volume expansion and increases end-expiratory lung volumes exacerbating dyspnoea [55]. Expiratory flow limitation is a common pathophysiological characteristic in this population [59] and is the result of the presence of emphysema and chronic bronchitis that collectively increase airway resistance [18]. Limited expiratory flow, impairs normal lung emptying [60], leading to increased end-expiratory lung volume both at rest (static hyperinflation) and during exercise (dynamic hyperinflation) [55].

The term static hyperinflation describes the situation when the respiratory muscles have been readjusted in a greater relaxation lung volume, due to the increase static lung compliance of emphysema [18] and is a typical pathophysiological characteristic of patients with COPD [55]. The increased lung volume during spontaneous breathing

increases airway conductance and limits patient's ventilatory capacity when the circumstances demand increased ventilation (i.e. exercise) [55].

During conditions requiring increased ventilation such as exercise, air trapping further increases as inspiratory volume increases and time of expiration decreases [60, 61]. Consequently, COPD patients do not have enough time to expire all the inspired amount of air when next inspiration begins. The phenomenon when additional air trapping in the lungs is added on the air which is already trapped in the lungs is called dynamic hyperinflation [55]. In fact, the greater the expiratory flow limitation and minute ventilation are, the greater the degree of dynamic hyperinflation is [19, 62].

Furthermore, dynamic hyperinflation increases the elastic loading of the respiratory muscles due to the increase of the end expiratory lung volume. As a result, work of breathing for a given amount of ventilation increases [19, 59, 63]. In addition, respiratory muscle operation is also affected by the degree of dynamic hyperinflation [18]. The greater the lung volume at the end of expiration the shorter the respiratory muscles become, affecting their contractility and reducing their ability to produce force, according to the length – tension relationship [64, 65], thus reducing the muscles ability to produce the required work to overcome the additional resistance caused by the expiratory flow limitation [66-68]. Another consequence of dynamic hyperinflation is the increased intrinsic positive alveolar end-expiratory pressure (PEEPi) [18]. Inhalation begins when alveolar pressure drops below atmospheric pressure. This is achieved by contracting the respiratory muscles and thus increasing lung volume above the relaxation volume. However, in COPD respiratory muscle length and ability to produce power is reduced due to the air trapped in the lungs, hence they should work harder to initiate inhalation as they have to overcome the increased inspiratory elastic load [69].

On the other hand, ventilatory requirement during exercise is increased in patients with COPD due to abnormal ventilatory mechanics secondary to altered breathing pattern resulting in increased work of breathing [18]. Loss of the elastic recoil and obstruction of the airways increase the compliance of the lungs in COPD patients [18]. Hence, adoption of a normal breathing pattern will require minimum energy making breathing easier due to lower pressures required to overcome the elastic recoil of the emphysematous lung [18]. In contrast, the fast and shallow breathing pattern that patients with COPD often adopt both at rest and during exercise [70, 71] has the opposite effect as the faster the breathing gets the less the compliance of the lung becomes [59] thus exacerbating breathlessness and limiting exercise tolerance [18].

In addition, compared to healthy age matched people, ventilatory requirement is greater in patients with COPD, due to the lower gas exchange capacity of the lung, increasing energy demands and workload of the respiratory muscles (Figure 2.3) [18]. The above is the consequence of a greater mismatch between alveolar ventilation and blood flow in the alveoli [18]. Taking into account that, in contrast to healthy people, lung dead space does not change during exercise in COPD [56, 72], minute ventilation has to increase in order to offset the absence of the additional space for gas exchange in the lungs and keep alveolar ventilation and blood gases in acceptable levels [18].

Another factor that increases ventilatory requirement in patients with COPD is the early metabolic acidosis which further stimulates ventilation [73, 74]. Early metabolic acidosis occurs mainly due to reduced oxygen delivery to locomotor muscles, low oxidative capacity of the peripheral muscles and abnormal regulation of the blood vessels [73-78]. This leads to greater minute ventilation during submaximal levels of exercise in patients with COPD compared to age matched healthy individuals as it is presented by the slope between minute ventilation and work rate [79-81].

The imbalance between the decreased ventilatory capacity and the increased ventilatory requirement exacerbates breathlessness [82-84] which is associated with the magnitude of exercise-induced dynamic hyperinflation [62, 70]. In addition, a study performing a multiple regression analysis has shown that changes in end-inspiratory lung volume expressed as fraction of total lung capacity was the strongest predictor for breathlessness [62]. Additionally, in the same study tidal volume, breathing frequency and end-expiratory lung volume contributed more than 60% to exertional breathlessness [62]; these results are confirmed by another study from the same group [70]. Assuming that total lung capacity does not significantly change during exercise in COPD [85], inspiratory reserve volume decreases by 3-fold compared to healthy age-matched individuals [86] due to the higher end-inspiratory lung volumes, limiting tidal volume expansion and increasing dyspnoea [70]. Finally, there are a number of studies providing indirect evidence of contribution of the exercise-induced dynamic hyperinflation and the abnormal ventilatory mechanics during exercise on exertional dyspnoea, as interventions targeting to reduce either operational lung volumes (i.e. pharmacologically, surgically or by inhalation of oxygen or heliox mixtures) and the work of breathing (i.e. application of non-invasive ventilation) have shown to lessen the degree of dyspnoea [34-36, 63, 87-91].

### **2.3.Circulatory effects of dynamic hyperinflation**

It is well documented that resting and dynamic lung hyperinflation causes adverse circulatory effects including impaired diastolic function, intrathoracic hypovolemia [92-96] and pulmonary arterial hypertension due to increased pulmonary vascular resistance [94, 97]. Furthermore, increased abdominal pressures that generated to overcome the expiratory flow limitation reduce venous return and thus cardiac output secondary to impaired blood volume return from the periphery due to compression of the inferior

vena cava [57, 94, 98-100]. Moreover, increased expiratory muscle recruitment increases alveolar pressures by compressing blood vessels in the alveolar walls, decreasing left ventricular preload secondary to further reduction in venous return [98]. Thus, generating expiratory pressure at a level seen during exercise in patients with COPD [101] can potentially compromise venous return and left ventricular preload and thus limit the normal increase in cardiac output with increasing exercise intensity [18]. In addition, left ventricular function can be potentially impaired during exercise in patients with COPD as left ventricular afterload increases due to the large negative intrathoracic pressure swings generated to overcome the increased inspiratory elastic and resistive loads [57, 99] (Figure 2.2).

Likewise, increased lung volumes at rest and during exercise are associated with increased pulmonary arterial pressure and vascular resistance [57, 94, 99, 100, 102], leading to both increased right ventricular afterload [94, 96, 97, 102] and increased right ventricular end-diastolic pressure [57, 100], thereby reducing right ventricular ejection fraction [57, 100] (Figure 2.2a & b). The reduction in the right ventricular ejection fraction reduces left ventricular ejection fraction [96, 103], whilst left ventricular end-diastolic and end-systolic volumes, as well as stroke volume are all decreased [104] (Figure 2.2a & b).

When lung volume is close to normal functional residual capacity, the pulmonary vascular resistance is minimal. However, pulmonary vascular resistance increases progressively, along with the increase in lung volume as result of dynamic hyperinflation [57, 94, 99, 100, 102, 105-107]. In patients with COPD, the degree of dynamic hyperinflation is associated with the development of exercise pulmonary hypertension during exercise [100, 107-109], potentially contributing to increased right ventricular afterload [94, 96, 97, 102, 105-107, 109] (Figure 2.2a & b). Furthermore,



chronic lung diseases are associated with structural changes in pulmonary circulation, such as loss of vascularity, as well as changes in capillary structure, such as loss of alveolar wall structure and the associated capillaries, and thus with a reduction in the total cross-sectional area of the pulmonary capillary bed [105]. The latter, can further increase the mismatch between ventilation and perfusion with increased cardiac output during exercise [105]. These changes may result in reduced density of the pulmonary vascular bed, further contributing to increased vascular resistance, thus increasing right ventricular afterload [105] (Figure 2.2a & b).

Although elevated right ventricular afterload appears to be the primary cardiovascular effect of chronic lung disease, a reduction in preload may also compromise right ventricle function. These conditions arise as a result of hyperinflation in patients with COPD, secondary to restriction of venous return by increased intrathoracic pressure. This may occur with dynamic hyperinflation during exercise, or in the setting of relative intravascular volume depletion [98] (Figure 2.2a & b).

Moreover, in COPD patients, left ventricular diastolic function could be impaired, due to the ventricular interdependence in the distension of the right ventricle. This is because of increased pulmonary vascular resistance which may impede left ventricular diastolic filling [96, 103, 104, 106, 107, 109], thereby contributing to the decrease in left ventricular afterload (Figure 2.2a & b). The resulting increase in pulmonary venous pressure could contribute to overall pulmonary vascular resistance and/or to the development of dyspnoea during exercise [96, 103-107, 109].

#### **2.4.Limited energy supply to the locomotor muscles**

In addition to the circulatory impairment dynamic hyperinflation also imposes adverse effects on oxygen transportation to the working muscles. In addition to

expiratory flow limitation, the increased airway resistance and the energetically wasteful breathing pattern increase work of breathing and thus, the energy requirements of the respiratory muscles [110, 111]. The increased energy requirement of the respiratory muscles, achieved by applying expiratory load has been found to redistribute blood flow from the peripheral to respiratory muscles in healthy individuals during exercise [112-115].

There is evidence that exercise performance is also limited as a result of inadequate energy supply to the working muscles as oxygen supplementation has been found to increase the maximum power generated by whole body and smaller muscles indicating that muscle capacity to produce power is limited by oxygen availability [116-118]. In fact the performance of the smaller muscles increased more compared to whole-body exercise indicating that more energy was available for those muscles due to lack of respiratory muscle competition for energy [116-118]. These findings are further supported by another study which reported that patients who did not reach their ventilatory ceiling leg blood flow, oxygen uptake and work capacity were all greater compared to those patients that reached their ventilatory ceiling and thus energy requirements of the respiratory muscles were greater [119]. In contrast, when exercise performed with heliox supplementation arterial oxygen content was increased whilst peripheral and respiratory muscle fatigue was reduced [119], suggesting a relationship between peripheral muscle fatigue and pulmonary limitation [18]. However, not all studies agree with this concept, as it is reported that blood flow of the intercostal muscles is limited at high levels of exercise, whilst quadriceps muscle perfusion was sustained during an incremental exercise test in COPD patients [120].

### **2.5.Methods to assess dynamic hyperinflation**

There are two commonly used methods to assess dynamic hyperinflation during exercise, namely i) inspiratory capacity manoeuvres and ii) via optoelectronic plethysmography, both having advantages and disadvantages. Decrease in inspiratory capacity during exercise reflects an increase in end-expiratory lung volume. Studies that have used the flow through a pneumotachograph to assess dynamic hyperinflation, consistently reported reduced inspiratory capacity by an average of 200 mL, during exercise in patients with COPD [19, 55, 62, 81, 90, 121, 122] (Figure 2.3). This method measures the amount of air inspired and it is simple to apply in patients who are familiar with the spirometry procedure. However, this method takes into account the assumption that total lung capacity remains stable during exercise [18]. Furthermore, this method relies on the effort of the subject when performing the inspiratory capacity manoeuvre and thus might underestimate the magnitude of dynamic hyperinflation during high levels of exercise when patients are perceived respiratory muscle discomfort and breathlessness.

In contrast, when dynamic hyperinflation is assessed by breath-by-breath changes in end-expiratory chest wall volume using optoelectronic plethysmography either large increases [85, 86] at peak exercise (by 750 ml) in early hyperinflators or smaller increases in the range of 250 ml in late hyperinflators [86], or no changes in end-expiratory chest wall volume [123, 124] have been reported. The main advantage of this method is the breath-by-breath recording of the dynamic changes of end-inspiratory and end-expiratory thoracoabdominal volumes. However, changes in thoracoabdominal volumes reflect changes in lung volumes, gas compression and decompression in the lungs and blood shifts between the periphery and the trunk [125].

An additional advantage of utilising OEP during exercise is that it provides important information on compartmental end-inspiratory and end-expiratory volume regulation (ribcage and abdomen), during exercise in patients with COPD [126]. In fact, a number of studies highlight that late hyperinflators and evolumics offset rib cage dynamic hyperinflation by recruitment of expiratory abdominal muscles which is not the case in patients who demonstrate progressive dynamic hyperinflation during exercise.

## **2.6. Ergogenic approaches to reduce dynamic hyperinflation**

Over the past two decades different approaches have been employed to reduce dynamic hyperinflation and increase exercise tolerance in patients with COPD namely bronchodilators [27], oxygen supplementation [26] and heliox supplementation [28], interval exercise [127] and non-invasive ventilation [24, 128].

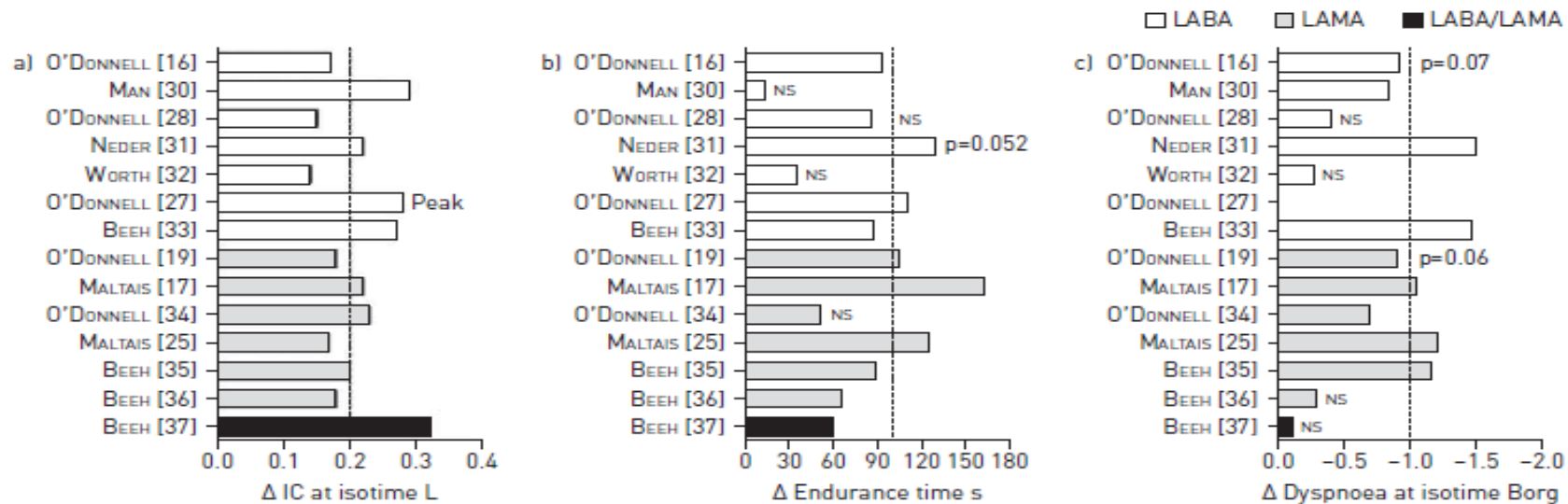
### **2.6.1. Effect of bronchodilators on dynamic hyperinflation and exercise tolerance**

Use of inhaled bronchodilators have shown to increase tolerance [27, 87, 90, 122, 129-135] to constant load exercise and peak incremental exercise assessed during a cardiopulmonary exercise test by reducing dynamic hyperinflation (eg. greater inspiratory capacity) and breathlessness in patients with moderate to severe COPD [27, 87, 90, 122, 129-135].

Bronchodilators reduce dynamic hyperinflation by reducing inspiratory threshold loading of the inspiratory muscles, allowing patients to achieve the required levels of minute ventilation with lower neural drive and work of breathing and thus, lower breathlessness [27, 70, 87, 136-138]. Furthermore, the lower end-expiratory lung volume with bronchodilators increases inspiratory reserve volume (IRV) and thus, allows tidal volume to increase more, before it reaches the critical respiratory mechanical constraints during exercise [27, 87, 134, 135, 137, 139]. Accordingly, the

mismatch between the inspiratory neural drive and the mechanical response of the respiratory system is reduced allowing greater tidal volume expansion with lower respiratory muscle effort [137].

A number of randomised clinical trials, reported varying evidence on the effect of use of bronchodilators on breathlessness and exercise tolerance in patients with moderate to severe COPD most likely due to the subjective nature of the method that is used to record breathlessness (Borg scale) and the small number of patients that participated in the studies [122, 129, 131-134, 140-143] (Figure 2.3) [27]. Moreover, the improvement of lung mechanics with the use of bronchodilators, as described above, is relative small and thus, patients with severe COPD are not greatly benefited during exercise [27, 137]. Finally, bronchodilators cannot affect other factors that limit exercise tolerance in patients with COPD such as circulatory factors [18, 27].

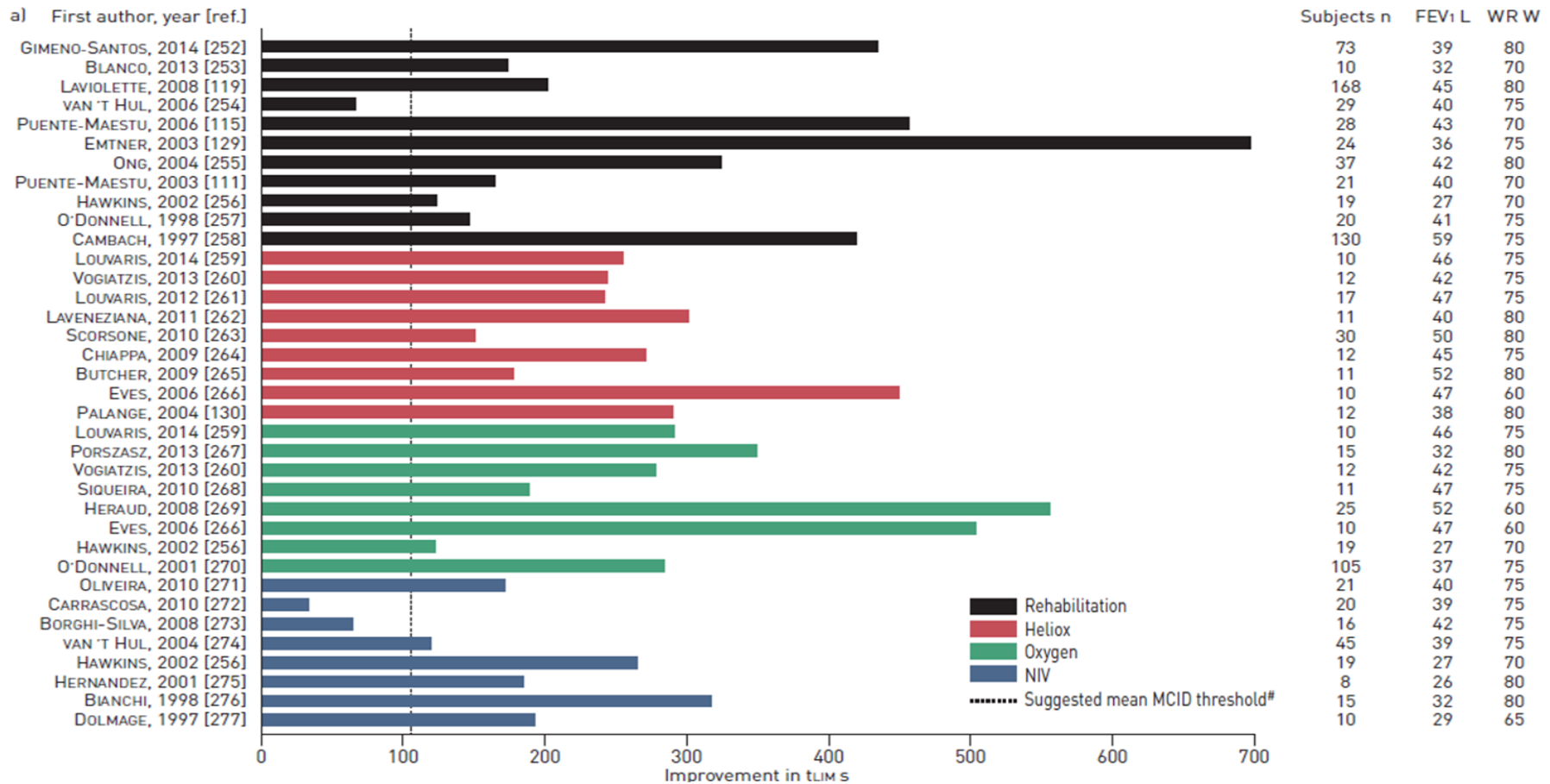


**Figure 2.3.** Improvements in response to long-acting  $\beta$ 2-agonists (LABA), long-acting muscarinic antagonists (LAMA) and LABA/LAMA combinations compared with placebo are shown for a) exercise measurements of IC at a standardised time during exercise (iso-time), b) constant-WR cycle exercise endurance time, and c) dyspnoea intensity ratings at iso-time. Treatment differences in these randomised, placebo-controlled studies are statistically significant ( $p < 0.05$ ) unless indicated otherwise (not significant (NS)) [27].

### **2.6.2. Effect of oxygen supplementation on dynamic hyperinflation and exercise tolerance**

A number of studies reported a clinically meaningful increase in exercise to tolerance in patients with COPD when oxygen supplementation was applied (Figure 2.4) [24, 26, 52, 144-149]. Application of oxygen supplementation increases exercise tolerance mainly by reducing breathlessness. However, the mechanism by which breathlessness is reduced is different compared to that with bronchodilators. Likewise bronchodilators, ventilatory demand is lower with oxygen supplementation compared to room air breathing, resulting in lower operational lung volumes and thus, delaying the onset of ventilatory constraints that exacerbates breathlessness [26].

Furthermore, oxygen supplementation improves oxygen transport and utilisation in patients with COPD. In fact, arterial oxygen saturation increases with oxygen supplementation compared to room air breathing, resulting to greater oxygen availability in the peripheral working muscles [149], thereby delaying metabolic acidosis [149]. Metabolic acidosis is associated with increased respiratory neural drive and ventilation due to the additional CO<sub>2</sub> production secondary to the buffering of the hydrogen ions [150].



**Figure 2.4.** a) Absolute changes in endurance time at the limit of tolerance (tLIM) during constant work-rate exercise with non-pharmacological interventions in chronic obstructive pulmonary disease patients. FEV<sub>1</sub>: forced expiratory volume in 1 second; WR: work-rate; NIV: non-invasive ventilation; MCID: minimum clinically important difference. #: suggested mean MCID thresholds 105 s (lower limit of 95% CI 60 s) [24].



### **2.6.3. Effect of heliox supplementation on dynamic hyperinflation and exercise tolerance**

It is well documented that heliox administration also induces clinically meaningful increases in exercise tolerance in patients with moderate-to-severe COPD [24]. A number of studies reported that exercise tolerance is increased by an average of approximately 220 seconds compared to room air breathing [144, 146, 149, 151-155] (Figure 2.4).

Patients with COPD experience greater turbulent flow within the large airways even during low breathing frequency [156] and as a result airflow limitation and work of breathing are both increased secondary to greater airway resistance [28]. Because heliox density is approximately one third of the room air, it allows smoother flow of the air secondary to less turbulence within the large airways [28]. A review conducted by Hunt and colleagues [157] reported reduced dynamic hyperinflation and work of breathing as the main factors improving exercise tolerance in patients with moderate to severe COPD when patients breathed a heliox gas mixture compared to room air [152, 157].

Nevertheless, heliox administration has also positive circulatory effects and metabolic effects. In fact, it is previously reported that heliox administration increased peak oxygen uptake by 15% with small improvements in cardiac output and oxygen extraction [155, 158]. Authors concluded that reducing the work of the respiratory muscles allowed more blood flow to the locomotor muscles and thus, increased exercise capacity for a given cardiac output [158]. Increased systemic oxygen delivery, systemic oxygen content, and reduced exercise-induced muscle fatigue is also reported in a number of studies administering heliox during exercise in patients with moderate-to-severe COPD [144, 154, 159]. Finally in the study by Laveneziana and colleagues it was reported that heliox administration significantly accelerated mean response time for

heart rate; the above acceleration was significantly associated with the reduction in exercise-induced dynamic hyperinflation and the increase in exercise endurance time [153].

#### **2.6.4. Effect of interval exercise on dynamic hyperinflation and exercise tolerance in COPD**

The majority of patients with moderate-to-severe COPD cannot sustain high intensities of exercise for a long period of time [160, 161]. Furthermore, exercise of higher intensity of exercise is associated with greater physiological benefits in patients with COPD [75]. Interval exercise was initially introduced in 1960 to allow greater duration of high intensity of training in healthy individuals [162, 163], however, in the past two decades it is broadly applied in patients with COPD [23, 164, 165].

Interval exercise provides tolerable training loads whilst maintaining an effective stimulus for peripheral muscle adaptation in patients with moderately severe and severe COPD. Exercise training protocols of repeated brief bouts of high-intensity interval exercise (30 to 120 sec), followed by equally brief recovery periods, have demonstrated prolonged exercise tolerance compared to continuous exercise, secondary to smaller magnitudes of dynamic hyperinflation and breathlessness. Hence, with interval exercise patients can exercise longer at higher training loads before symptoms become intolerable [29]. Evidence suggests that interval exercise training is effective across a wide spectrum of severity in COPD [166], including patients with profound peripheral muscle loss [167].

The first study indicating interval exercise as an alternative training modality to continuous exercise was published by Vogiatzis and colleagues in 2002 [127]. During interval exercise, mean training intensity throughout 25 training sessions was almost

double compared to the mean training intensity during continuous exercise (124% versus 67% WR<sub>peak</sub>) [127]. In addition, both breathlessness and cardiac output were lower with interval exercise compared to continuous exercise indicating lower cardiovascular and ventilatory loads [127] thus, providing evidence of the effectiveness of interval exercise in a setting of pulmonary rehabilitation [127].

The above study was followed by another study from the same group, comparing the acute physiological responses during continuous and interval exercise in patients with moderate-to-severe COPD [29]. Authors reported a 3-fold increase in exercise tolerance, mainly due to lower ventilatory requirements, lower metabolic acidosis and lower symptoms of breathlessness and leg discomfort [29]. These findings were further supported by lower metabolic requirement (oxygen uptake, carbon dioxide production and respiratory exchange ratio) and greater ventilatory responses (greater inspiratory capacity and inspiratory reserved volume and lower minute ventilation, tidal volume, breathing frequency, dead space) [29]. Interestingly, oxygen uptake, minute ventilation and heart rate were not different between the exercise and the recovery phases during the interval exercise [29] suggesting that interval exercise is associated with stable and lower metabolic demands, minute ventilation and rate of dynamic hyperinflation although exercise duration is much greater compared to continuous exercise [29].

### **2.7. Non-invasive ventilation**

Non-invasive ventilation (NIV) is widely used since 1980s as an effective way to treat patients with respiratory failure [168-171] both in the acute setting (during hospitalisation and ICU) [172] and at home (during daily living) [173]. The aim of NIV is to assist ventilation mainly by reducing work of breathing, improving inspiratory flow rate, controlling ventilation and resetting the central respiratory drive [173]. At the early days of NIV the number of the available modalities and ventilatory methods was very

limited. Nowadays, due to technological breakthroughs there are more than 30 different brands offering a wide number of ventilatory options [174]. As a result, different ventilatory modalities are available, but the large majority of the devices deliver either volume or pressure targeted ventilation [32].

Volume targeted ventilators deliver a fixed volume of air during a given time. During respiration airway pressure is not constant therefore, the delivered pressure varies throughout the duty cycle to achieve the targeted volume when volume targeted ventilators are applied [32]. In contrast, pressure targeted ventilators aim at maintaining the airway pressure constant, therefore the volume of the delivered air in the airways varies accordingly during each breath [32]. The combination of these two modalities creates a hybrid ventilatory modality which is capable of maintaining the targeted tidal volume by estimating the delivered tidal volume [32].

However, recent modes of ventilation have a more physiological background in delivering assistance flow consequently, their function is more complex. The most commonly used non-invasive ventilatory modalities are the following: continuous positive airway pressure (CPAP), proportional assisted ventilation (PAV), inspiratory pressure support (IPS) and pressure support ventilation (PSV).

### **2.7.1. Physiological effects of NIV at resting conditions**

#### **2.7.1.1. Effects of NIV on work of breathing**

Work of breathing (WoB) is assessed by measuring intrathoracic (esophageal and transdiaphragmatic) pressures using balloon catheters. In patients with different respiratory diseases and disease severity, it is well established that application of non-invasive ventilation reduces inspiratory effort [175]. Compared to spontaneous breathing NIV methods providing air with relatively high pressures (greater than 10

cmH<sub>2</sub>O), have been reported to reduce oesophageal [43, 175-183] and diaphragmatic pressures [175, 178, 179, 181, 183-188] (Appendix A Table 1) equivalent to an average of 0.41 Joules/L [43, 174, 175, 177, 182, 185, 188] (Appendix A Table 1). In addition, when positive end expiratory pressure was applied intrinsic PEEP (PEEPi) has consistently been reported to decrease by an average of 0.86 cmH<sub>2</sub>O [48, 175, 178-181, 183-188] compared to spontaneous breathing (Appendix A Table 1). Finally, compared to spontaneous breathing application of NIV reduces electromyographic diaphragmatic activation [175, 177, 178, 183, 187, 189-191] (Appendix A Table 1).

However, the effect on WoB varies between different NIV methods. Compared to spontaneous breathing Pressure Support Ventilation (PSV) has been reported to reduce oesophageal [43, 177-180, 182] and diaphragmatic pressures [177-179, 184-186, 188] (Appendix A Table 1). Work of breathing is also reduced when PSV is applied, whilst PEEPi and electromyographic diaphragmatic activation are both reduced compared to spontaneous breathing [43, 48, 177-180, 182, 184-186, 188] (Appendix A Table 1).

Compared to spontaneous breathing, Continuous Positive Airway Pressure (CPAP) has been reported to reduce oesophageal [176] and diaphragmatic pressures [184, 188], whilst WoB [188] and PEEPi were reduced [184, 188] (Appendix A Table 2).

Proportional Assist Ventilation (PAV) reduces oesophageal, [43, 179, 182, 183] and diaphragmatic pressures [179, 183], similarly to PSV. Furthermore, WoB, [43, 182] and electromyographic diaphragmatic activation [183] are reduced (Appendix A Table 2). On the other hand the effect on PEEPi is less clear as three studies reported a reduction [48, 179, 183], whilst one study found an increase [182] (Appendix A Table 2). The reduction in WoB and diaphragmatic activation is similar to PSV and greater than

CPAP. In contrast, the reduction in PEEP<sub>i</sub> is similar with PAV and PSV but lower compared to CPAP (Appendix A Table 2).

There is limited evidences in the literature about the effect of the application of Bi-level Positive Airway Pressure (BiPAP) on the WoB [191, 192] [86, 87] (Appendix A Table 2). In the study of Renston and colleagues application of inspiratory positive airway pressure (IPAP) (18 cmH<sub>2</sub>O) and expiratory positive airway pressure (EPAP) (2 cmH<sub>2</sub>O) reduced diaphragmatic activation by 66%, compared to control breathing [191] (Appendix A Table 2). However, application of lower IPAP (10 cmH<sub>2</sub>O) and greater EPAP (4 cmH<sub>2</sub>O) does not have any effect at the WoB when measured in Joules per litre [192] (Appendix A Table 2). Finally, compared to spontaneous breathing application of 20 cmH<sub>2</sub>O during inspiration and 7 cmH<sub>2</sub>O during expiration has been reported to decrease oesophageal pressure [176] (Appendix A Table 2).

#### 2.7.1.2. Effects of NIV on breathing pattern

In patients with different respiratory diseases and disease severity, it is well established that application of non-invasive ventilation improves breathing pattern compared to spontaneous breathing [60]. During application of different NIV methods that provide air with relatively high pressures (greater than 10 cmH<sub>2</sub>O) minute ventilation increases [48, 175-181, 183-185, 187, 188, 193] mainly due to an increase in tidal volume [43, 48, 176-188, 191, 193], whilst breathing frequency is reduced [43, 48, 176-188, 191-193] compared to normal breathing. Compared to control breathing, application of NIV is not altering inspiratory time [48, 177, 184-186], whilst expiratory time [48, 177, 178, 184, 186] and total duty cycle time [177, 184, 186] are slightly increased. This leads to a decrease of inspiratory time over total duty cycle ratio [43, 48, 177-184, 186].

Compared to control breathing, application of PSV has shown to increase minute ventilation [177-180, 184, 185, 188] secondary to increased tidal volume [43, 48, 177-180, 182, 184-186, 188], despite the reduction in breathing frequency [43, 48, 177-180, 182, 184, 186, 188] (Appendix A Table 3). Furthermore, PSV application increases total duty cycle time [184, 186] compared to spontaneous breathing, due to a small increase in both inspiratory [48, 177, 184-186] and expiratory times [48, 177, 178, 184, 186] (Appendix A Table 3). As a result, inspiratory time over total duty cycle ratio is slightly reduced compared to normal breathing when PSV is applied [43, 48, 177-180, 182, 184] (Appendix A Table 3).

Compared to spontaneous breathing, application of CPAP has adverse effects on breathing pattern. When CPAP is applied minute ventilation is reduced [176, 188] compared to quiet breathing, due to a reduction in both tidal volume [176, 188] and breathing frequency [176, 188] (Appendix A Table 4). In contrast, in the study by Appendini and colleagues [184] minute ventilation was greater (by 0.5 litres) compared to normal breathing mainly due to an increase in breathing frequency, whilst tidal volume remains unchanged [184] when CPAP applied compared to normal breathing (Appendix A Table 4). Accordingly, inspiratory and expiratory times were slightly reduced when CPAP was applied leading to a small reduction in total duty cycle ratio by 0.3 seconds, compared to spontaneous breathing [184] (Appendix A Table 4). The discrepancy between the findings with CPAP is most likely due to the variability of the population included in these studies.

In contrast to CPAP, application of PAV increased tidal volume [43, 48, 179, 182, 183], and minute ventilation [48, 179, 183], whilst neither breathing frequency nor total duty cycle ratio were affected [43, 48, 179, 182, 183] compared to spontaneous breathing (Appendix A Table 4). However, in the study by Poggi and colleagues,

compared to normal breathing, expiratory time was greater (by 0.33 seconds) when PAV applied [48] (Appendix A Table 4).

Application of IPAP (20 cmH<sub>2</sub>O) increases minute ventilation compared to normal breathing, secondary to greater tidal volume, whilst breathing frequency is lower [176, 187] (Appendix A Table 4). However, when EPAP (7 mH<sub>2</sub>O) was added to the above IPAP pressure the improvement in minute ventilation, tidal volume and breathing frequency was limited [176] (Appendix A Table 4).

### 2.7.1.3. Effects of NIV on central haemodynamic responses

It is well documented that application of NIV during resting conditions causes adverse effects on circulatory responses both in healthy individuals and in patients with COPD [50, 51, 175]. In healthy individuals application of CPAP has been found to decrease cardiac index [194], cardiac output, secondary to a reduction in stroke volume [195-197], whilst heart rate and blood pressure remained unchanged [195-197]. Similar findings have been reported in patients with COPD as application of NIV has been found to decrease cardiac output secondary to a reduction in stroke volume whilst there was no effect on heart rate and blood pressure [198-201].

During normal inspiration, pleural pressure becomes more negative, compared to expiration, mainly as a result of the contraction of the diaphragm whilst alveolar pressure equals atmospheric pressure to allow the air to flow in the lungs [50]. Additionally, expiration is passive and based mainly on elastic recoil forces of the lung and the relaxation of the diaphragm [50]. In contrast, during NIV application, both alveolar and pleural pressures become positive during inspiration, whilst additional application of PEEP results in positive pleural pressure throughout the respiratory cycle [50].



The main consequences of the aforementioned alternations in the alveolar and pleural pressures are the following: (i) increased ventilation/perfusion mismatch by compressing the alveolar vessels and increasing pulmonary vascular resistance and (ii) reduced venous return secondary to compression of the large intrathoracic blood vessels and increased right atrial pressure due to the greater intrathoracic pressure [50, 202, 203]. Normally, a relatively small pressure of 4-8 mmHg is required to allow blood return to the heart [204], consequently increases in intrathoracic pressures can cause large decreases in stroke volume and thus cardiac output [51]. Increasing mean systemic filling pressure by increasing stressed volume or vessel tone can mitigate the reduction in venous return [205].

#### 2.7.1.4. Physiological effects of PEEP

During application of NIV, it is common to apply external positive end-expiratory pressure (PEEP<sub>e</sub>) to counterbalance the negative effects of PEEP<sub>i</sub>. In fact, application of PEEP<sub>e</sub> has been found to reduce the work of breathing, normalise breathing pattern and improve blood gas levels and synchronisation of the breathing between the patient and the ventilator [168-170]. Nevertheless, PEEP<sub>e</sub> level needs to be optimal to be beneficial for the patients [206]. If PEEP<sub>e</sub> is lower than PEEP<sub>i</sub> then the positive effects are minimised [206, 207]. On the other hand, when PEEP<sub>e</sub> exceeds PEEP<sub>i</sub>, this would increase dynamic hyperinflation and intrathoracic pressure swings, potentially adversely affecting venous return and cardiac output [171-173]. Accordingly, the applied level of PEEP<sub>e</sub> should be individualised in each patient.

A study by Milesi and colleagues investigated the capability of a new ventilator to adjust breath-by-breath the applied PEEP<sub>e</sub> relative to PEEP<sub>i</sub> across different postures in patients with COPD. The study showed that the optimal PEEP<sub>e</sub> for a population of moderate to severe COPD in the seated position was approximately 4 cmH<sub>2</sub>O [206].

However, the pressure of PEEPe that minimises PEEPi cannot be predicted by either baseline lung function, anthropometric characteristics or combination of those, suggesting that PEEPe was optimal to abolish expiratory flow limitation in less than one third of the patients in sited position (i.e. 8 out of 26) [206]. These 8 patients had better lung function and less dynamic hyperinflation compared to the patients who did exhibit abolished expiratory flow limitation when PEEPe of 4 cmH<sub>2</sub>O applied [206].

### **2.7.2. Effect of NIV application on dynamic hyperinflation and exercise tolerance**

Over the past three decades a number of studies investigated the acute effects of NIV application on exercise tolerance in COPD patients [24, 49, 208]. Accordingly, it is well established that application of a variety of different NIV methods increases exercise tolerance in this population (Appendix A Table 5 & Table 6) [24, 49, 208].

Four studies investigated the effect of continuous positive airway pressure (CPAP) application on exercise tolerance [35, 36, 44, 46] (Appendix A Table 5 & Table 6). In the study by Bianchi and colleagues exercise tolerance was increased by 2.4 minutes when CPAP of 6 cmH<sub>2</sub>O was applied compared to sham [44]. The increase in exercise tolerance was secondary to lower breathlessness however, minute ventilation and inspiratory flow remained unchanged [44]. Similar findings reported in the study by Dolmage and colleagues where exercise tolerance was increased by 1.7 minutes when CPAP of 5 cmH<sub>2</sub>O was applied compared to sham CPAP [46]. However, in the latter study there were no differences in breathlessness or in ventilatory responses [46]. O'Donnell reported that application of CPAP of 4-5 cmH<sub>2</sub>O increased exercise tolerance by 2.8 minutes compared to sham secondary to lower breathlessness and respiratory rate at exercise iso-time, whilst there was no difference in dynamic hyperinflation [34]. The findings on dynamic hyperinflation are similar to those of Petrof and colleagues who also reported that application of CPAP of 7.5-10.0 cmH<sub>2</sub>O

did not reduce end-expiratory lung volumes compared to normal breathing [36]. In contrast, when CPAP of 6 cmH<sub>2</sub>O was applied during walking on a treadmill exercise tolerance or breathlessness were not improved in patients with severe COPD [37].

Application of proportional assist ventilation (PAV) has been also found to increase exercise tolerance in patients with COPD as reported in five studies [44-47, 209] (Appendix A Table 5 & Table 6). Bianchi and colleagues reported increased exercise tolerance compared to sham by an average of 5.3 minutes [44]. The increase in exercise tolerance was accompanied by lower breathlessness (2 units on 1-10 Borg scale), greater tidal volume (by 140 ml) and greater inspiratory flow (by 150 ml) [44]. In addition, Hernandez and colleagues reported an increase in exercise tolerance by 3.1 minutes with PAV compared to normal breathing secondary to better ventilatory responses (i.e. greater tidal volume, lower breathing frequency and greater minute ventilation), greater duty cycle and better inspiratory and expiratory flow at iso-time [47]. In contrast, in the study by Dolmage and colleagues exercise tolerance was increased only by 0.5 minutes when PAV was applied compared to sham, whilst there was no difference in any ventilatory variables [46]. However, when PAV was combined with CPAP exercise tolerance increased two fold compared to sham whilst minute ventilation was greater secondary to greater tidal volume [46]. Similar increase in exercise tolerance (0.5 minutes) was also reported in the study by Carrascossa and colleagues when PAV was applied compared to control attributed to the high variability of the response of the patients when PAV was applied [45]. Finally, another study that applied PAV during submaximal exercise reported an increase in exercise tolerance compared to sham by 1 minute, mainly due to lower symptoms of breathlessness and leg discomfort at iso-time and greater oxygen availability in the locomotor muscles

[209]. The discrepancy of the above findings between the studies can be explained from the differences in the protocols applied.

Inspiratory pressure support (IPS) has been used in three studies and the findings suggest that patients can be benefited from its application during exercise [37, 42, 210] (Appendix A Table 5 & Table 6). When IPS was applied during walking on a treadmill patients covered greater distance (149 meters more) compared to control breathing secondary to lower breathlessness [37]. Furthermore, when IPS was applied during cycling in patients with COPD, exercise tolerance was increased by 43% in one study [42] and by 64% in another study [210] by improving breathing pattern [42, 210] and by reducing dynamic hyperinflation [210] at exercise iso-time.

Finally, when pressure support ventilation (PSV) was applied during cycling, patients with COPD were able to increase their exercise tolerance by 3.3 minutes compared to sham, secondary to lower breathlessness and better breathing pattern [44] (Appendix A Table 5 & Table 6).

## 3. General methods

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### ***3.1. Study population and patient recruitment***

#### ***3.1.1. Patient cohorts***

Originally 29 COPD patients were screened and 24 patients met the eligibility criteria in the present study. The investigations were carried out following the rules of the Declaration of Helsinki of 1975 [211], revised in 2013. NHS Research Ethics Committee approval (REC: 17/NE/0085) and Clinical Trials registration (NCT03068026) were obtained. Data were collected at the Respiratory Department, North Tyneside General Hospital. All participants provided written consent [20] (Appendix B).

Eligible patients were identified from those referred to pulmonary rehabilitation, by the multidisciplinary respiratory team of North Tyneside General Hospital which comprised of the usual care team, physicians, physiotherapists and specialist nurses, working within the trust, who provided initial information about the trial. The principal investigator then confirmed eligibility and discussed full details of the trial. Patients were given time to consider whether they were happy to participate in the study, including the equipment and testing procedures involved.

Part of the clinical study described in Chapters 4 and 5 was the follow up assessment of the usability, applicability and comfort of using the VitaBreath device during activities of daily living (Chapter 7). Thus, the twenty-four (24) patients who completed the study described in Chapters 4 and 5 participated in the follow up assessment under the same NHS Research Ethics Committee approval (REC: 17/NE/0085) and the same Clinical Trials registration (NCT03068026).

### **3.1.2. Patient recruitment into a further study**

For the study presented in Chapter 6 (effect of pNIV on thoracoabdominal volumes during exercise), seven patients from the original cohort presented in Chapters 4, 5 and 7 agreed to participate in the aforementioned study. The respiratory research team at North Tyneside General hospital contacted those who wished to be considered for further research and provided initial information about the trial. Patients were provided with an information sheet for the study and were given time to consider whether to participate in the trial, before written informed consent was obtained (Appendix C).

### **3.2. Inclusion and exclusion criteria**

Inclusion criteria [20]:

- 1) Male or female aged 40 years or older.
- 2) Current or previous smoking history: 10 or more pack years.
- 3) Spirometry confirmed stable COPD (GOLD stages II-IV) under optimal medical therapy.
- 4) Exhibit substantial exercise-induced dynamic hyperinflation (change in IC from baseline  $> 0.15$  L) [19] (only for studies presented in Chapters 5, 6 and 7).

Exclusion criteria [20]:

- 1) Orthopaedic, neurological or other concomitant diseases that significantly impair normal biomechanical movement patterns, as judged by the investigator.
- 2) Moderate or severe COPD exacerbation within 6 weeks [212].
- 3) Unstable cardiac arrhythmia.
- 4) Unstable ischaemic heart disease, including myocardial infarction within 6 weeks.

- 5) Moderate or severe aortic stenosis or hypertrophic obstructive cardiomyopathy.
- 6) Uncontrolled hypertension.
- 7) Uncontrolled hypotension (SBP<85mmHg).
- 8) Uncontrolled diabetes.
- 9) Intolerance of the VitaBreath device (only for studies presented in Chapters 5, 6 and 7).

### **3.3. Baseline assessments**

Prior to the cardiopulmonary exercise test (CPET) (relevant to studies presented in Chapters 4, 5. and 7) and prior to the visit to Northumbria University (study presented in Chapter 6), patients underwent full lung function assessment in order to confirm their eligibility to the study and determine the severity of COPD by assessing: 1) forced expiratory volume at the first second (FEV<sub>1</sub>) and forced vital capacity (FVC), and b) resting lung volumes including: total lung capacity (TLC), inspiratory capacity (IC), functional residual capacity (FRC), residual volume (RV) and diffusion capacity (DLco). Lung function assessment was conducted at the Lung Function Laboratory of the North Tyneside General Hospital. Before each test, all devices were calibrated based on the manufacturer's instructions.

Resting heart function was assessed by resting electrocardiogram (ECG) at the Cardiology Unit of the North Tyneside General Hospital in order to ensure that there were no existing cardiovascular complications. Medical history and physical examination were then performed by a clinician to confirm that each patient was eligible to participate in the study.

### **3.4. Participant preparation**

#### **3.4.1. Chapters 4 and 5**

After baseline assessment and confirmation of patient's eligibility, patients were prepared for the ramp incremental exercise test (CPET) (Chapter 4) and for the high- or the moderate-intensity intermittent exercise test (Chapter 5) according to the following steps: i) the skin sites were cleaned with an alcohol wipe and then the cardio-impedance (PhysioFlow) electrodes were placed (according to figure 3.3), ii) the gas exchange system (K4b<sup>2</sup> Cosmed) was positioned in the harness and then placed on the patient (Figure 3.1) to allow ventilatory, gas exchange and metabolic recordings during exercise, iii) the cycle ergometer seat was set to the correct height for the participant and iv) when the participant was on the cycle ergometer, a blood pressure arm cuff and the pulse oximeter were placed on the right arm and the finger of the left hand, respectively. Before the test started a nose clip and mouthpiece were fitted, and the investigator confirmed the CPET protocol and explained how the participants should communicate if they wanted to stop the test.



**Figure 3.1.** Placement of the harness and K4b<sup>2</sup> on the patient.



### 3.4.2. Chapter 6

During the visit to Northumbria University (Chapter 6), upon arrival to the laboratory, and prior to any intervention, adhesive skin markers for Opto-Electronic Plethysmography (OEP) (to assess thoracoabdominal wall dynamic hyperinflation), and adhesive optodes for portable cardio-impedance recordings (to assess circulatory responses) were attached to the skin following the same procedure described above. All procedures were explained in detail prior to each trial.

## 3.5. Interventions

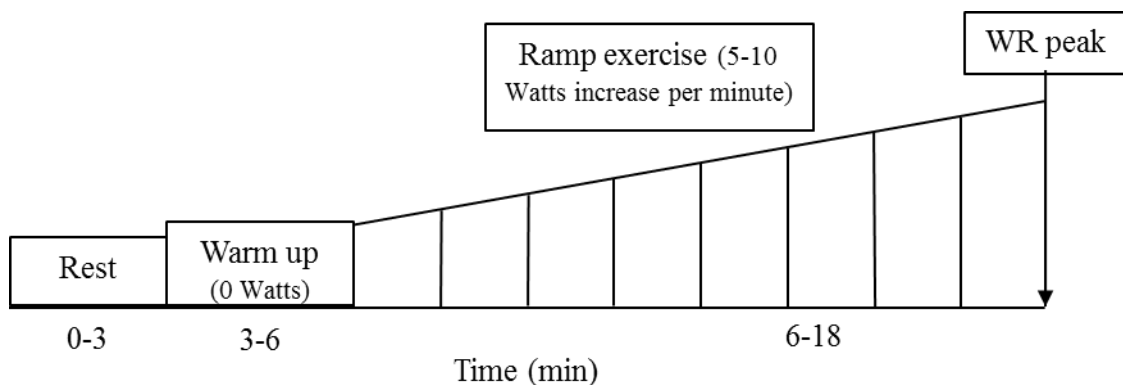
### 3.5.1. Ramp incremental cardiopulmonary exercise test (CPET) (Chapter 4)

All ramp incremental CPETs were performed on an electromagnetically braked cycle ergometer (Ergoselect 200, ergoline GmbH, Bitz, Germany) with patients maintaining a pedalling frequency of 50–60 rpm [20]. The ramp incremental CPET (Figure 3.2) consisted of a 3-mins of rest period, followed by 3-min unloaded pedalling prior to ramp incremental loading of 5 or 10W [20]. The following pulmonary gas exchange and ventilatory variables were recorded breath-by-breath via a portable gas exchange analyser (K4b<sup>2</sup>, Cosmed, Shepperton, UK) throughout the test: oxygen uptake ( $\dot{V}O_2$ ), carbon dioxide output ( $\dot{V}CO_2$ ), respiratory exchange ratio (RER), minute ventilation ( $\dot{V}_E$ ), tidal volume ( $V_T$ ), and breathing frequency (bf) [20]. Central haemodynamic responses were recorded continuously throughout the CPETs by the Physio Flow device (Enduro, PF-07, Manatec Biomedical, Folschviller, France) at a frequency of 6 seconds [20]. Arterial oxygen saturation and blood pressure were measured by pulse oximetry (Nonin 8600; Nonin Medical, Plymouth, MN, USA) and a sphygmomanometer (MABIS Healthcare PRECISION<sup>TM</sup>), respectively [20]. The modified Borg Scale was used to rate the magnitude of dyspnoea and leg discomfort at the end of the test [20, 213]. Inspiratory capacity (IC) manoeuvres were performed at rest, every 2 min during

cycling and at peak exercise, in order to evaluate the rate of dynamic hyperinflation (DH) [19, 20]. A 3-litre air pump was used to perform the volume calibration (Cosmed). The O<sub>2</sub> and CO<sub>2</sub> calibration for the gas exchange analyser were performed using a gas concentration of 16% and 5% for O<sub>2</sub> and CO<sub>2</sub>, respectively. Both calibrations were performed prior to each test in accordance with the manufacturer instructions.

The peak work rate (WR<sub>peak</sub>) was defined as the maximum mean of the last 30 seconds. At least one of the following criteria were adopted for determining whether a patient reached the limit of exercise tolerance [214]:

- i) A plateau in  $\dot{V}O_2$  [214].
- ii) Peak exercise ventilation ( $\dot{V}_{Epeak}$ ) exceeding 85% of or estimated Maximum Voluntary Ventilation (MVV).
- iii) Evidence of presence of dynamic hyperinflation indicated by a decrease from baseline in inspiratory capacity (IC) greater than 150 mL during exercise [19] .
- iv) Maximal RER during exercise exceeding 1.03.
- v) The patient reaching a HR at or above calculated HR<sub>max</sub>.
- vi)  $\dot{V}O_{2peak}$  exceeds  $\dot{V}O_{2peak}$  predicted.



**Figure 3.2.** Ramp incremental exercise protocol.

### 3.5.2. High intensity intermittent exercise protocol (Chapter 5)

The high-intensity intermittent exercise protocol (sustained at 80% WRpeak) consisted of repetitive 2-min exercise bouts, separated by 2-min recovery periods to the limit of tolerance (Figure 3.3a) [20]. This was defined as the point at which the patient signalled the inability to continue exercising or could not maintain the required pedalling rate (i.e., 50–60 revolutions/min), despite being encouraged by the investigators [20]. IC manoeuvres were performed on the 2<sup>nd</sup> minute of each exercise bout. During the 1<sup>st</sup> min of each recovery period, participants used either pNIV (VitaBreath device) or PLB [20]. During the 2<sup>nd</sup> min of each recovery period, participants performed an IC manoeuvre to assess the magnitude of dynamic hyperinflation (DH) and scored the intensity of their breathlessness and leg discomfort using the Borg scale (Figure 3.3a) [20]. Blood pressure measurements were performed on the 2<sup>nd</sup> minute of each exercise bout following each IC manoeuvre [20].

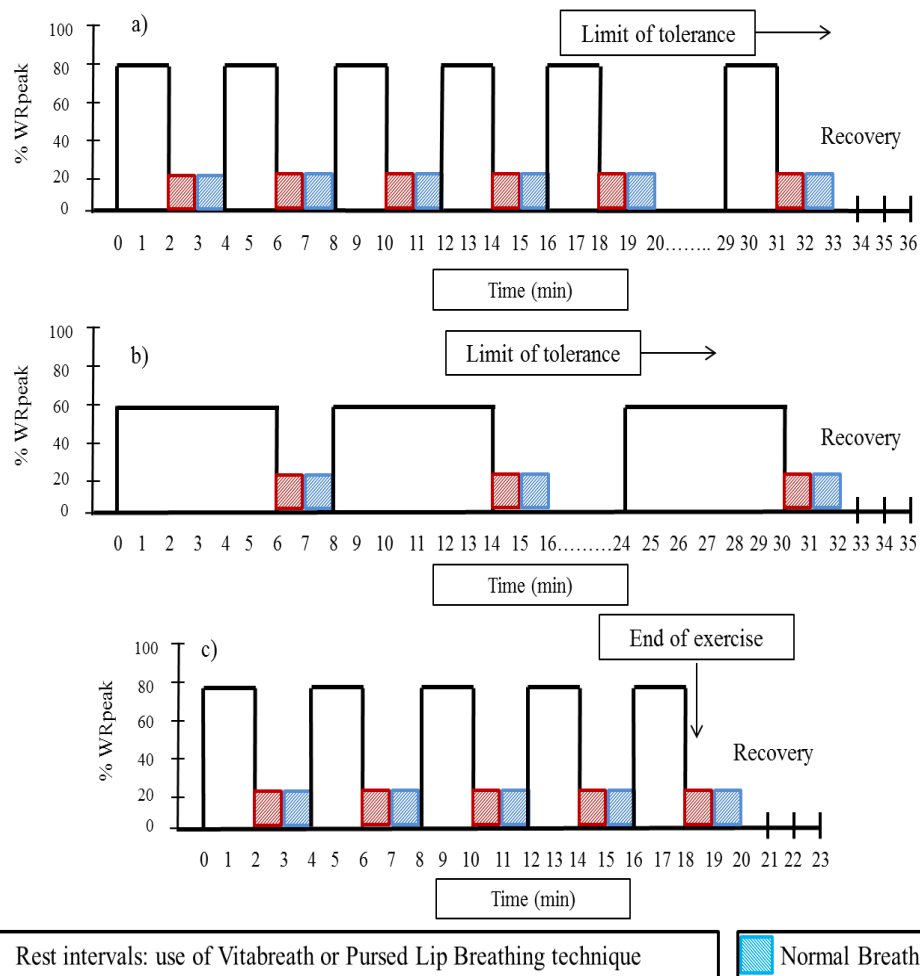
### 3.5.3. Moderate intensity intermittent exercise protocol (Chapter 5)

The moderate-intensity intermittent exercise protocol (sustained at 60% WRpeak) consisted of repetitive 6-min exercise bouts, separated by 2-min recovery periods to the limit of tolerance as described above [20]. Use of pNIV or PLB, and assessments were performed as above. IC manoeuvres followed by blood pressure measurements, were performed on the 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> minute of each exercise bout [20]. An additional IC manoeuvre followed by breathlessness and leg discomfort recordings using the modified Borg scale were performed on the 2<sup>nd</sup> minute of each recovery period following completion of each exercise bout (Figure 3.3b) [20].

### 3.5.4. High intensity intermittent exercise protocol (Chapter 6)

Patients underwent two intermittent exercise protocols on a cycle ergometer (Figure 3.3c). The exercise protocol consisted of five repeated 2-min exercise bouts at 80% of

predefined WRpeak (Chapter 4), separated by 2-min recovery periods, to allow application of the VitaBreath device or the PLB technique. During the first minute of each recovery period, patients breathed through the VitaBreath device or adopted the pursed lip breathing technique. During the second minute of each recovery period patients breathed normally. Patients also scored the intensity of their perceived dyspnoea using the Borg 1-10 scale. Cardiac output and stroke volume were measured non-invasively using a cardio-impedance method (physio-flow) throughout the exercise and recovery periods. In addition, arterial oxygen saturation was recorded throughout the exercise and recovery periods using a pulse oximeter.



**Figure 3.3.** Exercise protocols: (a) High-intensity 2-min intermittent exercise protocol to the limit of tolerance (Chapter 5) (b) Moderate-intensity 6-min intermittent exercise protocol to the limit of tolerance (Chapter 5) and (c) Five consecutive bouts of high-intensity 2-min intermittent exercise protocol (Chapter 6). Within the two protocols (high-intensity (a) or moderate-intensity (b)), each patient performed two more visits/exercise tests using pNIV and PLB during recovery from exercise in balanced order. Within the high-intensity protocol (c) each patient performed two more exercise tests using pNIV and PLB during recovery from exercise in balanced order in one visit. Typical examples of high- and moderate-intensity exercise bouts are shown by open squares and recovery periods by shadowed squares. pNIV or PLB was applied during the first minute of recovery whereas an inspiratory capacity manoeuvre was performed on the second minute of recovery (a and b) [20].

### 3.6. Familiarisation protocol (Chapter 5)

Twenty-four patients who completed the ramp incremental cardiopulmonary exercise test (Chapter 4) participated in the familiarisation program. The aim of the familiarisation exercise program was to avoid early termination during either moderate- or high-intensity exercise trials due to excessive leg discomfort. In addition, patients were familiarised with the two different exercise modalities (high and moderate

intensity intermittent exercise) and the use of the VitaBreath device, to ensure that the patient would feel comfortable to use this during the experimental exercise protocols/data collection. Patients were familiarised with both intermittent protocols as they were then randomised to perform one of the protocols.

### **3.7. Familiarisation Programme (4 weeks) (Chapter 5)**

The duration of the familiarisation programme was 4 weeks with a frequency of two exercise sessions per week [165]. The exercise programme, consisted of interval exercise on a bicycle ergometer with either 2 minutes of work at 80% of WR<sub>peak</sub> interspersed by 2 minutes of rest (see section 3.5.2), or 6 minutes of work at 60% of WR<sub>peak</sub> interspersed by 2 minutes of rest (see section 3.5.4), for 30 minutes. The initial load was individualised for each patient and was adjusted after each session, based on a target dyspnoea score of 4 on the modified Borg scale by the end of each session. When patients rated their dyspnoea at 3 or less the workload was increased by 5-10 watts at the next training session. The increase in workload with progressive familiarisation visits was towards the intended target workload (i.e. 60% and 80 % of WR<sub>peak</sub>), in order to minimise the risk of inducing significant changes in exercise capacity during the familiarisation period due to training. During the familiarisation period, patients were taught how to score their breathlessness and leg discomfort using the modified Borg scale and how to use of the VitaBreath device, and during cycling. Additionally, patients were familiarised with the correct adoption of the pursed lip breathing (PLB) technique during the recovery periods between successive exercise bouts. Patients used the VitaBreath device and PLB at the first minute of each recovery period during the intermittent exercise protocols.

### **3.8. Application of portable non-invasive ventilation**

The VitaBreath device (Philips, Respironics, Morrisville, PA, USA) is a portable, handheld, battery-powered, non-invasive ventilation (pNIV) device intended to reduce activity-related shortness of breath [215]. It delivers 18 cmH<sub>2</sub>O inspiratory and 8 cmH<sub>2</sub>O expiratory pressures, but can only be used during recovery periods interspersing bouts of physical activity [215]. Prior the application of the VitaBreath device, the level of the inspiratory and expiratory pressure was assessed using a differential pressure transducer (Validye Corp., Northbridge, CA, USA) and it was confirmed that the pressures levels provided by the manufacturer were accurate (Appendix D).

### **3.9. Application of pursed lip breathing**

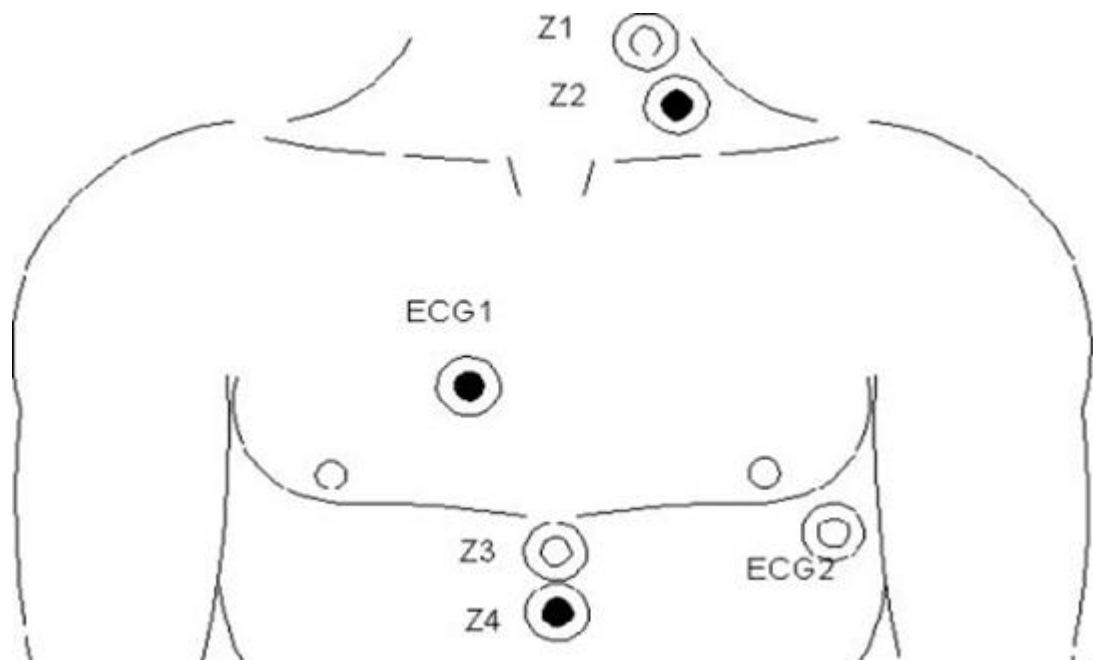
The pursed lip breathing technique is a commonly used breathing technique that patients with COPD learn to adopt, in order to reduce expiratory flow limitation and thus the degree of dynamic hyperinflation during exercise [216-218]. When patients adopt this technique, they should inspire through their nose and expire through their mouth, with their lips pursed the same way they would blow a candle. A respiratory nurse trained the COPD patients how to use the pursed lip breathing technique during recovery periods between consecutive exercise bouts, and at the end of exercise.

### **3.10. Assessment of central haemodynamic responses**

Cardiac Output (CO), heart rate (HR) and stroke volume (SV) were recorded continuously at rest, during exercise and in recovery by the PhysioFlow device (Enduro, PF-07, Manatec Biomedical, Folschviller, France) at a frequency of 6 seconds [20]. The cardio-impedance method has been used for more than 50 years in order to non-invasively record beat by beat changes in cardiac output [219]. The equations used to calculate the stroke volume were modified by Berstein [220]. During the last two decades, the method of cardio-impedance (PhysioFlow) has been used to continuously

record heart rate at rest and during exercise. Estimation of cardiac output is based on the resistance encountered by the alternating current passing through the chest. Then, a specific algorithm analyses these changes and displays the continuous non-invasive measurements of hemodynamic parameters [221].

This device (PhysioFlow, PF-07, Enduro) emits a high-frequency (75 kHz) and low-intensity (3.8 mA peak-to-peak) alternating current through six electrodes placed on the chest of the patients, for abduction and reception of electrical signals [222] (Figure 3.4).



**Figure 3.4.** Appropriate placement of the 6 electrodes of the Physio Flow, (Enduro, PF-07) cardio-impedance device. Z1 & Z3: transmitter electrodes, Z2 & Z4: receiver electrodes, ECG1 and ECG2: electrocardiographic signal monitoring electrodes.

Bio-impedance cardiography is a non-invasive method to record cardiac output, heart rate and stroke volume. The cardiac output recorded by the device (PhysioFlow, PF-07, Enduro Manatec, Macheren, France) is based on the following equation:

$$\text{Equation 1. } \text{COPF} = \text{HRPF} \times \text{SVI} \times \text{BSA}$$



According to the equation, COPF (litres/minute) is the asking cardiac output, HRPF (pulses/minute) is the heart rate calculated from the time interval of RRs determined by the electrocardiographic signal, SVI (ml/m<sup>2</sup>) is the stroke volume index per square unit of body surface area and finally the BSA (m<sup>2</sup>) is the body surface expressed in (m<sup>2</sup>), calculated according to the Haycock equation:

$$\text{Equation 2. } BSA = 0.024265 \times BM^{0.5378} \times H^{0.3964}$$

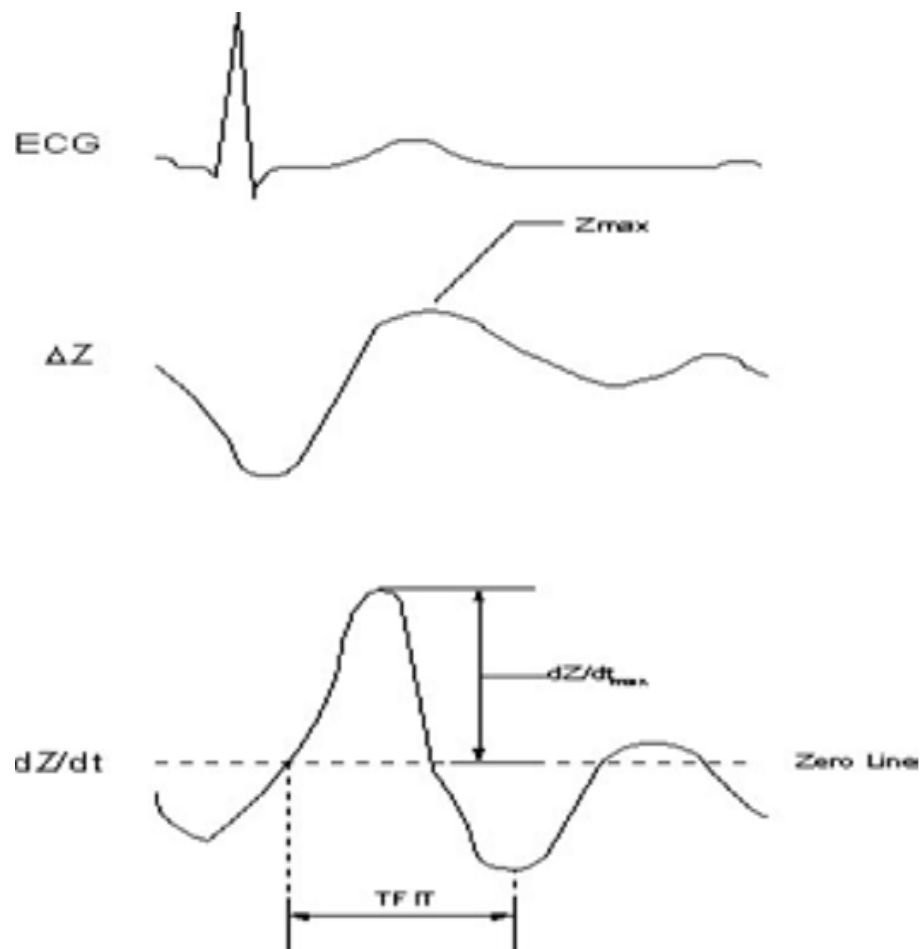
According to the equation, BM (kg) is body mass and H (cm) is height. Based on equation 1 for the SVI calculation, the stroke volume (SV) of the patient, measured by the rheographic method, is based primarily on the changes in the intra-thoracic current resistance (Z) during the extrusion of blood from the ventricles. The procedure for initiating the device included inputting the patients' demographic characteristics, evaluation of the stroke volume index (SVi), and inputting systolic and diastolic blood pressure values recorded at rest.

The calculation of SVi was initially performed during the calibration phase of the system, based on the recording of 30 consecutive heart beats with the patient sitting on the cycle ergometer, remaining still and silent.

$$\text{Equation 3. } SV_{ical} = k \times [(dZ/dt_{max}) / (Z_{max} - Z_{min})] \times W \text{ (TFITcal)}$$

According to equation, k: constant, DZ / dt<sub>max</sub>: contractility index, Z<sub>max</sub>-Z<sub>min</sub> = change in electrical conduction during cardiac contraction, W = algorithm that takes into account blood pressure (systolic-diastolic blood pressure), as recorded by a sphygmomanometer. Finally, the TFITcal index is the thoracic flow inversion time measured in the first mathematical derivative of the conductivity signal. This is the time period between the first zero value at the onset of the cardiac cycle (start of the QRS

pattern on the electrocardiogram) and at the first lower point immediately after the peak of the ejection speed ( $dZ / dt_{max}$ ) (Figure 3.5).



**Figure 3.5.** Waveforms from PhysioFlow, Enduro, PF-07. ΔZ: current resistance, Zmax: peak resistance value, dz/dt: the ratio of the change of the resistance signal over the time required to reach the signal its maximum value.

The advantages of using this non-invasive method are that there is no risk of injury to the patient, which can be the case with the cardiac catheterization method [223], its relatively low cost, it's simple to operate and it allows continuous recording of cardiac output at rest and during exercise [224].

Reliability of the PhysioFlow has been tested during rest and exercise on a cycle ergometer in healthy [225, 226], and patients with respiratory or cardiac diseases [222, 227-229]. Results revealed that PhysioFlow slightly over-estimated the values of cardiac output during both rest and exercise [222, 224, 227-229]. The accuracy in beat

by beat heart rate recordings can be affected by respiratory effort, subcutaneous fat and the poor positioning or contact of the electrodes [230]. In addition, exercise causes rapid and large changes to the aforementioned factors, making it more difficult to calculate cardiac output [231, 232]. However, new software has been developed to optimize signal quality by providing a better data collection process, as the modified equation used to calculate stroke volume does not require the estimation of blood resistance, and the exact position of the electrodes is not essential to validate cardiac output [227, 229].

Systolic and diastolic blood pressures were measured manually from the left arm using a sphygmomanometer and a stethoscope at rest, every three minutes during exercise and during the last minute of exercise. When undertaken properly, manual measurements of blood pressure is considered more accurate than automated blood pressure, which have limited accuracy (65%) during cycling exercise [233]. To improve reliability, measures were taken by the same researcher throughout the exercise test.

Peak heart rate was calculated using the following formula:

$$\text{HR}_{\text{peak}} = 220 - \text{age} \text{ [234]}$$

From measurements of oxygen uptake and cardiac output, whole body arteriovenous oxygen difference content was calculated using the Fick equation [20, 221]:

$$\text{VO}_2 = \text{Cardiac Output} \times (\text{CaO}_2 - \text{CvO}_2)$$

Arterial O<sub>2</sub> content (CaO<sub>2</sub>) was estimated as:

$$\text{CaO}_2 \text{ (ml/100 ml)} = 1.39 \times (\text{Hb}) \times \text{SpO}_2 \text{ [20]}$$

Where (Hb) is haemoglobin concentration [209] and SpO<sub>2</sub> is the oxygen saturation, measured by a pulse oximeter. Systemic oxygen delivery (DO<sub>2</sub>) was estimated by the following equation [20, 235]:

$$DO_2 = \text{Cardiac Output} \times \text{Arterial Oxygen Content (CaO}_{2\text{est}}), \text{ litres/min}$$

### 3.10.1. Kinetic analysis of central haemodynamic variables

The kinetic response of cardiac output, heart rate and stroke volume refers to 63% of the rate of change in their values in the transition from rest to exercise (on-transient) and in the transition from exercise to recovery (off-transient) until the values reach a stable state. In recent years, kinetic analysis has been extensively applied to investigate the physiological mechanisms involved in altering the energy requirement of the organism. To date, there is no accurate interpretation of the physiological mechanisms that affect the cardiac output kinetic response at 63% of its exponential growth until its stabilization phase during high intensity exercise [236].

For the analysis of the kinetic response of cardiac output, the final minute of the last exercise bout and the first 3 minutes of recovery were used (off-transient response) for each exercise trial. The analysis was performed using Sigmaplot 11 software. This software uses the mono-exponential equation below to calculate the time required for a given variable to reach a steady phase as follows:

$$\text{Off-transient} \rightarrow Y(t) = Y(SS) + A(1 - e^{-(t-T_d)/\tau}) \quad [237, 238]$$

**3.11. Assessment of metabolic variables, breathing pattern and dynamic hyperinflation (Chapters 4 and 5)**

Metabolic and respiratory variables were measured breath-by-breath using a portable metabolic cart (K4b<sup>2</sup>, Cosmed, Shepperton, UK). Patients breathed through a disposable mouthpiece whilst using a nose clip and the following data were recorded: minute ventilation ( $V_E$ ), tidal volume ( $V_T$ ), inspiratory and expiratory time ( $T_i$  and  $T_e$  respectively), breathing frequency (bf), oxygen uptake ( $VO_2$ ), and carbon dioxide output ( $VCO_2$ ). Before each test, the system was calibrated for volume using a 3 litres syringe (Cosmed) and gas calibration using a gas mixture containing 16%  $O_2$  and 5 %  $CO_2$  according to manufacturer instructions.

The measurement and evaluation of dynamic hyperinflation was performed by assessing the inspiratory capacity (IC). The patient was sat on the cycle ergometer breathing normally through a mouthpiece, which was connected to the metabolic cart. After a few normal breaths, patients were instructed after a normal expiration to perform a maximum inspiratory effort up to the point of total lung capacity (TLC) and then to breath normally again.

Inspiratory capacity manoeuvres were performed twice at rest and then the best manoeuvre was selected, ensuring that the difference between the two manoeuvres was less than 5% or 60ml [62]. Patients experiencing dynamic hyperinflation during exercise had to exhibit a reduction in inspiratory capacity (IC) from resting values  $\geq 4.5\%$  of the predicted normal value (reduction in the maximum inspiratory capacity compared to the resting value expressed as a percentage of the normal predicted value of IC at rest) or a difference from resting values of  $\geq 150$  ml [19].

A plateau in oxygen uptake was identified by no change or increase of less than 150 ml per minute in oxygen uptake ( $\text{VO}_2$ ) in relation to the corresponding increase in work load [239]. MVV was calculated using the formula below:

$$\text{FEV}_1 \times 37.5 \text{ [240]}$$

### **3.12. Recordings of oxygen saturation**

Oxygen saturation was recorded throughout all trials using a pulse oximeter, which was placed on the right hand to avoid interference during blood pressure measurements. A meta-analysis of 21 oximeter models found a correlation coefficient ranging from  $r = 0.986$  to  $r = 0.591$ , with the majority of models being accurate within 2% (1 SD) or 5% (2 SD) of in vitro oximetry, when  $\text{SpO}_2$  is within the range of 70-100%. Additionally, measurements taken from the finger were found to be more accurate than those taken from the ear [241].

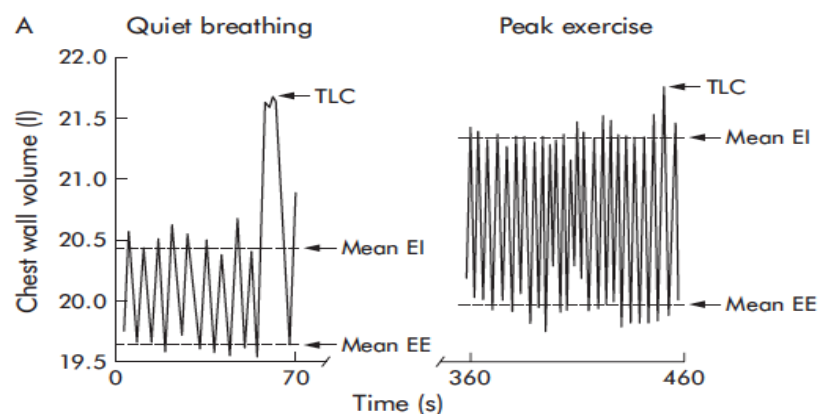
### **3.13. Recordings of perceived symptoms**

Perception of dyspnoea and leg discomfort was recorded at the end of each test using the modified Borg scale [213]. This is a 10 point scale, where each point reflects a specific level of discomfort starting from 0 = nothing at all to 10 = maximal [213].

### **3.14. Operational thoracoabdominal volume measurements (Chapter 6)**

During both trials, chest thoracoabdominal kinematics were measured by the OEP (BTS, Milano, Italy) as follows: the movement of 89 retro-reflective markers placed front and back over the chest wall from clavicles to pubis were recorded [242]. Each marker was tracked by eight video cameras (Smart System BTS, Milan, Italy), four on the front of the subject and four behind [242]. Subjects were instructed to grasp handles positioned at the mid sternum level, which lifted the arms away from the rib cage so that the lateral markers could be visualised [242]. At baseline, patients were instructed after

3–4 regular tidal breaths to make two maximal inspiratory capacity (IC) efforts from End-Expiratory Chest Wall (EEcw) Volume to Total Chest Wall Capacity (TLCcw), in order to assess chest wall volume at TLC (TLCcw) and calculate Inspiratory Reserve Chest Wall Volume (IRVcw) at rest (Figure 3.6). Dedicated software reconstructed the three-dimensional coordinates of the markers in real time by stereophotogrammetry and calculated total and compartmental chest wall volume and volume variations using Gauss's theorem [242-244]. The chest wall was modelled as being composed of three compartments—the pulmonary and abdominal rib cage ( $V_{rcp}$  and  $V_{rca}$ ), and the abdomen ( $V_{ab}$ ) [242]. Total thoracoabdominal volume ( $V_{cw}$ ) is the sum of the three compartmental volumes [242, 245].



**Figure 3.6.** Typical experimental tracings of absolute chest wall volumes in a patient with COPD during quiet breathing (left panel) and at peak exercise (right panel). A gradual shift in volumes during exercise occurs because of an increase in mean end-inspiratory (EI) and mean end-expiratory (EE) chest wall volumes indicated by the dashed line. Chest wall volumes at total lung capacity (TLC) are indicated by an arrow following an inspiratory capacity manoeuvre.

OEP has been used for the last two decades to non-invasively assess the total and compartmental chest wall volume kinematics ( $V_{cw}$ ,  $V_{rcp}$ ,  $V_{rca}$  and  $V_{ab}$ ), the total and compartmental breathing volumes (tidal volume, end-expiratory and end-inspiratory volumes) and aspects of the breathing circle (inspiratory and expiratory time, total duty cycle time, minute ventilation and breathing frequency), on a breath-by-breath basis

[245]. The validity, accuracy and reliability of the OEP have been assessed in different ways. OEP has a 30 $\mu$ m threshold for detecting linear movement, meaning that the software can detect changes in the position of reflecting markers, when the movement of the markers exceeds 30 $\mu$ m [245, 246]. This is translated to a minimum change of around 9 ml of thacoabdominal volume for a normal adult [245]. Marker size and the number of cameras can affect OEP accuracy. In fact, the number of cameras can vary from 4 to 8 and markers from 6- to 12-mm diameters, but the greatest accuracy has been shown when more cameras and spherical 6-mm markers are applied [245, 246]. On the other hand, the accuracy of OEP to estimate dynamic volumes is not influenced by the magnitude of the thorax's movement [245, 246]. The accuracy of the measurement of the volume recorded by OEP was investigated in the study by Massaroni and colleagues using a volume calibration device. They found that the volume measurement accuracy was always better than 6.0% of measured volume, with a volume repeatability of  $\pm 2.7$  ml [247].

The validity of OEP to measure respiratory volume variations was assessed in healthy individuals by Aliverti and colleagues [248], by comparing the changes in chest wall volumes assessed by OEP, with lung volume variations measured by spirometers and pneumotachometers, which are considered the gold standard methods [249]. The maximum difference between spirometer and OEP measurements was reported to be less than 4%. In addition, the discrepancy of lung volume variations between OEP, spirometer and pneumotachography was lower than 5% in both the supine and prone position, in healthy subjects during both quiet and deep breathing [248].

Finally, intra-rater and inter-rater reliability of OEP has been assessed by the study of Vieira and colleagues, both at rest and during submaximal exercise on a cycle



ergometer. The intra-class correlation coefficient was higher than 0.75 and the coefficient of variation was lower than 10% [250].

The working principles of OEP are the same as those of 3D motion capture [245]. In particular, the 8 cameras that capture the position of the 89 reflecting markers are connected with a computer. The input and output information is analysed by software that computes the marker 3D trajectories, integrating the information collected from each camera [245]. Then, a geometrical model is applied: a closed surface is defined starting from connecting each triplet of markers to form a triangle. From each closed surface, the volume contained in this surface is calculated [245].

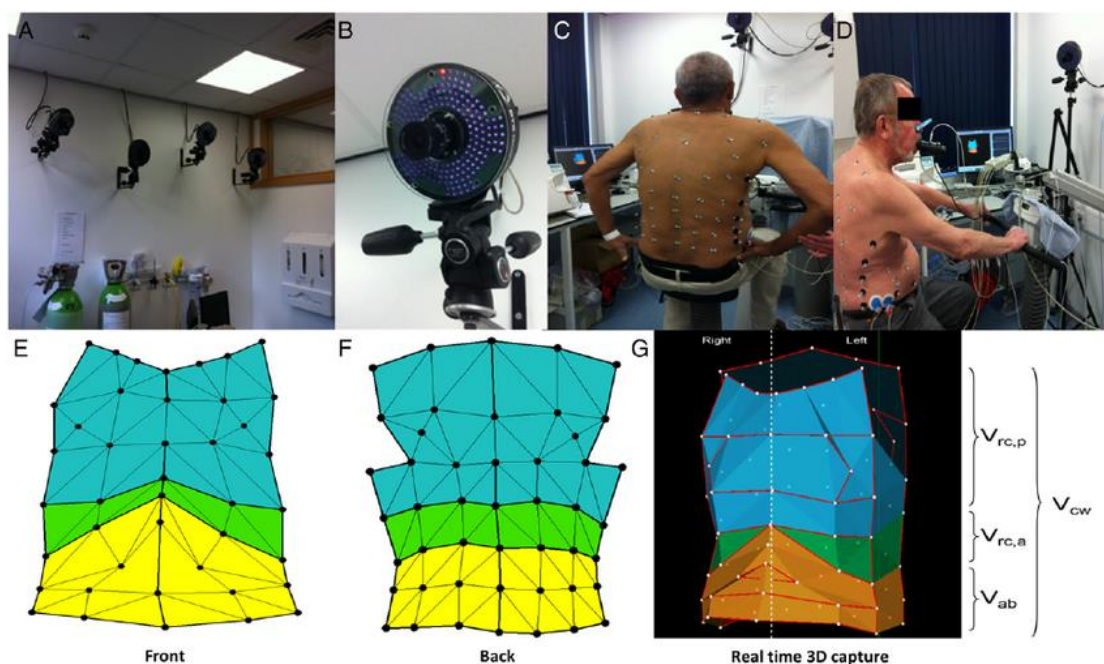
For each triangle – identified by 3 markers – the area (S) and the direction of normal vector (n) are calculated and the volume contained in this surface can be calculated using the Gauss theorem [243, 244] as in the following equation:

$$\int_S \vec{F} \cdot \vec{n} dS = \int_V dV = V, \quad [245],$$

where F is an arbitrary vector, S is a closed surface, V is the volume enclosed by S, and n is the normal unit vector on S [245].

The OEP thoracoabdominal wall (CW) model can be divided into 3 compartments, consisting of the pulmonary rib cage (RCp), the abdominal rib cage (RCa), and the abdomen (Ab) (Figure 3.7). The 3-compartment model allows the following phenomena to be considered: (a) that RCp and RCa are exposed at different pressures during inspiration, (b) the diaphragm acts directly only on RCa, and (c) non-diaphragmatic inspiratory muscles act largely on RCp and not on RCa [251]. Regarding the abdomen (Ab), Ab volume change is defined as the volume swept by the abdominal wall [251-

253], and it is the result of the conjunct action of the diaphragm and expiratory abdominal muscles [245].



**Figure 3.7.** OEP cameras (A & B), OEP markers placed on patient sitting on a cycle ergometer (C & D), graphical presentation of the 3D model and the three compartments (E, F & G).

### **3.15. Assessment of usability, applicability and comfort of using the VitaBreath device during activities of daily living**

Data were collected via telephone interview conducted by a research respiratory nurse at the Respiratory Medicine Department, North Tyneside General Hospital [20]. Support was provided to the patients either by the respiratory nurses or the investigator via phone if necessary.

### **3.16. Sample size justification (Chapters 4, 5 and 7)**

Verification of sample size within each exercise modality was based on the study by Bianchi and colleagues [44] comparing pressure support ventilation (PSV) to control breathing during exercise [20]. Using the mean difference in endurance time (3.4 min) between PSV and control breathing, and standard deviation (SD) (4.6 min), an alpha

significance level of 0.05 (2-sided) and 90% power, a minimum total sample size of 10 patients was calculated to be sufficient to detect significant differences in endurance time between pNIV and PLB trials within each exercise modality [20]. To compensate for possible dropouts (i.e., 20%), a total sample size of 24 patients was recruited [20]. Randomisation was performed following the CPET by independent staff within North Tyneside General Hospital and stratified by WRpeak (<50 or ≥50 watts) and FEV<sub>1</sub> (<50 or ≥50% predicted) using a block size of 4. The study team was blinded to the randomisation sequence [20].

### **3.17. Statistical analysis**

#### **3.17.1. Chapter 4**

This study was an observational study and therefore only descriptive statistical analysis has been performed within the results. The data collected is expressed as absolute values and presented as mean±SD or expressed as percentages of the total sample size (%) unless otherwise stated. The reference values of normal physiological responses during CPET for healthy, age matched subjects are presented in Table 3.1 [254, 255]. The methodology used to identify if maximal effort was reached by patients during the test and which exercise responses limited exercise tolerance are presented in Figure 3.8 [214].

Table 3.1 Normal physiological responses during CPET

Variable	Normative Value
VO <sub>2</sub>	>83-84% predicted
V <sub>E</sub> /MVV	<0.75-0.80
V <sub>E</sub> /VCO <sub>2</sub>	<34
V <sub>T</sub> /IC	<0.70-0.75
Bf	<50-60 breaths/min
HR	HRmax >90% age predicted
VO <sub>2</sub> /HR	>80%
SpO <sub>2</sub>	>93%

VO<sub>2</sub>, oxygen uptake; VE, minute ventilation; MVV, Maximum voluntary ventilation; VCO<sub>2</sub>, carbon dioxide expired; VT, tidal volume; IC, inspiratory capacity; bf, breathing frequency; HR, heart rate; SpO<sub>2</sub>, arterial oxygen saturation. [9, 255]

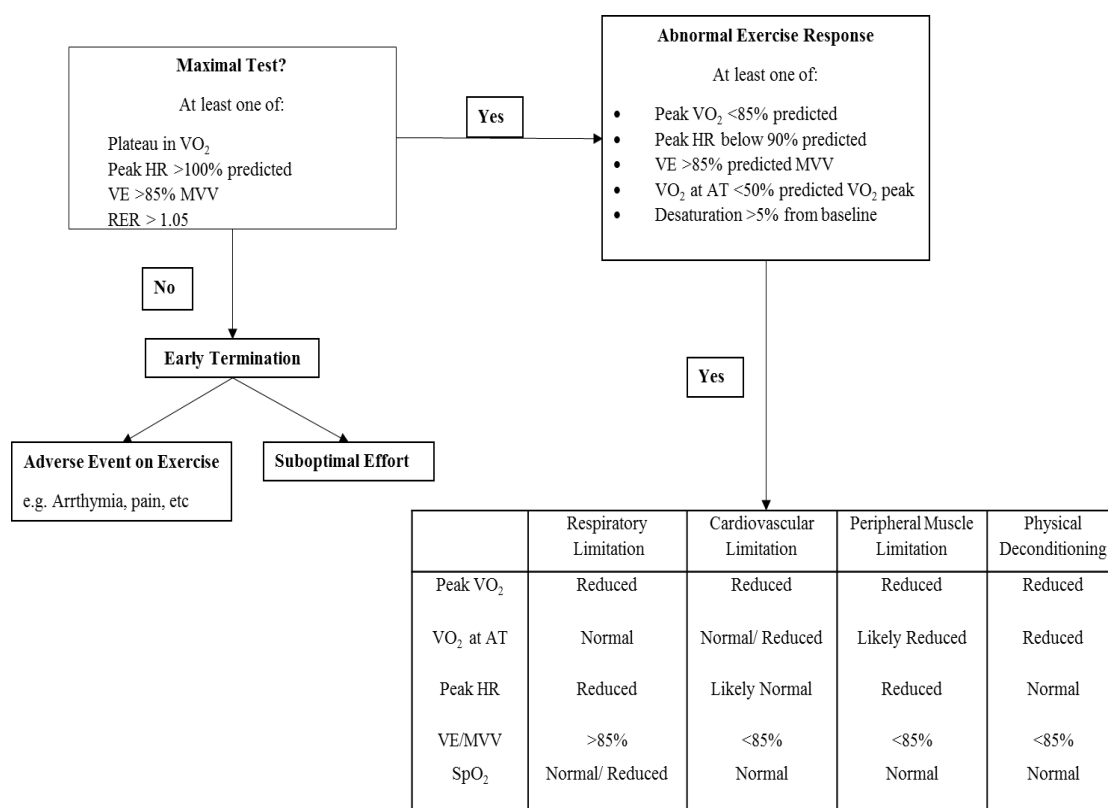


Figure 3.8. Methodology to determine whether patients achieved peak effort during exercise (top left diagram), whether patients exercise response was abnormal (top right diagram) and to detect locus of limitation (bottom diagram) [214].

### 3.17.2. Chapter 5

Data are presented as mean $\pm$ SD unless otherwise stated. Independent sample t-tests were employed to detect differences between the two groups in baseline characteristics and physiological responses during peak exercise. Independent sample t-tests were employed to detect differences in exercise tolerance (minutes) between moderate- and high-intensity exercise modalities and paired samples t-test between pNIV and PLB breathing modalities. Paired sample t-tests were employed to detect changes in mean response time of central haemodynamics between pNIV and PLB application. For each individual patient, the duration of exercise tolerance (including the recovery phases) when using the PLB technique was divided into four percentiles (i.e., 25%, 50%, 75% and 100%) of total endurance time in order to normalise endurance time across all patients [20]. A two-way ANOVA with repeated measurements followed by appropriate post hoc analysis was employed to compare changes at iso-time across these four percentiles between the PLB and pNIV trials for: IC, CO, DO<sub>2</sub>, breathlessness and leg discomfort. For IC, the change between recovery periods and the end of exercise bouts was calculated [20]. Analysis of data for the familiarisation phase included one-way ANOVA to detect differences in exercise load, symptoms of breathlessness and leg discomfort, heart rate and arterial oxygen saturation across the 8 sessions. Level of significance for all analyses was  $p < 0.05$ .

For the analysis between DH responders and DH non-responder (see below) data are presented as mean $\pm$ SEM rather than SD because the comparisons of interest were in the mean values of various physiological variables under the two different breathing modalities (pNIV and PLB). Additionally, as exercise time was different between the pNIV and PLB trials within the high- and moderate-intensity intermittent protocols, physiological measures were compared at the time point where the shortest trial (pNIV

or PLB) was terminated (i.e. at exercise iso-time) [24]. Dynamic hyperinflation (DH) response at exercise iso-time was calculated as the difference in inspiratory capacity (IC) between PLB and pNIV [(i.e.: IC pNIV - IC PLB (a positive value indicating improvement with pNIV)]. Patients who showed a clinically significant increase in IC ( $\geq 4.5\%$  of predicted resting IC [19]) when using pNIV compared to the PLB technique at exercise iso-time were identified as 'DH non-responders'. Patients showing a less than the clinically significant increase, [19] or a decrease in IC using pNIV compared to PLB were defined as 'DH non-responders'. Independent sample t-tests were carried out to compare variables between responders and non-responders for the baseline demographic and lung function characteristics. Two-way ANOVA with repeated measures followed by LSD pot-hoc analysis was employed to compare physiological changes at exercise iso-time between pNIV and PLB techniques in both responders and non-responders. The level of significance for all analyses was set at  $p < 0.05$ .

### 3.17.3. Chapter 6

Data are presented as mean $\pm$ SD unless otherwise reported. The Shapiro-Wilk test was used to check that data was normally distributed. Thoracoabdominal and circulatory responses across the 5 exercise bouts using the pNIV method or the PLB technique were averaged over the last minute of each exercise bout, and over each minute of recovery. Two way repeated measures ANOVA was employed to detect differences across different time-points [baseline, exercise, first minute of recovery (with pNIV or PLB) and second minute of recovery (quiet breathing)] between the two breathing conditions (i.e. with and without use of the VitaBreath device) followed by LSD post-hoc test for the following variables (compartmental thoracoabdominal volumes and central haemodynamic data). Paired t-tests were employed to compare breathing pattern

and ventilatory responses during the first minute of recovery between the pNIV and PLB methods. The level of significance for all analysis was set at  $p < 0.05$ .

#### 3.17.4. Chapter 7

Data are presented as median (IQR) or absolute number (%). The Wilcoxon signed-rank test was used for comparing 2- and 12-week interval scale (Likert style) data and McNemar's test for nominal response data. The level of significance for the analyses was set at  $p < 0.05$  [20].

## 4. Locus of exercise intolerance in the COPD population studied

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### 4.1. Introduction

Patients with COPD exhibit lower exercise capacity compared to age matched healthy individuals [17, 86]. Exercise intolerance in patients with COPD is multifactorial and includes ventilatory, gas exchange, central haemodynamic and locomotor muscle abnormalities [18]. These abnormalities impair adequate oxygen transport to the working muscles thereby limiting oxygen utilisation and exacerbating leg discomfort [18].

Patients with COPD often have reduced ventilatory capacity due to expiratory flow limitation that causes air trapping in the lungs, a phenomenon called hyperinflation [18, 55]. Hyperinflation is getting worse with increased ventilation (dynamic hyperinflation) and further increases end-expiratory lung volumes [55]. The increased end-expiratory lung volumes result in greater work of breathing, hence increasing metabolic requirements of the respiratory muscles [18].

In addition, dynamic hyperinflation increases intrathoracic pressure swings, which reduce venous return and thus cardiac output [57, 94, 98, 99]. This further impairs oxygen transport to the locomotor muscles [18]. Moreover, increased respiratory muscle work may potentially increase the competition for blood flow between the respiratory and locomotor muscles [18].

Non-invasive ventilation (NIV) is widely used as an effective way to treat patients with respiratory failure [168-171] both in the acute setting (during hospitalisation and ICU) [172] and at home (during daily living) [173]. The aim of NIV is to assist ventilation mainly by reducing the work of breathing, improving inspiratory flow rate,



controlling ventilation and resetting the central respiratory drive [175]. Thus, the main benefit of NIV is the improvement in expiratory flow limitation and dynamic hyperinflation collectively resulting in reduced work of breathing.

The overarching purpose of this dissertation was to study the effects of portable NIV (pNIV) on dynamic hyperinflation, breathlessness and exercise tolerance in patients with COPD. Accordingly, the scope of the present cross sectional study was to identify patients experiencing profound exercise-induced dynamic hyperinflation as the primary locus of exercise limitation in order to subsequently investigate the effect of pNIV on dynamic hyperinflation on this population.

#### **4.1.1. Main outcomes**

##### **4.1.1.1. Primary Outcome**

The primary outcome of the study was the manifestation of dynamic hyperinflation during incremental cardiopulmonary exercise testing (CPET).

##### **4.1.1.2. Secondary Outcomes**

Secondary outcomes included the following:

- Ventilatory factors (breathing frequency, tidal volume, minute ventilation, minute ventilation / maximal voluntary ventilation, dyspnoea, minute ventilation / oxygen uptake and minute ventilation / carbon dioxide output)
- Haemodynamic factors (heart rate, stroke volume, cardiac output, systemic oxygen delivery, systolic blood pressure, diastolic blood pressure and mean blood pressure)
- Metabolic factors (oxygen uptake, carbon dioxide production, oxygen uptake relative to work rate, leg discomfort)

## **4.2.Methods**

### **4.2.1. Study design**

This was a cross sectional study investigating respiratory, central haemodynamic and metabolic factors during a cardiopulmonary exercise test to the limit of tolerance (Figure 3.2). During this study patients underwent a ramp incremental CPET in order to determine the locus of exercise limitation, magnitude of dynamic hyperinflation and peak exercise capacity (WR<sub>peak</sub>). Patients were on optimal bronchodilator therapy including daily LAMA and LABA prior to their participation in the study. Tests were performed without supplemental oxygen.

## **4.3.Results**

### **4.3.1. Patient characteristics**

Demographic characteristics of patients who performed the ramp incremental CPET are presented in table 4.1. Patients exhibited severe airway obstruction (GOLD stage 3) [1] and lung hyperinflation at rest. Prior to participation in the study, all patients were confirmed as previous smokers, had no exacerbations within the last six weeks and no other uncontrolled comorbidities, in accordance with the study inclusion and exclusion criteria. Five (20.8%) of the patients were current smokers, with 14 (58.3%) having been admitted to hospital for an exacerbation of COPD (ECOPD) in the past 12 months. The median number of ECOPD (hospital or community managed) in the past 12 months was 2 (1–4.75). The median extended MRC dyspnoea score (eMRCD) was 3.6 (3–4) (Table 4.1) [20, 212, 256].

Table 4.1 Demographic characteristics of patients at baseline.

<b>Variable</b>	<b>n = 24</b>
Gender (M/F)	10/14
Age (years)	67±8
BMI	26.3±6.9
FEV <sub>1</sub> (litres)	1.14±0.59
FEV <sub>1</sub> (% predicted)	46±18
FVC (litres)	2.71±0.85
FVC (% predicted)	89±20
FEV <sub>1</sub> /FVC (%)	41±13
RV (litres)	4.53±1.56
RV (% predicted)	205±63
IC (litres)	2.00±0.67
IC (% predicted)	79±22
TLC (litres)	7.30±1.66
TLC (% predicted)	130±24
FRC (litres)	5.31±1.55
FRC (% predicted)	173±44
IC/TLC (%)	28±9
RV/TLC (%)	59±10
DLco (litres)	2.99±1.97
DLco (% predicted)	38±18
eMRC	3.6±0.5

BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in the first second; FVC, forced vital capacity; RV, residual volumes; IC, inspiratory capacity; TLC, total lung capacity; FRC, functional residual capacity; DLco, transfer factor of the lung for carbon monoxide; eMRC, median extended MRC dyspnoea score, M, male; F, female; values are mean ± standard deviation (SD) [20].

#### **4.3.2. Cardiopulmonary exercise test (CPET)**

Peak exercise capacity was severely impaired; patients exhibited profound exercise-induced dynamic hyperinflation and moderate arterial oxygen desaturation, at the limit of tolerance during the incremental CPET (Table 4.2) [20]. WR<sub>peak</sub> and VO<sub>2peak</sub> were substantially reduced compared to normal predicted levels, and minute ventilation exceeded 85% of MVV (Table 4.2).

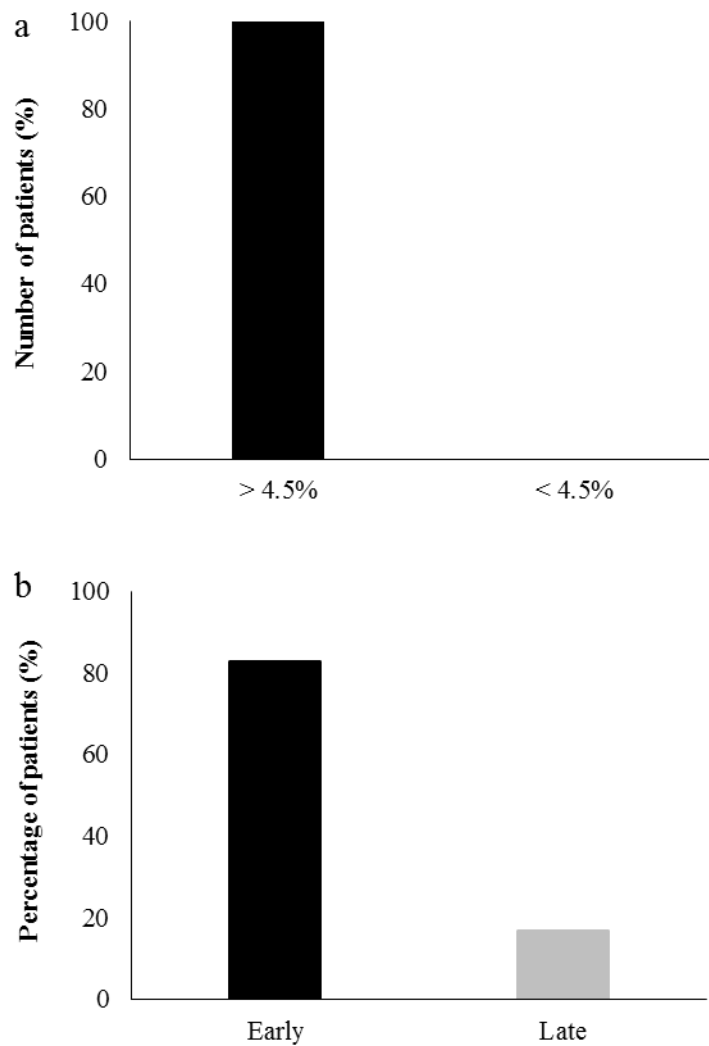
Table 4.2 Peak physiological variables at the limit of tolerance during cardiopulmonary exercise test (CPET).

Variable	All (n=24)
WR (Watts)	48±26
WR (% predicted)	46±23
CPET duration (minutes)	6.8±2.5
VO <sub>2</sub> (ml/kg/min)	13.5±3.7
VO <sub>2</sub> (% predicted)	60±17
VCO <sub>2</sub> (ml/min)	909±463
RER	0.91±0.08
bf (breaths/min)	30±6
V <sub>T</sub> (litres)	1.2±0.5
V <sub>E</sub> (l/min)	37.5±18.1
V <sub>E</sub> /VO <sub>2</sub>	38±5
V <sub>E</sub> /VCO <sub>2</sub>	42±7
V <sub>E</sub> /MVV (%)	99±24
ΔIC from rest (litres)	0.55±0.35
V <sub>T</sub> /IC (%)	60±10
SpO <sub>2</sub> (%)	92±4
CO (L/min)	10.7±2.9
HR (beats/min)	112±17
HR (% predicted)	73±11
SV (ml)	96±22
VO <sub>2</sub> /HR (ml/beat)	8.7±3.2
SBP (mmHg)	150±18
DBP (mmHg)	88±10
Dyspnoea (Borg 1–10)	4.0±1.1
Leg discomfort (Borg 1–10)	3.6±1.4

WR, work rate; VO<sub>2</sub>, oxygen uptake; VCO<sub>2</sub>, carbon dioxide expired; RER, respiratory exchange ratio; bf, breathing frequency; V<sub>T</sub>, tidal volume; V<sub>E</sub>, minute ventilation; MVV, Maximum voluntary ventilation; ΔIC, change from rest in inspiratory capacity; SpO<sub>2</sub>, arterial oxygen saturation; CO, cardiac output; HR, heart rate; SV, stroke volume; SBP, systolic blood pressure; DBP, diastolic blood pressure; Values are mean ± SD.

#### 4.3.2.1. Presence and pattern of dynamic hyperinflation

All 24 patients (100%) manifested exercise-induced dynamic hyperinflation as inspiratory capacity was reduced from baseline by more than 4.5% of predicted or by more than 150 ml at the limit of tolerance during the ramp incremental CPET [19] (Figure 4.1a). Furthermore, the results revealed that 83% of patients were hyperinflated in the early stages of exercise (early hyperinflators) whilst 17% of the patients were hyperinflated close to the end of the exercise (late hyperinflators) [85] (Figure 4.1b).



**Figure 4.1.** a) Percentage of patients hyperinflated during the ramp incremental CPET and b) percentage of patients that hyperinflated in early (black column) and late (grey column) stages of exercise.

#### 4.3.2.2. Ventilatory variables

At the limit of tolerance,  $V_E/MVV$  was  $99 \pm 24\%$  indicating that patients reached their ventilatory ceiling, whilst  $V_T/IC$  was  $60 \pm 10\%$  indicating mechanical restriction to tidal volume expansion. In addition, the average change in inspiratory capacity from baseline was  $0.55 \pm 0.35$  litres, whilst data also demonstrated mild to moderate arterial oxygen desaturation. Furthermore, at the limit of tolerance moderate to severe dyspnoea was reported by the patients ( $4.0 \pm 1.1$ ) (Table 4.2).

#### 4.3.2.3. Central haemodynamic variables

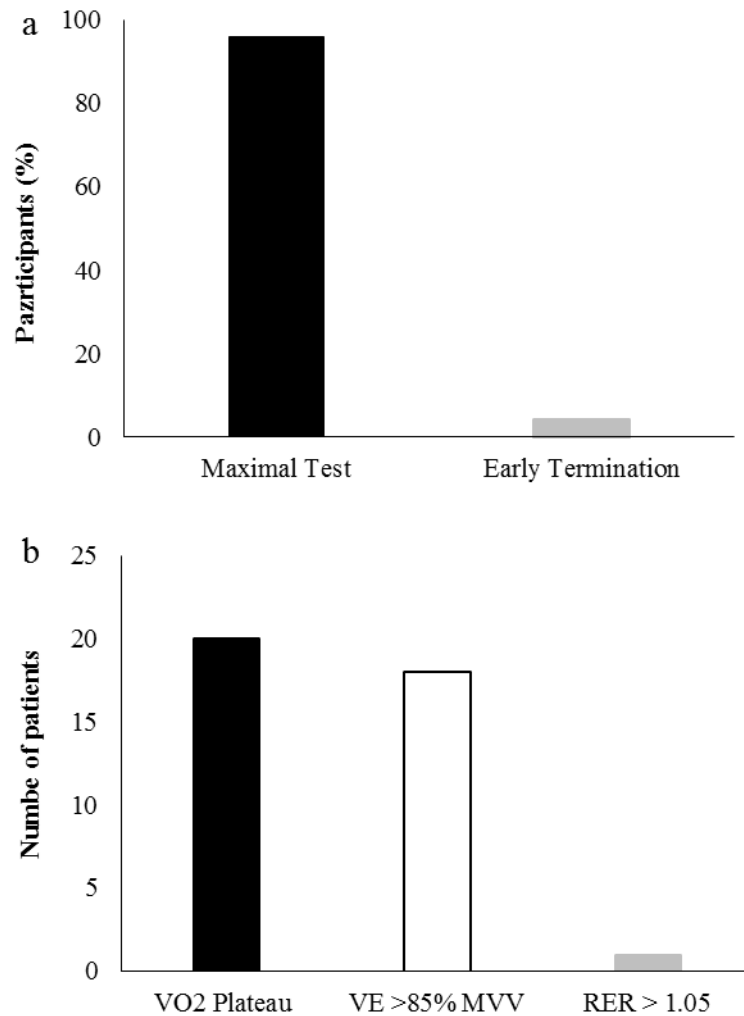
At the limit of tolerance cardiac output was  $10.7 \pm 2.9$  litres and heart rate reached 73% of peak predicted heart rate ( $112 \pm 17$  beats/min). Peak oxygen pulse was  $8.7 \pm 3.2$  ml/beat, whilst both systolic and diastolic blood pressures were increased at the limit of tolerance ( $150 \pm 18$  mmHg and  $88 \pm 10$  mmHg, respectively), responding appropriately during exercise (Table 4.2).

#### 4.3.2.4. Metabolic variables

Peak exercise capacity was severely impaired reaching  $46 \pm 23\%$  of predicted ( $48 \pm 26$  Watts). Peak oxygen uptake was also impaired reaching only  $60 \pm 17\%$  of predicted ( $13.5 \pm 3.7$  ml/min/kg); whilst  $\dot{V}CO_2$  was  $909 \pm 463$  ml/min. Accordingly, average respiratory exchange ratio (RER) was relatively low ( $0.91 \pm 0.08$ ). Finally, at the limit of tolerance patients felt moderate leg discomfort assessed by the Borg scale ( $3.6 \pm 1.4$ ) (Table 4.2).

#### 4.3.2.5. Determinants of peak exercise capacity

According the recent European Respiratory Society (ERS) statement on standardisation of CPET in chronic lung diseases [214], 23 patients (96%) reached their peak exercise capacity whilst only 1 patient (4%) stopped the test before reaching maximal effort (Figure 4.2a). Peak exercise capacity was established by a  $\dot{V}O_2$  plateau in 20 patients,  $\dot{V}_E/MVV$  greater than 85% in 18 patients and RER greater than 1.05 in 1 patient. None of the patients increased heart rate more than 90% predicted (Figure 4.2b).

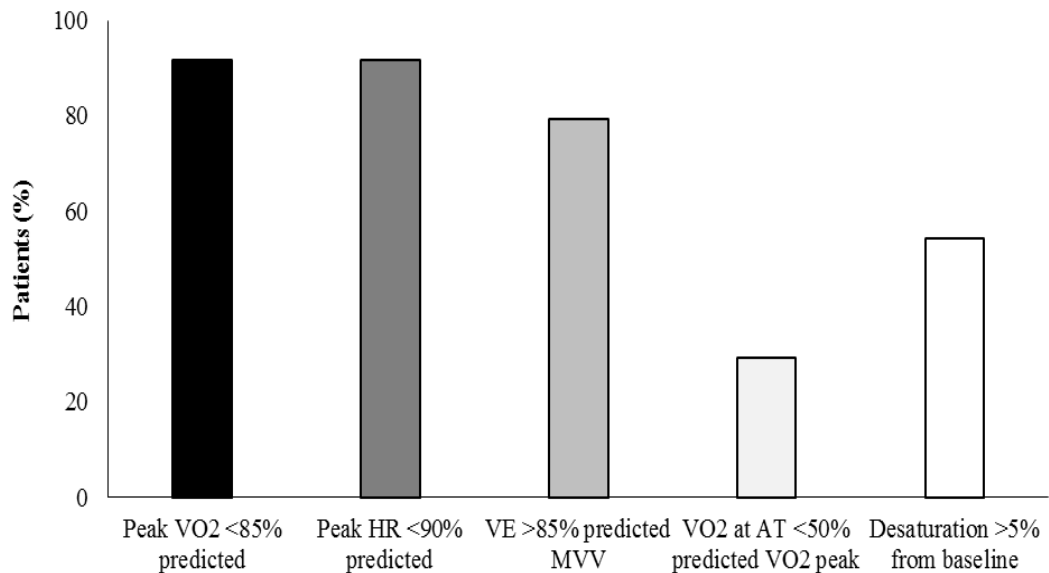


**Figure 4.2.** a) Presence of patients who reached peak (maximal) effort during exercise (black column) and patients who did not reach peak effort (grey column) and b) number of patients who met the criteria to determine maximal effort during the CPET. VO<sub>2</sub>, oxygen uptake; V<sub>E</sub>, minute ventilation; MVV, maximal voluntary ventilation; RER, respiratory exchange ratio.

#### 4.3.2.6. Evaluation of the abnormal exercise responses

As previously mentioned, 23 participants reached peak/maximal effort during exercise during the ramp incremental CPET. The exercise response was abnormal relative to normal predicted values according to the criteria shown in Figure 3.8 [214]. Particularly, in 21 patients (92%) peak oxygen uptake was less than 85% of predicted and peak heart rate was lower than 90% of predicted (Figure 4.3). Moreover, in 18 patients (79%) minute ventilation exceeded 85% of voluntary minute ventilation

indicating presence of ventilatory constraints, whilst 12 patients (54%) were severely desaturated (more than 5%) from baseline (Figure 4.3). Finally, in 7 patients (29%) oxygen uptake was less than 50% of predicted at the anaerobic threshold (Figure 4.3).



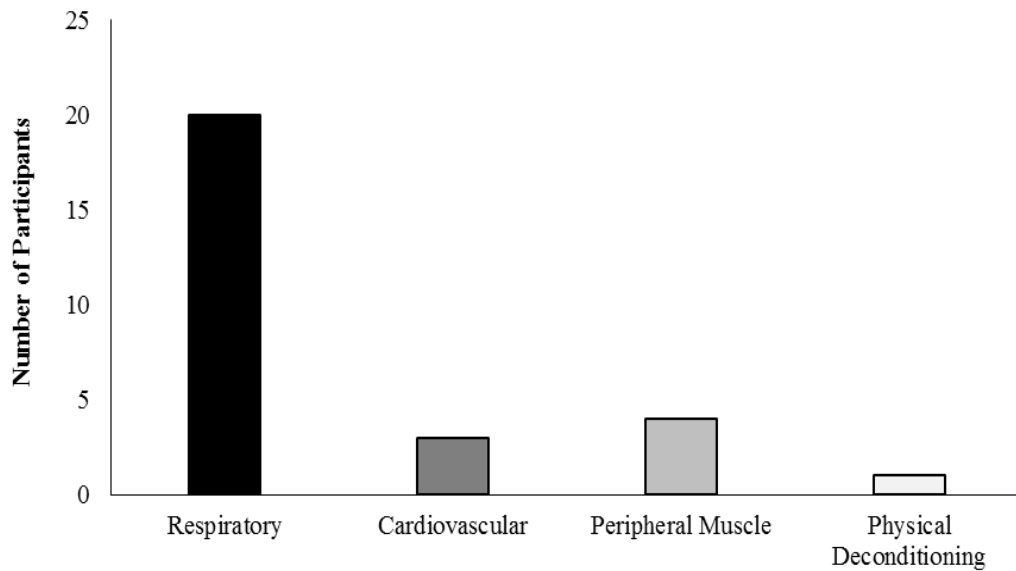
**Figure 4.3.** Presence of abnormal responses during ramp incremental CPET. VO<sub>2</sub>, oxygen uptake; HR, heart rate; V<sub>E</sub>, minute ventilation; MVV, maximal voluntary ventilation; AT, anaerobic threshold.

#### 4.3.2.7. Locus of exercise limitation

The limitation of exercise in patients with COPD can be the result of abnormal response of the respiratory, cardiovascular or peripheral cellular muscle metabolic function or a combination of abnormalities in all physiological systems [18]. The data revealed that 19 patients (83%) were limited by only one, 3 patients (13%) were limited by two, whilst 1 patient (4%) was limited by three of the aforementioned physiological system abnormalities. In twenty of the patients who achieve peak effort during the ramp incremental CPET (87%), exercise was limited due to respiratory function abnormalities (Figure 4.4). Three patients (13%) had cardiovascular limitations, four patients (17%) had peripheral muscle dysfunction and only one patient (4%) had physical



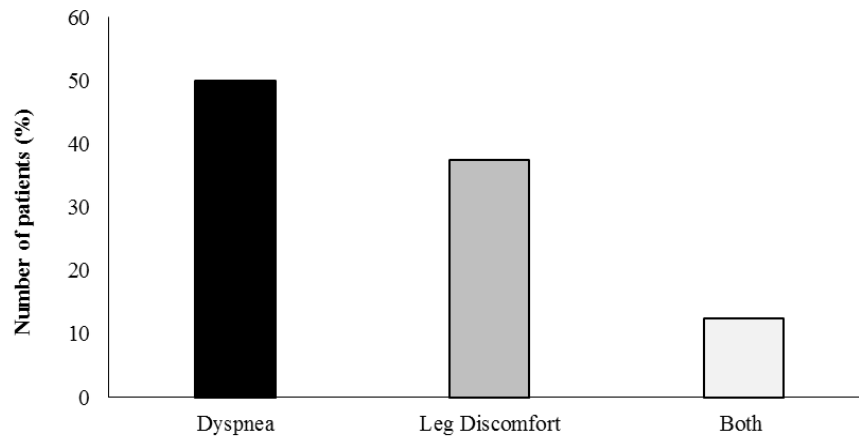
deconditioning (Figure 4.4). The primary locus of limitation was determined based on how many of the criteria within the different physiological systems were met (Figure 3.8) [214].



**Figure 4.4.** Primary locus of exercise limitation.

#### 4.3.2.8. *Perceived symptoms at the limit of tolerance*

The main symptom limiting exercise tolerance in the present study was breathlessness as 50% of the patients (n=12) reported this as the main reason for stopping the exercise. In contrast, 37% of the patients (n=9) reported that the main symptom that limited their exercise tolerance was leg discomfort, whilst 13% (n=3) of the patients reported that both symptoms were equally severe at the end of exercise, thus causing them to terminate exercise (Figure 4.5).



**Figure 4.5.** Reported reason for exercise termination

#### **4.4. Discussion**

The main finding of the current study was that all 24 participants were dynamically hyperinflated (Figure 4.2a) and the majority of participants were hyperinflated during the early stages of the ramp incremental CPET (Figure 4.2b). As a result the primary locus of exercise limitation was of respiratory origin (Figure 4.4) and the major limiting symptom was breathlessness (Figure 4.5). None of the participants reached the predicted maximal levels of exercise during the ramp incremental cardiopulmonary exercise test (Figure 4.1a).

Dynamic hyperinflation is a key factor that limits exercise tolerance in patients with COPD [19] due to its effects on respiratory function [18, 19], oxygen transportation [18] and respiratory mechanics [98]. Previous studies have estimated that the phenomenon of dynamic hyperinflation during exercise manifests in approximately 80-85% of patients with moderate to severe COPD [19, 257]. However, a study by Vogiatzis and colleagues suggested that dynamic hyperinflation occurs in all patients with moderate to severe or severe COPD but at different levels of exercise [85]. In fact, it was found that 60% of patients with severe COPD were hyperinflated during the early stages of a

CPET [85]. In the present study all patients were hyperinflated at the limit of tolerance; 20 patients (83%) were hyperinflated in the early stages of exercise (early hyperinflators), whilst 4 patients (17%) were hyperinflated only at the very late stages of exercise (late hyperinflators), confirming the results from the study by Vogiatzis and colleagues [85].

Despite the presence of dynamic hyperinflation in all patients, 23 out of 24 patients were able to achieve true peak levels of effort during the ramp incremental CPET. When CPET is performed correctly it is considered the gold standard to identify the factors limiting exercise tolerance [258]. In the present study, CPET was performed in accordance to the European Respiratory Society statement on standardisation of CPET in chronic lung diseases [214] and the outcomes were assessed based on the same guidelines [214]. Ideally, a ramp incremental CPET should last between 8 and 12 minutes in order to be able to record valid diagnostic information [259]; however this is not always applicable in patients with COPD due to the pathophysiology of the disease. In the present study the average duration of the CPET was 6.8 minutes, which is in accordance with other studies in patients of similar severity of COPD [85, 260]. Although patients were able to reach maximal effort during exercise this was only 46% of the predicted normal peak work rate for this population. During the test one patient did not meet any of the criteria to characterise the effort as maximal. However, at the end of the CPET this patient reported severe leg discomfort and moderate breathlessness (5 and 3 in Borg scale, respectively), suggesting that early termination of the test was mainly due to physical deconditioning.

Lower aerobic capacity in patients with COPD compared to age matched healthy sedentary individuals is well established [18, 255]. In the present study the average peak oxygen uptake ( $\text{VO}_2\text{peak}$ ) was 60% predicted and in the majority of patients (n=22).

These results are in accordance with the literature in patients with COPD, where the average peak oxygen uptake ranges between 50% and 62% predicted [19, 85]. Low oxygen uptake is the result of dysfunction in the systems involved in oxygen transport to the working muscles [18], which eventually limits exercise capacity. In addition,  $\text{VO}_2$  at anaerobic threshold is another variable that is used to determine normal physiological responses during the CPET [214]. When  $\text{VO}_2$  at anaerobic threshold is less than 50% of predicted  $\text{VO}_{2\text{peak}}$  it is deemed to be an abnormal response [214, 255], considering that normal values for healthy, age matched subjects usually exceed 83% predicted [255]. In the present study 7 out of 24 participants had a  $\text{VO}_2$  of less than 50% of predicted  $\text{VO}_2$ . The causes of reduced  $\text{VO}_2$  both at the anaerobic threshold and at the limit of tolerance include i) low arterial oxygen content due to gas exchange abnormalities [18] ii) reduced cardiac output and oxygen transport due to reduced venous return secondary to dynamic hyperinflation and increased intrathoracic pressures swings [18, 258] and iii) low oxidative capacity of the locomotor muscles [18].

In the present study reduced cardiac output was also associated with increased heart rate reserve as peak heart rate reached only 73% predicted. This was mainly the result of the low peak exercise capacity of the patients, as exercise testing was terminated, primarily due to ventilatory restrictions well before the cardiovascular system was highly taxed [18]. In fact, in the current study ventilatory reserve as reflected by the ratio of  $V_E/\text{MVV}$  was 99%. In healthy people  $V_E/\text{MVV}$  does not exceed 80% [255] at peak exercise. Values exceeding 85% are considered abnormal [214, 258] and are associated with the presence of dynamic hyperinflation [19, 85, 261] and increased breathlessness during exercise [70, 262] and thus, it is a common factor that limits exercise tolerance in patients with COPD [18].

The present study succeeded in identifying patients with ventilatory constraints as the main locus of exercise limitation. The most common factor limiting exercise appeared to be the respiratory system, which as a primary limiting factor was evident in 87% of the patients. This was expected as respiratory limitation is a defining characteristic during exercise in patients with COPD, as the pathophysiology of the disease is strongly associated with expiratory flow limitation during high levels of ventilation leading to dynamic hyperinflation [18, 19, 29, 85, 257]. Furthermore, small number of patients also manifested additional limitations of the cardiovascular system and to a lesser degree of muscle cellular dysfunction [18, 263, 264].

Symptom sensation is another factor that contributes to exercise limitation. In the present study half of the patients reported breathlessness, whilst 9 patients reported leg discomfort as the primary reason for stopping exercise. Finally, 3 patients reported that breathlessness and leg discomfort were equally intolerable at the limit of tolerance. These findings provide further evidence of the interaction between the different impaired physiological systems, as explained earlier in this section. The data of the present study are in line with other studies that used the same ramp incremental CPET protocol in patients with COPD [85].

#### *Study limitations*

The present study has some limitations. Firstly, dynamic hyperinflation was assessed using inspiratory capacity (IC) manoeuvres. IC manoeuvres are deemed to be a reliable method to assess dynamic hyperinflation [19, 85], however they are dependent on the ability of the patient to perform the manoeuvre properly during exercise. Patients were familiarised with the manoeuvre, but it is possible that this may have influenced the recording data in some cases. Another limitation of the study was that patients might

have overestimated or underestimated their symptoms of breathlessness and leg discomfort at the limit of tolerance. To minimise this, all patients were familiarised with the Borg scale prior to the test and some patients used this scale during past rehabilitation programmes. Moreover, the seat of the bike was uncomfortable for most of the patients, however this did not prevent patients from completing the test successfully.

#### **4.5. Conclusions**

The present study identified dynamic hyperinflation as the main factor limiting exercise tolerance in patients with moderate to severe and severe COPD. The purpose of the study was to confirm the presence of dynamic hyperinflation and abnormal ventilatory response in this population, and thus to confirm patient eligibility to participate in subsequent studies investigating the effect of pNIV application on exercise tolerance. Accordingly, Chapter 5 reports on the effect of pNIV application on exercise tolerance in patients with COPD.

## **5. Acute effects of the use of the VitaBreath device during exercise in patients with Chronic Obstructive Pulmonary Disease (COPD)**

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### **5.1. Introduction**

Exercise training is the cornerstone of Pulmonary Rehabilitation (PR), inducing clinically meaningful improvements in exercise tolerance in patients with chronic obstructive pulmonary disease (COPD) [20, 265]. Dynamic hyperinflation (DH) during exercise limits the normal increase in tidal volume, worsening breathlessness and reducing exercise capacity [19, 20]. Additionally, DH and the concomitant high mean intrathoracic pressure swings are associated with adverse effects on central hemodynamic regulation, reducing the supply of oxygenated blood to deconditioned peripheral muscles [18, 20, 21]. This contributes to leg discomfort and further limits exercise tolerance. Different ergogenic strategies have been successfully employed to reduce exercise-induced breathlessness and leg discomfort, including oxygen and heliox supplementation, non-invasive ventilation (NIV) and various intermittent exercise modalities [20, 22-25]. Oxygen supplementation is commonly used during exercise in order to reduce desaturation and breathlessness [20, 26]. Heliox supplementation is beneficial but impractical and expensive, therefore it is primarily used for research purposes [28]. Standard NIV is infrequently used due to the difficulties associated with applying bulky equipment and the need for close supervision during exercise training [20, 49].

The VitaBreath (Philips, Respironics, Morrisville, PA, USA) is a portable, handheld, battery-powered, non-invasive ventilation device (pNIV) intended to reduce activity-related shortness of breath [20, 215]. It delivers 18 cm H<sub>2</sub>O inspiratory and 8 cm H<sub>2</sub>O expiratory pressures, but can only be used during recovery periods interspersing bouts

of physical activity. The purpose of this study was to test the effect of pNIV compared to pursed lip breathing (PLB) on dynamic hyperinflation, breathlessness and exercise tolerance in patients with COPD [20]. A secondary aim of the present study was to compare the baseline characteristics, the respiratory and circulatory responses during exercise and qualitative outcomes between dynamic hyperinflation DH responders and DH non-responders. Response was defined in terms of DH as it is an objective physiological index that determines the clinical response. Exercise tolerance comprised two different intermittent protocol modalities, namely moderate-intensity (6 min at 60% peak work rate (WR<sub>peak</sub>)) and high-intensity (2 min at 80% WR<sub>peak</sub>) exercise [20]. As both modalities are recommended by the British Thoracic Society and joint American Thoracic Society/European Respiratory Society guidelines for PR [165, 266], the purpose was to explore whether pNIV support was equally as effective during exercise comprising different intensity and duration characteristics [20].

It was hypothesised that the use of pNIV compared to PLB would increase exercise tolerance by reducing dynamic hyperinflation and the intensity of breathlessness during bouts of moderate- or high-intensity intermittent exercise and would confer greater benefit if used more frequently with the high-intensity protocol [20].

### **5.1.1. Main outcomes**

#### **5.1.1.1. Primary Outcome**

The primary outcome of the study was exercise tolerance during moderate and high intensity exercise [20].



### 5.1.1.2. Secondary Outcomes

Secondary outcomes include the following [20]:

- Dynamic hyperinflation
- Symptoms of breathlessness and leg discomfort
- Central haemodynamic responses (cardiac output, stroke volume and heart rate, systemic oxygen delivery, systolic blood pressure, diastolic blood pressure and mean blood pressure)
- Respiratory and gas exchange responses (oxygen uptake, carbon dioxide production, minute ventilation, tidal volume, breathing frequency and inspiratory capacity)

## 5.2. Methods

### 5.2.1. Study design

This was a randomised, open-label cross-over trial comparing the use of pNIV to PLB during recovery periods in two different intermittent exercise regimes (Figure 3.3 a & b) [20]. Prior to exercise testing all patients underwent a 4-week familiarisation programme to be accustomed with the exercise protocols, the use of the VitaBreath device and the correct adoption of PLB with guidance from a physiotherapist [20]. Following the familiarisation phase, patients were randomly assigned to a high-intensity (HI) or a moderate-intensity (MOD) protocol [20]. Within these groups, each patient performed two visits using both pNIV and PLB during recovery from exercise in a balanced order (Figure 3.3 a & b) [20]. Patients were on optimal bronchodilator therapy including daily LAMA and LABA and no changes to medication were made during the trial. Tests were performed without supplemental oxygen [20].

### **5.3.Results**

#### **5.3.1. Patient characteristics and peak exercise data between high-intensity and moderate-intensity**

Patients randomised to the two different exercise modalities were matched in terms of demographic and clinical characteristics, exhibiting severe airflow limitation and lung hyperinflation at rest without resting hypoxemia (Table 5.1.) [20]. In addition, patients in the two different exercise modalities were matched in terms of their peak exercise capacity and the responses during the ramp incremental CPET (Table 5.2.) (findings from the ramp incremental CPET are presented in details in Chapter 4). Prior to randomisation, all participants were confirmed as previous smokers, had no exacerbations within the last six weeks and no other uncontrolled comorbidities, in accordance with the study inclusion and exclusion criteria [20]. Five (20.8%) of the patients were current smokers, with 14 (58.3%) having been admitted to hospital for an exacerbation of COPD (ECOPD) in the past 12 months. The median number of ECOPD (hospital or community managed) in the past 12 months was 2 (1–4.75) [20]. The median extended MRC dyspnoea score (eMRCD) was 4 (3–4) [212, 256].

Table 5.1 Demographic characteristics of patients at baseline.

<b>Variable</b>	<b>High-Intensity (n = 13)</b>	<b>Moderate- intensity (n = 11)</b>	<b>p-Value</b>
Gender (M/F)	5/8	5/6	
Age (years)	66±7	68±10	0.510
BMI	26.9±6.9	25.6±6.8	0.659
FEV <sub>1</sub> (% predicted)	46±15	46±21	0.948
FVC (% predicted)	87±18	91±21	0.605
FEV <sub>1</sub> /FVC (%)	43±14	37±12	0.487
IC (litres)	1.96±0.56	2.03±0.78	0.810
IC (% predicted)	79±22	78±23	0.807
TLC (% predicted)	130±29	131±15	0.975
FRC (% predicted)	172±49	175±37	0.845
DLco (% predicted)	38±18	38±20	0.980

M, male; F, female; BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in the first second; FVC, forced vital capacity; IC, inspiratory capacity; TLC, total lung capacity; FRC, functional residual capacity; DLco, transfer factor of the lung for carbon monoxide; WR, work rate, values presented as mean ± standard deviation (SD) [20].

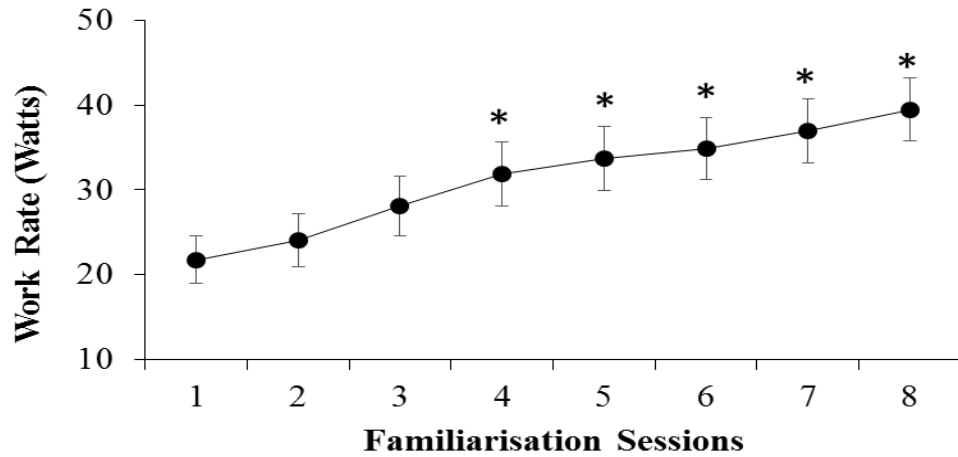
Table 5.2. Peak physiological variables at the limit of tolerance during cardiopulmonary exercise testing (CPET).

Variable	High-Intensity (n = 13)	Moderate-Intensity (n = 11)	p-Value
WR (Watts)	48±25	48±26	0.977
WR (% predicted)	46±19	45±26	0.883
VO <sub>2</sub> (ml/kg/min)	13.5±3.9	13.4±3.2	0.808
VO <sub>2</sub> (% predicted)	60±12	61±21	0.911
VCO <sub>2</sub> (ml/min)	907±471	912±476	0.981
RQ	0.89±0.06	0.93±0.09	0.287
bf (breaths/min)	31±5	29±6	0.551
V <sub>T</sub> (litres)	1.2±0.5	1.2±0.5	0.917
V <sub>E</sub> (l/min)	39.1±20.2	35.5±16.0	0.633
V <sub>E</sub> /VO <sub>2</sub> (%)	39±5	37±6	0.620
V <sub>E</sub> /VCO <sub>2</sub> (%)	43±9	41±8	0.407
V <sub>E</sub> /MVV (%)	1.00±0.21	0.99±0.26	0.787
ΔIC from rest (litres)	0.60±0.38	0.47±0.33	0.399
V <sub>T</sub> /IC (%)	61±10	58±10	0.407
SpO <sub>2</sub> (%)	92±5	92±3	0.827
CO (L/min)	10.5±3.9	11.2±2.7	0.635
HR (beats/min)	113±15	110±18	0.728
HR (% predicted)	74±10	72±12	0.651
SV (ml)	94±30	101±19	0.513
VO <sub>2</sub> /HR (ml/beat)	8.8±3.6	8.6±2.9	0.905
SBP (mmHg)	149±15	151±22	0.817
DBP (mmHg)	89±6	87±13	0.466
Dyspnoea (Borg 1-10)	4.2±1.2	3.8±0.7	0.269
Leg discomfort (Borg 1-10)	3.8±1.1	3.3±1.6	0.442

WR, work rate; VO<sub>2</sub>, oxygen uptake; VCO<sub>2</sub>, carbon dioxide expired; RQ, respiratory quotient for oxygen uptake; bf, breathing frequency; V<sub>T</sub>, tidal volume; V<sub>E</sub>, minute ventilation; MVV, Maximum voluntary ventilation; ΔIC, change from rest in inspiratory capacity; SpO<sub>2</sub>, arterial oxygen saturation; CO, cardiac output; HR, heart rate; SV, stroke volume; SBP, systolic blood pressure; DBP, diastolic blood pressure; Values are mean ± SD.

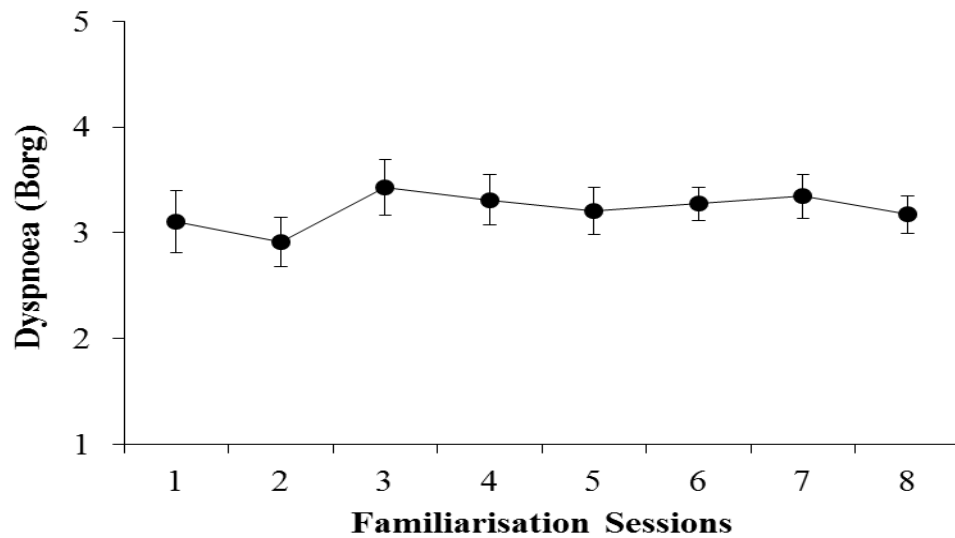
### **5.3.2. Effect of familiarisation program on exercise capacity, symptoms, heart rate and oxygen saturation**

Exercise capacity was significantly increased at the end of the familiarisation period by 86% (38.3±19.4 Watts) compared to the first session (20.6±15.0 Watts) (p=0.002) (Figure 5.1).

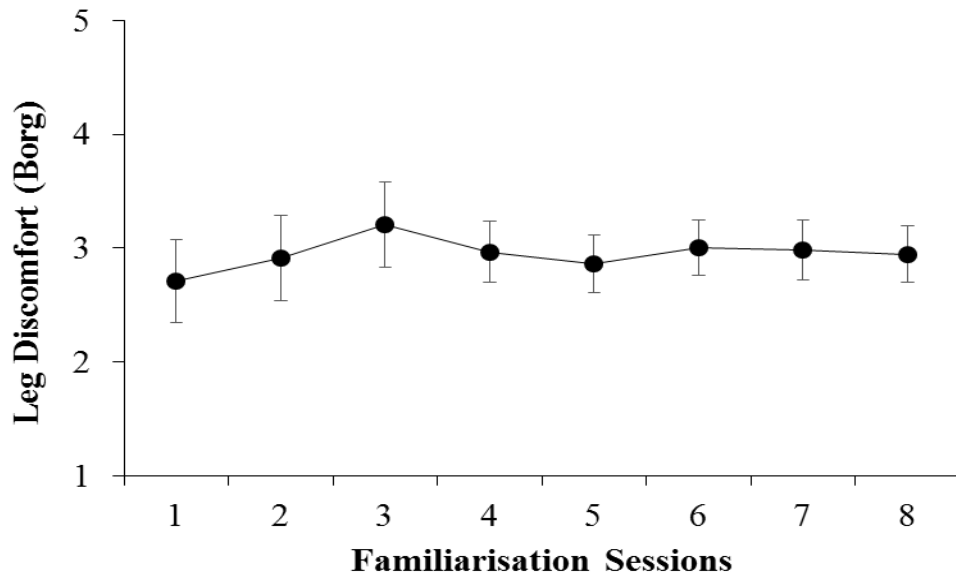


**Figure 5.1.** Progression of work rate during each familiarisation session. \*= $p < 0.05$  compared to 1<sup>st</sup> session. Data are presented as mean  $\pm$  standard error of the mean (SEM).

Despite the increase in work load, symptoms of both dyspnoea ( $p=0.835$ ) (Figure 5.2) and leg discomfort ( $p=0.982$ ) (Figure 5.3) remained unchanged during the eight familiarisation sessions indicating true physiological training effects.

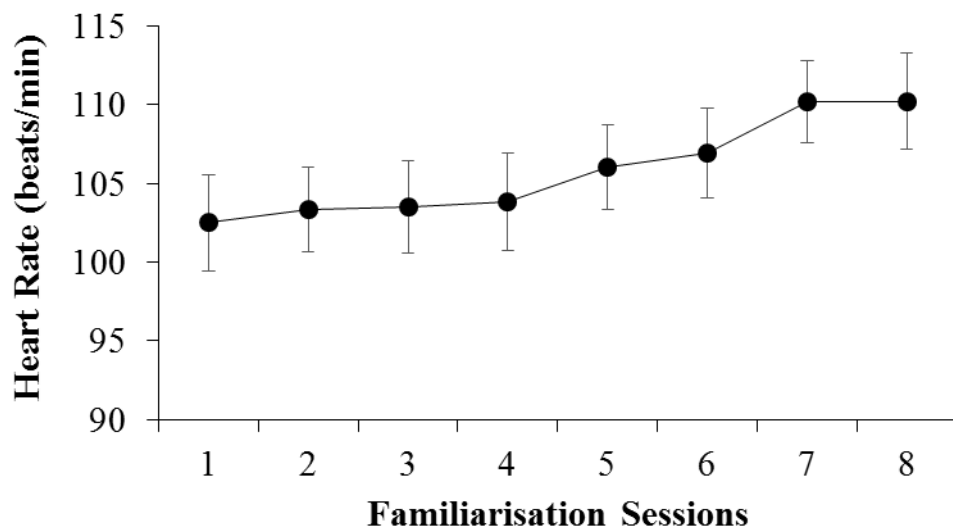


**Figure 5.2.** Progression of dyspnoea during each familiarisation session. Data are presented as mean  $\pm$  standard error of the mean (SEM).

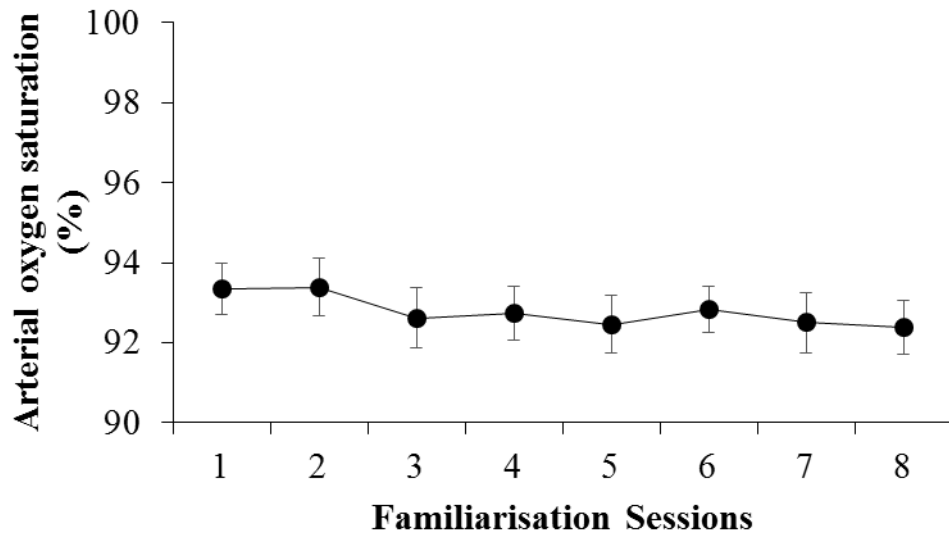


**Figure 5.3.** Progression of leg discomfort during each familiarisation session. Data are presented as mean  $\pm$  standard error of the mean (SEM).

Furthermore, during the exercise familiarisation sessions heart rate was not increased ( $p=0.423$ ) (Figure 5.4), whilst arterial oxygen saturation was unaffected ( $p=0.973$ ) (Figure 5.5) during the eight familiarisation sessions.



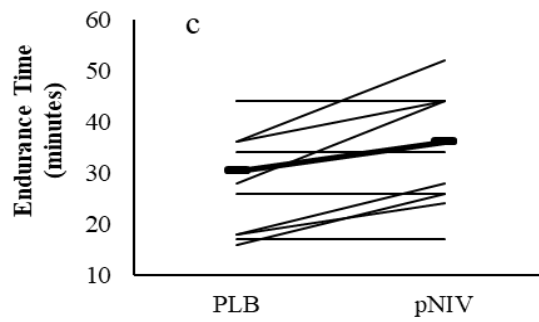
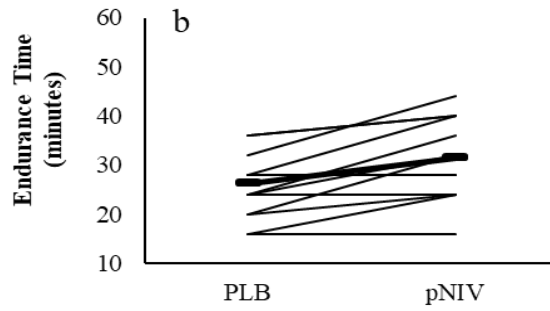
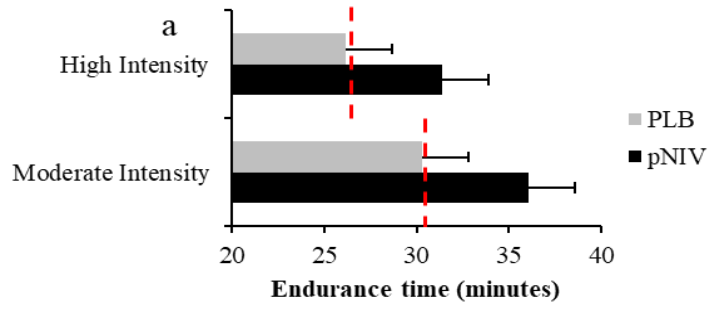
**Figure 5.4.** Progression of heart rate during each familiarisation session. Data are presented as mean  $\pm$  standard error of the mean (SEM).



**Figure 5.5.** Progression of arterial oxygen saturation during each familiarisation session. Data are presented as mean  $\pm$  standard error of the mean (SEM).

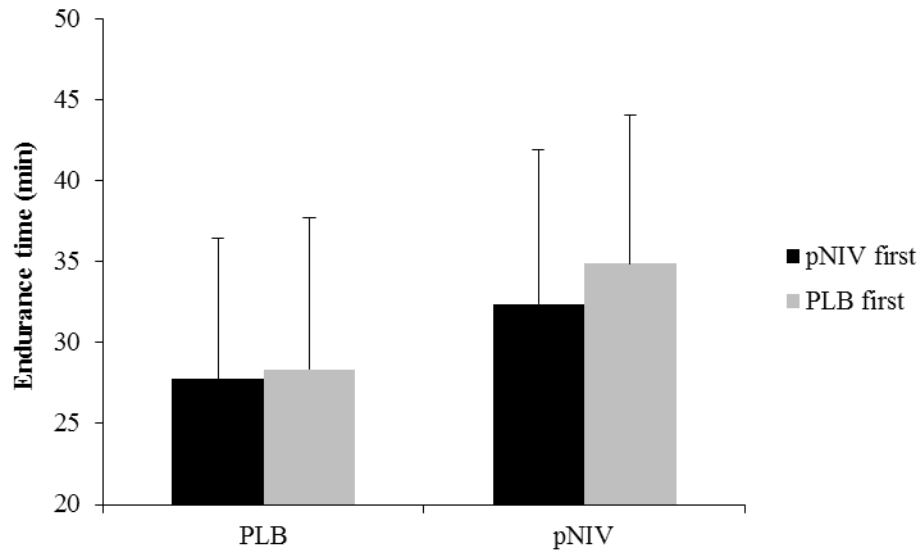
**5.3.3. Effect of pNIV on endurance time during high- and moderate-intensity exercise**

Compared to PLB, pNIV increased exercise endurance time for both intermittent exercise modalities (HI-pNIV: from  $26.2 \pm 6.9$  to  $31.4 \pm 8.3$  min ( $p = 0.008$ ); MOD-pNIV: from  $30.3 \pm 11.3$  to  $36.1 \pm 11.0$  min ( $p = 0.016$ )) without differences in the magnitude of improvement between the two exercise modalities ( $p = 0.244$ ) (Figure 5.6) [20]. The order of testing (pNIV or PLB first) did not affect exercise endurance time ( $p=0.820$ ) (Figure 5.7).



**Figure 5.6.** a) Exercise endurance time using pNIV (black bars) and PLB (grey bars) during high- and moderate-intensity exercise protocols. Dotted lines denote exercise iso-time. Effect of pNIV on individual patient exercise endurance time during b) high-intensity and c) moderate-intensity exercise protocols. Thick lines denote mean values [20].



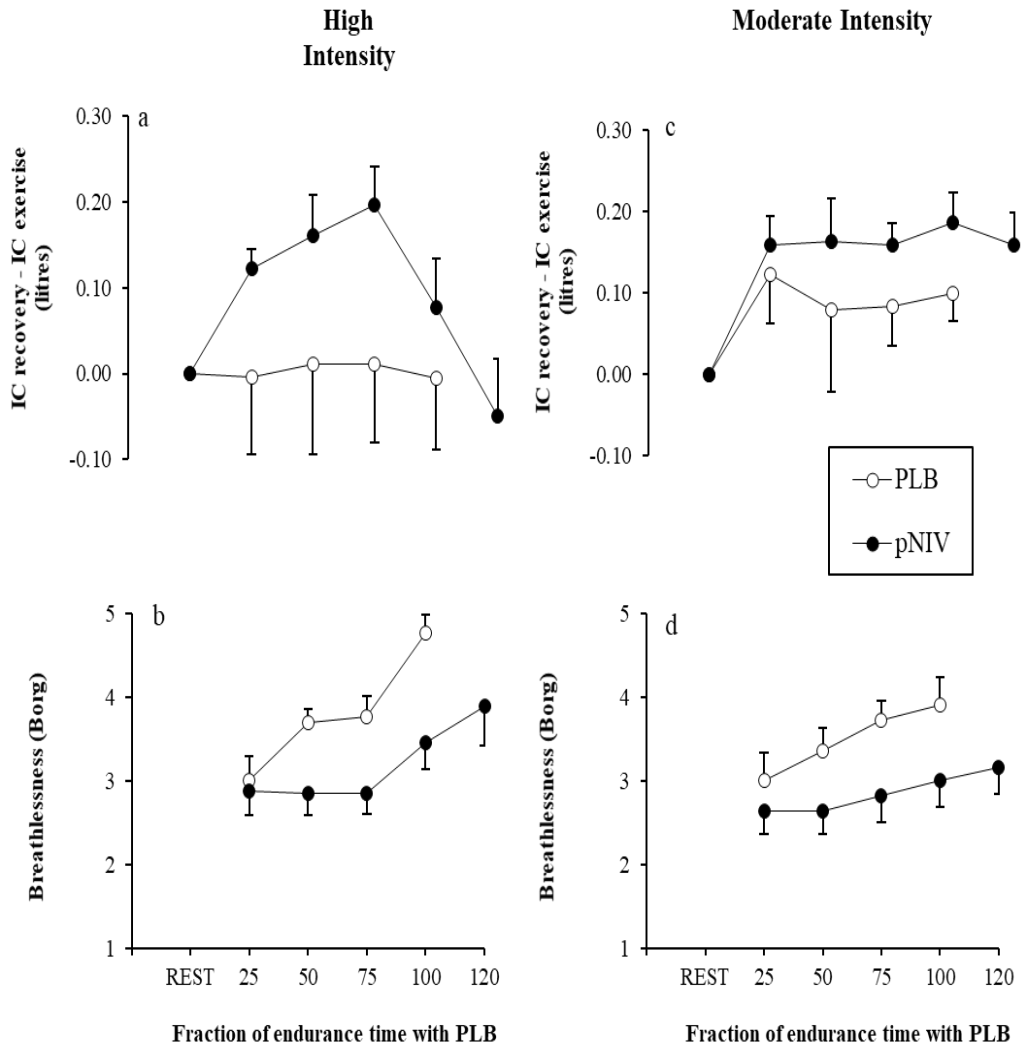


**Figure 5.7.** Exercise endurance time balancing the two breathing modalities (pNIV and PLB) when using pNIV in the first trial and PLB afterwards (black bars), or when using PLB in the first trial and pNIV afterwards (grey bars). Endurance time was not affected by the sequence of the breathing modality, whilst endurance time was consistently increased with pNIV compared to PLB.

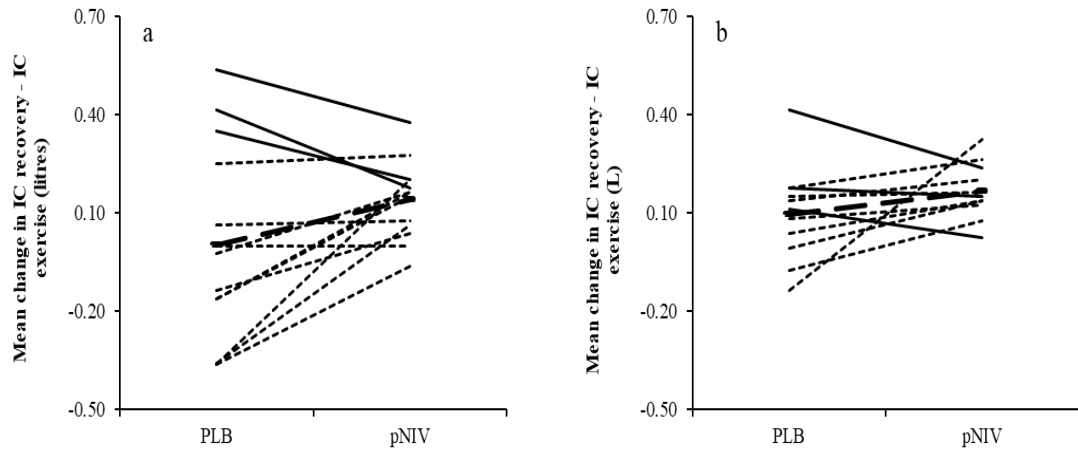
### **5.3.4. Effect of pNIV on Dynamic Hyperinflation**

#### **5.3.4.1. High- vs moderate-intensity**

The mean increase in IC during recovery periods compared to the end of exercise exceeded the clinically meaningful margin (i.e., >4.5% of predicted normal IC: 110–119 ml) [19, 24], when patients used pNIV for both HI-pNIV:  $140 \pm 110$  ml and MOD-pNIV:  $170 \pm 80$  ml exercise modalities (Figure 5.8.a & c). The mean change in IC in recovery compared to the end of exercise with PLB did not reach a clinically meaningful margin neither for HI-PLB:  $10 \pm 290$  ml nor for MOD-PLB:  $100 \pm 140$  ml exercise modalities (Figure 5.8.a & c). Compared to PLB at the limit of tolerance, the change in IC from rest was not different ( $p=0.379$ ) between the two intermittent exercise modalities with the use of pNIV (Table 5.5). However, in 6 out of 24 patients the improvement in dynamic hyperinflation was greater with PLB compared to pNIV (Figure 5.9) [20].



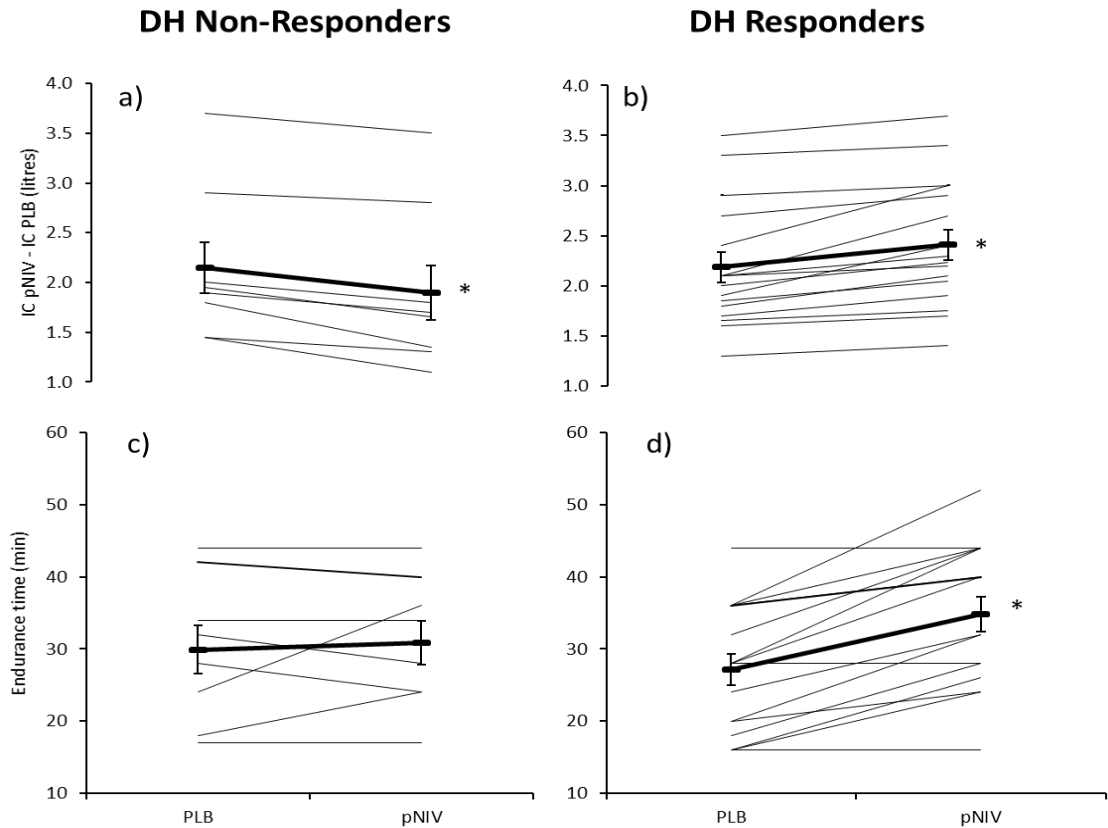
**Figure 5.8.** Effect of the application of pNIV (closed circles) compared to PLB (open circles) on inspiratory capacity calculated as the change between recovery periods and the end of high-intensity intermittent (a) and moderate-intensity (c) exercise bouts and symptoms of breathlessness during recovery from high-intensity (b) or moderate-intensity (d) exercise. Responses are shown for both PLB and pNIV at iso-time across the four percentiles (25%, 50%, 75% and 100%) of the total endurance time when using the PLB technique. Data are presented as mean  $\pm$  standard error of the mean (SEM) [20].



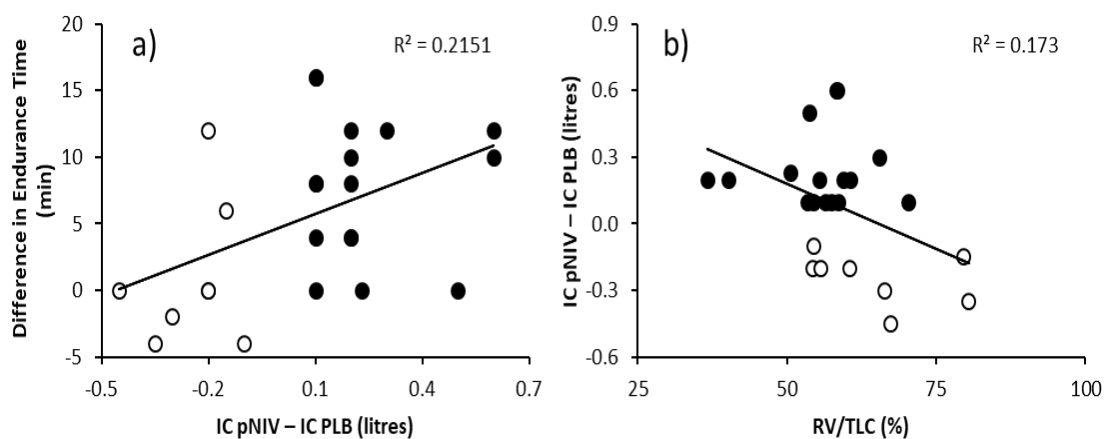
**Figure 5.9.** Effect of the application of pNIV on individual patient inspiratory capacity as the change between recovery periods and the end of a) high-intensity and b) moderate-intensity exercise. Solid lines indicate non-responders, thinner dotted lines indicate responders. There were 3 patients in each group who worsened DH in response to pNIV as compared to PLB [20].

#### 5.3.4.2. *DH responders vs DH non-responders*

Based on the dynamic hyperinflation data at exercise iso-time, 8 participants were identified as ‘DH non-responders’ to pNIV, whilst the remaining 16 participants were deemed as ‘DH responders’. At exercise iso-time in DH non-responders IC was  $240 \pm 40$  ml ( $p=0.001$ ) lower with pNIV compared to PLB, exceeding the minimum clinically important difference ( $>4.5\%$  of predicted resting IC) [19, 24], whilst IC was  $220 \pm 50$  ml ( $p=0.001$ ) greater in DH responders when pNIV was applied compared to PLB (Figure 5.10a & b & Table 5.4) as expected. Thus, demonstrating a significant difference ( $p=0.001$ ) in the magnitude of change in dynamic hyperinflation between the two groups. Across all 24 patients, the magnitude of change in exercise endurance time with pNIV compared to PLB was associated with the magnitude of change in dynamic hyperinflation ( $r=0.46$ ,  $p=0.022$ ) (Figure 5.11a). Furthermore, resting dynamic hyperinflation (inferred by RV/TLC %) was negatively associated with the magnitude of exercise-induced dynamic hyperinflation when using pNIV compared to PLB ( $r=-0.42$ ,  $p=0.043$ ) (Figure 5.11b).



**Figure 5.10.** (a & b): individual differences in inspiratory capacity (IC) at exercise iso-time and in endurance time (c & d) between pNIV and PLB, in DH non-responders (left panel) and DH responders (right panel) following the use of pNIV compared to PLB. Data presented as mean $\pm$ SEM. Thick lines denote mean values. Asterisks denote significant differences ( $p < 0.05$ ) between pNIV and PLB within each group.



**Figure 5.11.** a) Association between differences in endurance time and in inspiratory capacity (IC) between pNIV and PLB application at exercise iso-time and b) association between differences in IC when using pNIV compared to PLB at exercise iso-time with baseline residual volume as a fraction of total lung capacity ratio (RV/TLC). Open symbols denote DH non-responders and closed symbols DH responders.

**5.3.5. Baseline demographic and peak exercise data between DH responders and DH non-responders**

The baseline characteristics of the patients are presented in table 5.3. DH responders exhibited a tendency for greater FEV<sub>1</sub>, FVC, VC and resting IC compared to the DH non-responders. In addition, RV/TLC% was greater and IC/TLC was lower in DH non-responders compared to the DH responders (p=0.028 and p=0.047, respectively), indicating greater resting lung hyperinflation and mechanical restriction to tidal volume expansion (Table 5.3). In addition, DH non-responders had lower baseline peak exercise capacity (41±8% predicted) during cardiopulmonary exercise testing compared to DH responders (48±6%), but aerobic capacity as reflected by VO<sub>2</sub>peak was similar between the two groups (Table 5.3).

Table 5.3. Demographic and peak exercise data at baseline in DH non-responders and DH responders

	<b>DH Non-responders (n=8)</b>	<b>DH Responders (n=16)</b>	<b>p</b>
Gender (M/F)	4/4	6/10	
Age (years)	67±3	67±2	0.934
BMI	24.4±3.1	27.2±1.5	0.363
FEV <sub>1</sub> (litres)	0.96±0.20	1.23±0.16	0.297
FEV <sub>1</sub> (% predicted)	40±8	49±4	0.292
FVC (litres)	2.57±0.35	2.78±0.20	0.594
FVC (% predicted)	86±7	91±5	0.590
FEV <sub>1</sub> /FVC	37±5	43±3	0.298
VC (litres)	2.77±0.40	3.06±0.21	0.482
VC (% predicted)	89±8	97±5	0.380
FRC (litres)	5.62±0.43	5.15±0.44	0.513
FRC (% predicted)	188±14	166±12	0.288
RV (litres)	4.72±0.33	4.44±0.47	0.634
RV (% predicted)	218±20	198±17	0.470
TLC (litres)	7.36±0.49	7.28±0.47	0.916
TLC (% predicted)	135±6	128±7	0.564
IC (litres)	1.74±0.26	2.12±0.16	0.203
IC (% predicted)	70±7	84±6	0.164
IC/TLC (%)	24±3	30±2	0.047
RV/TLC (%)	65±4	56±2	0.028
DLco (litres)	2.60±1.01	3.17±0.44	0.556
DLco (% predicted)	33±11	40±5	0.494
WRpeak (% predicted)	41±8	48±6	0.471
VO <sub>2</sub> peak (% predicted)	59±7	61±4	0.722

M, male; F, female; BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in the first second; FVC, forced vital capacity; VC, vital capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; IC, inspiratory capacity; DLco, transfer factor of the lung for carbon monoxide; WR, work rate; VO<sub>2</sub>, oxygen uptake; values presented as mean ± standard error of the mean (SEM).

### **5.3.6. Effect of pNIV application on exercise tolerance in DH responders and DH**

#### **non-responders**

In DH non-responders, exercise endurance time was not different when using the pNIV device (30.9±3.4 min) compared to PLB (29.9±3.3 min) (p=0.603). In DH responders, exercise endurance time was significantly greater (p=0.001) with pNIV application (34.9±2.4 min) compared to PLB (27.1±2.3 min) (Figure 5.10c & 5.10d &

Table 5.4), thereby revealing a significant difference ( $p=0.008$ ) in the magnitude of improvement in endurance time between the two groups.

Table 5.4. Ventilatory and central haemodynamic responses with PLB and pNIV application at iso-time in DH non-responders and DH responders

	DH Non-Responders			DH Responders		
	PLB	pNIV	p	PLB	pNIV	p
Endurance time (min)	29.9±3.3	30.9±3.4	0.603	27.1±2.3	34.9±2.4 <sup>#</sup>	0.001
Minute ventilation (litres/min)	28.0±5.8	30.7±5.6	0.021	37.8±4.1	36.8±4.0 <sup>#</sup>	0.224
Tidal volume (litres)	1.0±0.2	1.0±0.2	0.482	1.2±0.1	1.3±0.1 <sup>#</sup>	0.018
bf (breaths/min)	28±2	30±2	0.046	30±1	29±1 <sup>#</sup>	0.216
IC (litres)	2.14±0.24	1.90±0.25	0.001	2.19±0.17	2.41±0.18 <sup>#</sup>	0.001
V <sub>T</sub> /IC (%)	47±3	53±3	0.001	56±2	53±2	0.010
Inspiratory time (sec)	0.8±0.1	0.7±0.1	0.017	0.8±0.1	0.8±0.1 <sup>#</sup>	0.059
Expiratory time (sec)	1.5±0.1	1.3±0.1	0.010	1.3±0.1	1.4±0.1 <sup>#</sup>	0.116
Duty cycle (sec)	2.3±0.1	2.0±0.1	0.008	2.1±0.1	2.2±0.1 <sup>#</sup>	0.071
Stroke volume (ml)	88±7	88±6	0.971	95±5	98±5	0.122
Heart rate (beats/min)	111±6	114±6	0.223	109±4	108±4	0.913
Cardiac output (litres/min)	9.5±0.9	9.9±0.8	0.335	10.3±0.6	10.9±0.6	0.035
Double Product (mmHg/beat/min)	24,681±1,126	26,185±1,006	0.009	25,649±796	25,951±711 <sup>#</sup>	0.423
Systolic blood pressure (mmHg)	136±9	148±8	0.024	148±6	151±5	0.377
Diastolic blood pressure (mmHg)	77±5	84±4	0.042	80±4	82±3	0.336
Mean blood pressure (mmHg)	96±6	106±5	0.006	103±4	105±4	0.237

PLB, pursed lip breathing; pNIV, portable non-invasive ventilation; V<sub>T</sub>, tidal volume; IC, inspiratory capacity; bf, breathing frequency <sup>#</sup>, significant differences ( $p<0.05$ ) in the pattern of response between the two groups; values presented as mean ± standard error of the mean (SEM)

Table 5.5. Metabolic and respiratory responses at the limit of tolerance of high- and moderate-intensity exercise.

Variable	High-Intensity			Moderate-Intensity		
	PLB	pNIV Support	<i>p</i> -Value	PLB	pNIV Support	<i>p</i> -Value
Work Rate (watts)	38±20 (80%)	38±20 (80%)	-	30±17 (60%)	30±17 (60%)	-
ΔIC (litres)	-0.37±0.31 (62%)	-0.37±0.28 (62%)	0.964	-0.29±0.25 (62%)	-0.27±0.24 (58%)	0.819
Dyspnoea (Borg)	4.8±1.2 (114%)	3.9±1.4 (93%)	0.005	4.0±1.1 (105%)	3.3±1.1 (87%)	0.004
Leg Discomfort (Borg)	4.5±1.5 (118%)	4.1±1.8 (108%)	0.027	4.1±1.2 (124%)	3.3±1.6 (100%)	0.011
VO <sub>2</sub> (ml/min/kg)	11.9±3.2 (88%)	12±3.5 (89%)	0.879	12.8±3.3 (96%)	12.7±3.1 (95%)	0.778
V <sub>E</sub> (litres/min)	34.8±18.4 (89%)	36.5±18.1 (93%)	0.206	34.6±14.6 (98%)	33.8±14.3 (95%)	0.444
V <sub>T</sub> (litres)	1.2±0.5 (100%)	1.2±0.5 (100%)	0.202	1.2±0.5 (100%)	1.2±0.5 (100%)	0.549
RF (breaths/min)	29±5 (94%)	30±5 (97%)	0.256	30±5 (103%)	29±3 (100%)	0.409
CO (litres/min)	9.9±2.6 (94%)	10.5±2.7 (100%)	0.070	10.3±2.4 (92%)	10.5±2.3 (94%)	0.193
HR (beats/min)	105±13 (93%)	108±15 (96%)	0.172	114±19 (104%)	114±16 (104%)	0.725
SV (ml/beat)	94±23 (100%)	96±22 (102%)	0.487	90±16 (89%)	91±13 (90%)	0.485
SBP (mmHg)	146±23 (98%)	158±23 (106%)	0.002	142±29 (94%)	148±22 (98%)	0.285
DBP (mmHg)	82±8 (92%)	89±9 (100%)	0.024	78±18 (90%)	84±17 (97%)	0.049
a-vO <sub>2</sub> (mL/100ml)	8.9±2.9	8.3±3.1	0.205	8.9±2.9	8.6±2.9	0.371
SpO <sub>2</sub> (%)	92±5	93±4	0.104	94±3	93±3	0.148

ΔIC, change from baseline in inspiratory capacity; VO<sub>2</sub>, oxygen uptake; V<sub>E</sub>, minute ventilation; V<sub>T</sub>, tidal volume; RF, breathing frequency; CO, cardiac output; HR, heart rate; SV, stroke volume; SBP, systolic blood pressure; DBP, diastolic blood pressure; a-vO<sub>2</sub>, whole body arteriovenous oxygen difference content; SpO<sub>2</sub>, arterial oxygen saturation; pNIV, portable Non-Invasive Ventilation; PLB, Pursed lip breathing technique. Values are mean ± SD [20] and as a fraction of peak values recorded during the CPET.



### **5.3.7. Perceived symptoms**

#### **5.3.7.1. High- vs moderate-intensity**

Compared to PLB across different fractions of total endurance, time application of pNIV was associated with a clinically meaningful reduction [24, 267] in breathlessness during HI-pNIV (by:  $1.2 \pm 1.7$ ,  $p=0.022$ ) and MOD-pMIV (by:  $1.0 \pm 0.7$ ,  $p=0.002$ ) exercise modalities (Figure 5.8 b & d). There were no significant differences ( $p=0.518$ ) in breathlessness scores between the two modalities with pNIV [20].

Compared to PLB across different fractions of total endurance time, the application of pNIV was associated with lower leg discomfort during HI-pNIV (by:  $0.5 \pm 0.8$ ,  $p=0.050$ ) and MOD-pNIV (by:  $0.8 \pm 1.1$  ( $p=0.031$ )) exercise modalities (Figure 5.12 c,f). There were no differences ( $p=0.268$ ) in leg discomfort scores between the two modalities with pNIV [20].

#### **5.3.7.2. DH responders vs DH non-responders**

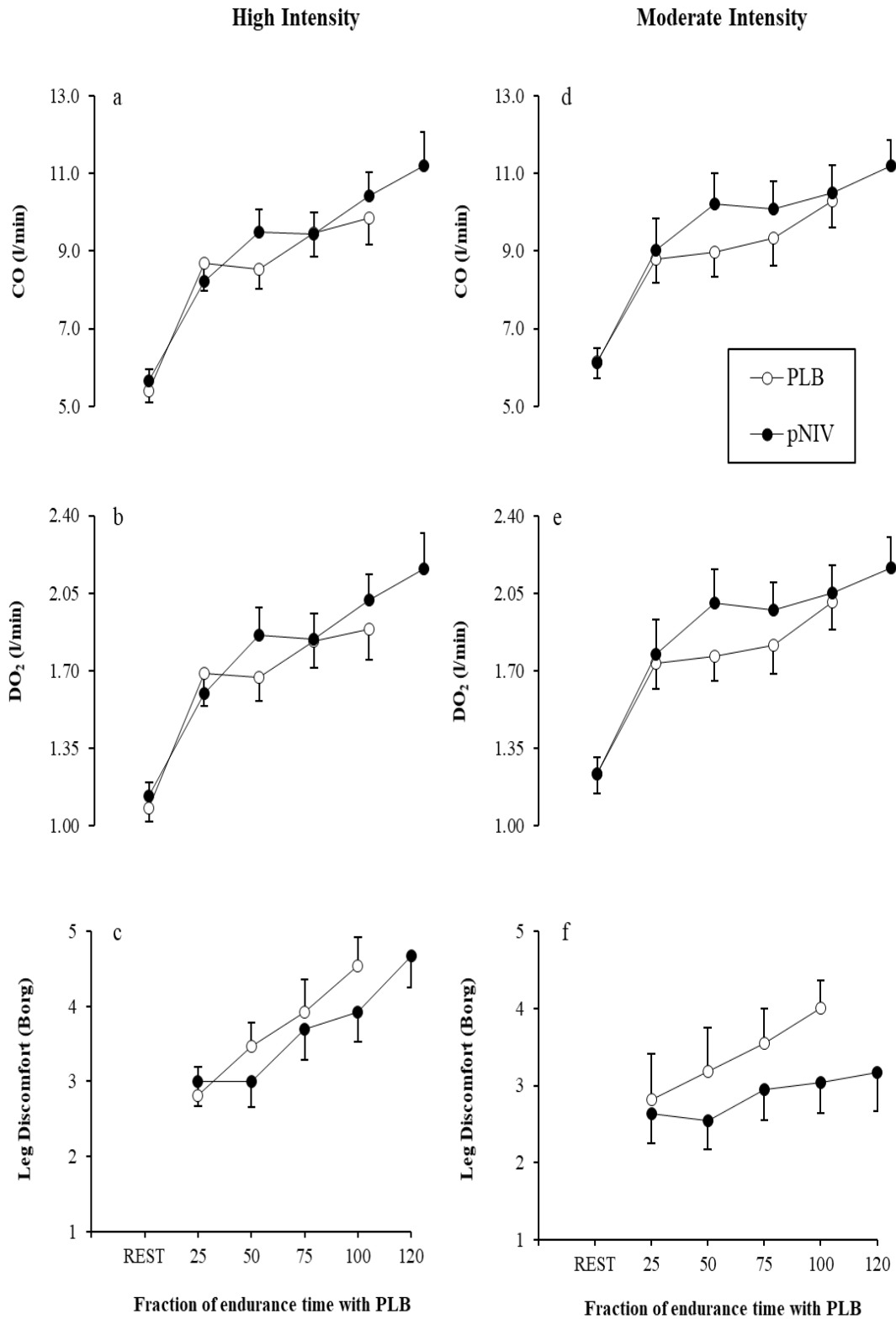
When patients were classified as DH responders or DH non-responders, at exercise iso-time, use of pNIV compared to PLB was associated with reduced breathlessness by a clinically meaningful margin (by  $1.3 \pm 0.3$  units,  $p=0.001$ ) in DH responders [24, 27]. In DH non-responders the reduction in breathlessness with the use of pNIV compared to PLB (by  $0.6 \pm 0.5$  units,  $p=0.118$ ) was not clinically meaningful. In addition, use of pNIV compared to PLB reduced leg discomfort in both DH responders and non-responders (by  $0.6 \pm 0.2$  units,  $p=0.026$  and by  $0.8 \pm 0.3$  units,  $p=0.034$ , respectively), albeit by non-clinically meaningful margins ( $<1.0$  unit on a Borg 1-10 scale) [267]. There was not a significant difference in the magnitude of improvement with pNIV compared to PLB in breathlessness ( $p=0.236$ ) and leg discomfort ( $p=0.650$ ) between the two groups.

### **5.3.8. Central haemodynamic responses and kinetics**

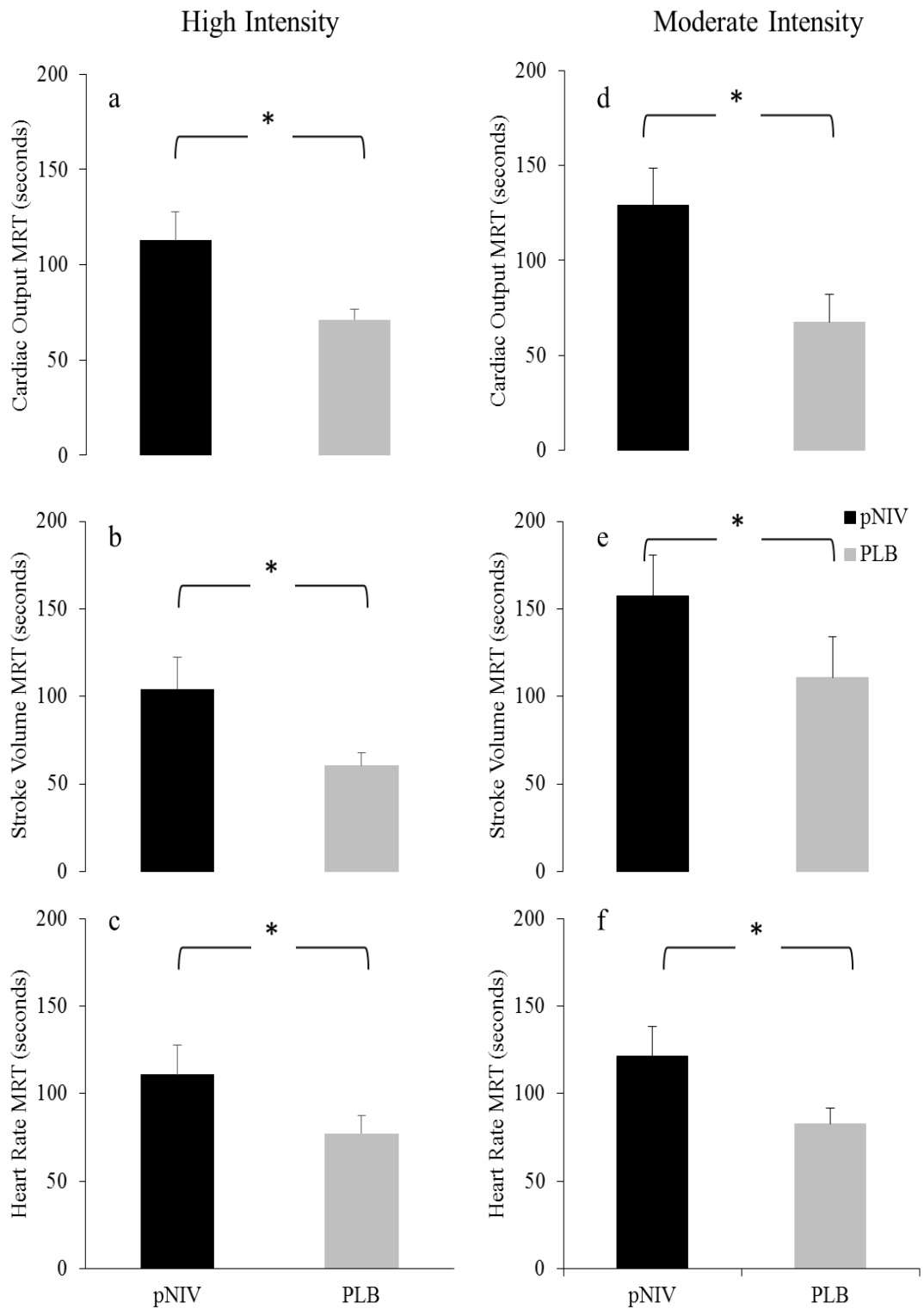
#### **5.3.8.1. High- vs moderate-intensity**

In comparison to PLB, across different fractions of total endurance time, CO and systemic oxygen delivery were greater with pNIV during both HI-pNIV (by  $0.3 \pm 1.1$  litres/min ( $p=0.035$ ) and by  $70 \pm 40$  ml/min ( $p=0.040$ ), respectively) and MOD-pNIV (by  $0.8 \pm 0.9$  litres/min ( $p=0.045$ ) and  $160 \pm 40$  ml/min ( $p=0.040$ ), respectively) exercise modalities (Figure 5.12). There were no differences ( $p=0.519$  and  $0.463$ , respectively) in these variables between the two exercise modalities with pNIV (Figure 5.12) [20].

Compared to PLB, at the limit of tolerance, off transient kinetic response of cardiac output, stroke volume and heart rate were significantly slower with pNIV during both HI-pNIV (CO by  $42 \pm 48$  sec ( $p=0.022$ ); SV by  $44 \pm 56$  sec ( $p=0.036$ ) and HR by  $34 \pm 36$  sec ( $p=0.017$ )) and MOD-pNIV (CO by  $61 \pm 52$  sec ( $p=0.007$ ); SV by  $39 \pm 52$  sec ( $p=0.054$ ); and HR by  $46 \pm 49$  sec ( $p=0.022$ )) (Figure 5.13).



**Figure 5.12.** Effect of the application of pNIV (closed circles) compared to PLB (open circles) on cardiac output (CO: a & d), estimated systemic oxygen delivery (DO<sub>2</sub>: b & e) and symptoms of leg discomfort (c & f) during high- and moderate-intensity exercise protocols, respectively. Responses are shown for both PLB and pNIV at iso-time across the four percentiles (25%, 50%, 75% and 100%) of the total endurance time when using the PLB technique. Data are presented as mean±SEM [20].



**Figure 5.13.** Effect of the application of pNIV (black bars) compared to PLB (grey bars) on mean response time (MRT) of cardiac output (a & d), stroke volume (b & e) and heart rate (c & f) during the recovery phase after termination of the high- (left panel) and moderate-intensity (right panel) exercise protocols. Data are presented as mean±SEM.

### 5.3.8.2. DH responders vs DH non-responders

There were no differences in stroke volume and heart rate responses with pNIV compared to PLB in either of the groups (Table 5.4). However, in DH responders cardiac output was greater with pNIV compared to PLB (by  $0.6 \pm 0.3$  litres/min,  $p=0.035$ ) (Table 5.4), whereas cardiac output was not different between pNIV and PLB in DH non-responders. In addition, in DH non-responders there was an increase in systolic (by  $12 \pm 5$  mmHg,  $p=0.024$ ), diastolic (by  $7 \pm 3$  mmHg,  $p=0.042$ ) and mean (by  $9 \pm 3$  mmHg,  $p=0.006$ ) blood pressure with the use of pNIV compared to PLB, whilst there were no differences in blood pressure between the two breathing modalities in DH responders (Table 5.4). In DH non-responders the increased systolic blood pressure resulted in a greater double product when pNIV was applied compared to PLB (by  $1,503 \pm 524$  mmHg/beat/min,  $p=0.009$ ), whilst there were no differences in the DH responders group (Table 5.4). Hence, there was a significant difference in the double product ( $p=0.044$ ) between DH responders and non-responders.

### 5.3.9. Breathing pattern

#### 5.3.9.1. High- vs moderate-intensity

In comparison to PLB, at the limit of tolerance, there was no difference both in breathing frequency and in tidal volume with pNIV during both HI-pNIV [ $(p=0.256)$  and  $(p=0.202)$ , respectively] and MOD-pNIV [ $(p=0.409)$  and  $(p=0.549)$ , respectively] exercise modalities (Table 5.5). Accordingly, compared to PLB, at the limit of tolerance, there was no difference in minute ventilation with pNIV during both HI-pNIV ( $p=0.206$ ) and MOD-pNIV ( $p=0.444$ ) (Table 5.5).

### 5.3.9.2. DH responders vs DH non-responders

In DH responders, at exercise iso-time application of pNIV compared to PLB reduced minute ventilation (by  $1.0 \pm 0.8$  litres,  $p=0.224$ ) due to lower breathing frequency (by  $1 \pm 1$  breaths/min  $p=0.216$ ), whilst tidal volume was increased (by  $0.1 \pm 0.02$  litres,  $p=0.018$ ) (Table 5.4). In contrast, in DH non-responders pNIV compared to PLB increased minute ventilation (by  $2.7 \pm 1.1$  litres,  $p=0.021$ ) secondary to increased breathing frequency (by  $2 \pm 1$  breaths/min,  $p=0.046$ ), whilst tidal volume was unaffected (Table 5.4). Thus, there was a significant difference in the breathing pattern between DH responders and non-responders with pNIV compared to PLB in minute ventilation ( $p=0.012$ ), breathing frequency ( $p=0.026$ ) and tidal volume ( $p=0.046$ ).

At exercise iso-time, the fraction of tidal volume to inspiratory capacity ( $V_T/IC$  %) was increased in DH non-responders (by  $6 \pm 2\%$ ,  $p=0.001$ ) with the use of pNIV compared to PLB, whereas  $V_T/IC$  % was decreased (by  $3 \pm 1\%$ ,  $p=0.010$ ) in DH responders (Table 5.4). In addition, at exercise iso-time in DH non-responders there was a reduction in inspiratory time (by  $0.1 \pm 0.03$  sec,  $p=0.017$ ) and expiratory time (by  $0.2 \pm 0.1$  sec,  $p=0.010$ ), and total duty cycle (by  $0.3 \pm 0.1$  sec,  $p=0.008$ ) with the use of pNIV compared to PLB (Table 5.4). There were no differences between pNIV and PLB in duty cycle in DH responders (Table 5.4). Thus, there was a significant difference in the pattern of response between DH responders and non-responders with pNIV compared to PLB in inspiratory time, expiratory time and duty cycle ( $p=0.004$ ;  $p=0.004$ ;  $p=0.002$ , respectively). DH responders and non-responders experienced similar exercise-induced arterial oxygen desaturation from baseline to exercise iso-time when pNIV was applied compared to PLB (Table 5.6).

#### 5.3.9.3. Metabolic responses

#### 5.3.9.4. High- vs moderate-intensity

In comparison to PLB, at the limit of tolerance, there was no difference in arterio-venous oxygen difference with pNIV during both HI-pNIV ( $p=0.205$ ) and MOD-pNIV ( $p=0.317$ ) exercise modalities (Table 5.5). Additionally, compared to PLB, both oxygen uptake and arterial oxygen saturation were similar at the limit of tolerance when pNIV was applied during both HI-pNIV [ $(p=0.879)$  and  $(p=0.104)$ , respectively] and MOD-pNIV [ $(p=0.778)$  and  $(p=0.148)$ , respectively] exercise modalities (Table 5.5).

#### 5.3.9.5. DH responders vs DH non-responders

In DH responders, arterio-venous oxygen difference was significantly lower with pNIV application compared to PLB ( $p=0.026$ ), whilst oxygen uptake and carbon dioxide production were similar at exercise iso-time when pNIV was applied compared to PLB (Table 5.6). Additionally, systemic oxygen delivery was greater at exercise iso-time in the DH responders group when pNIV were applied compared to PLB ( $p=0.016$ ). Furthermore, in DH non-responders arterio-venous oxygen difference, oxygen uptake and carbon dioxide production were similar when pNIV was applied compared to PLB at exercise iso-time (Table 5.6). Finally, there was no difference in systemic oxygen delivery in DH non-responders when pNIV was applied compared to PLB at exercise iso-time (Table 5.6).

Table 5.6. Metabolic responses with PLB and pNIV application at exercise iso-time in non-responders and responders

	DH Non-Responders			DH Responders		
	PLB	pNIV	p	PLB	pNIV	p
$\Delta$ SpO <sub>2</sub> (%)	-2.5±1.2	-2.6±1.0	0.839	-3.6±0.9	-2.8±0.7	0.158
Arteriovenous oxygen difference (ml/100ml)	8.6±1.0	8.3±1.0	0.409	9.0±0.7	8.3±0.7	0.026
Oxygen uptake (ml/kg/min)	12.3±1.2	12.7±1.1	0.232	12.2±0.8	11.9±0.8	0.206
Carbon dioxide (ml/min)	664±139	702±131	0.311	828±98	787±92	0.129
Systemic oxygen delivery (litres/min)	1.9±0.2	1.9±0.2	0.356	2.0±0.1	2.1±0.1	0.016

PLB, pursed lip breathing; pNIV, portable non-invasive ventilation;  $\Delta$ , change from baseline; SpO<sub>2</sub>, arterial oxygen saturation; values presented as mean±standard error of the mean (SEM)

#### **5.4. Discussion**

The major finding of the study is that the use of pNIV during recovery periods interspersing moderate- and high-intensity bouts of intermittent exercise significantly improved exercise tolerance compared to PLB [20]. This is probably due to more rapid recovery from exercise-induced dynamic hyperinflation, with associated improvements in cardiac output and systemic oxygen delivery [20]. The physiological responses shown were matched by a reduction in breathlessness and leg discomfort during the recovery from exercise [20]. However, at exercise iso-time, 8 patients did not improve dynamic hyperinflation (DH non-responders) whilst the remaining 16 patients reduced dynamic hyperinflation (DH responders). The analysis revealed that only DH responders showed an improvement in exercise tolerance with pNIV compared to PLB. DH non-responders showed similar exercise tolerance with pNIV and PLB. Compared to DH responders, DH non-responders had greater resting dynamic hyperinflation, thus greater mechanical restriction to tidal volume expansion during exercise, and tended towards more severe airflow obstruction. The application of pNIV worsened ventilatory



responses in DH non-responders, who adopted a more tachypnoeic breathing pattern, but improved the ventilatory response in DH responders.

NIV has previously been used during exercise training in patients with severe COPD, to lessen breathlessness and increase exercise capacity [20, 49, 208]. A Cochrane analysis of studies using NIV during exercise training, provides conflicting and moderate quality evidence of the beneficial effects on exercise capacity and therefore the role of this intervention remains unclear [20, 52, 268-271]. The main drawbacks of NIV described in this review were the difficulty and costs associated with using the equipment during pulmonary rehabilitation, including the time required to supervise patients during training [20, 269]. Nevertheless, recent meta-analyses conclude that there is a need for further randomised clinical trials [20, 269, 272].

The VitaBreath device is designed to overcome the problems associated with the use of traditional NIV, and is primarily intended to aid recovery from breathlessness after activities of daily living. It is light, handheld and battery operated. This, and future pNIV devices, may offer benefits within pulmonary rehabilitation, particularly in intermittent/interval training regimes. One technical limitation of the VitaBreath device is that the expiratory and inspiratory positive airway pressures (EPAP and IPAP, respectively) are fixed. Excessive EPAP can worsen hyperinflation and circulatory compromise. In the present study population, the majority of patients showed no worsening of DH or circulatory compromise whilst using pNIV during recovery periods. However, in six patients (three per group) the improvement in DH was greater with PLB than pNIV, thereby suggesting that the fixed pressures were sub-optimal in at least some of the patients. Accordingly, in future devices the ability to adjust EPAP and pressure support is desirable and could potentially be automated [20].

Recently, a non-invasive “open” ventilation (NIOV) system operating in conjunction with a portable oxygen tank was found to decrease respiratory muscle activation and dyspnoea, as well as improve cycle ergometer exercise tolerance [145]. In the current study the use of pNIV (VitaBreath) during intermittent exercise is associated with longer exercise endurance time (by 19–20%), with less DH and breathlessness [20]. Continuous positive pressure support throughout exercise is much less practical in daily life, but confers greater improvement in exercise tolerance, including the use of: continuous positive airway pressure (26–40%) [44, 46], proportional assist ventilation (23–43%) [44, 46, 209], pressure support ventilation (by 32–38%) [44, 210], inspiratory pressure support (46%) [42] and NIOV (by 245%) [145]. Notably, when the NIOV system was powered by compressed air rather than oxygen, exercise endurance time was increased only by 13% [145]. The aforementioned ventilation support strategies provide continuous unloading of the respiratory muscles and reduce the work of breathing [49, 208], and as such, are expected to yield greater improvements in exercise capacity compared to the intermittent application of pNIV during recovery from exercise [20]. This argument is further supported by the absence of a reduction in ventilatory requirement or an increase in arterial oxygen saturation during the successive bouts of high- or moderate-intensity exercise, with the application of pNIV compared to PLB in the present study (Table 3.4) [20]. Whilst intermittent use of pNIV offered less improvement in exercise tolerance, it is more practical in typical pulmonary rehabilitation settings and daily life [20]. Studies in the future may investigate the additive effect of oxygen supplementation to intermittent NIV support during typical pulmonary rehabilitation [20].

When patients categorised as DH responders and DH non-responders, application of pNIV induced a significant improvement in exercise tolerance in DH responders, whilst

in DH non-responders the improvement in exercise tolerance was of no account [273]. Findings within DH responders are supported by previous research into different NIV modes, where increases in exercise tolerance similar to the present study are reported [49, 208]. Lack of improvement in exercise endurance time in DH non-responders may be attributed to the failure of pNIV to relieve symptoms of breathlessness. There is strong evidence that a reduction in the mechanical restriction to tidal volume expansion is closely related to a reduction in symptoms of exertional breathlessness [19, 274, 275]. Therefore, the potential mechanism explaining the lack of improvement in exercise tolerance in DH non-responders when using pNIV compared to PLB is probably the failure to alleviate such mechanical constraints [27, 274, 275] and subsequently to reduce symptoms of breathlessness by a clinically meaningful amount ( $>1.0$  on a Borg 1-10 scale) as observed with the DH responders [24] .

Of note, in the present study patients scored relatively low breathlessness and leg discomfort at the limit of tolerance, both during high- and moderate-intensity exercise. Similar findings are also reported in other studies when repeated constant load exercise was performed [276, 277]. In the study by Mador and colleagues [277], the Borg scale was used to assess dyspnoea perception during 5 constant load tests at 66% of peak work rate. The study reported that patients were unable to distinguish the sense of respiratory effort and discomfort during exercise. Additionally, the variability of dyspnoea scores was greater compared to the objective exercise parameters, despite the fact that dyspnoea levels were correlated with objective indices of exercise intensity [277]. Moreover, a study by Belman and colleagues [276] reported that dyspnoea levels assessed by the Borg scale decreased progressively, especially at more strenuous levels of exercise when patients performed the same exercise test on four different days [276]. Furthermore, authors reported that the proportionately greater fall in the Borg ratings

with repetitive testing was independent of a true physiologic training effect, clearly suggesting a learning effect [276]. In the present study, there was a 4-week familiarisation period in order to minimise the potential learning effect between the two visits, most likely justifying the relatively low breathlessness score reported at the end of exercise by the patients.

A recent study by Souza and colleagues [278] reported that application of BiPAP (IPAP: 15 cmH<sub>2</sub>O, EPAP: 5 cmH<sub>2</sub>O) in moderate COPD reduced operational lung volumes and breathlessness, increasing exercise tolerance at different levels of exercise [278]. However, in contrast to the present study BiPAP was applied throughout exercise and IPAP and EPAP pressures were tailored to a level that was comfortable to the individual patient [278]. The VitaBreath device delivers fixed pressures of 18 cmH<sub>2</sub>O during inspiration and 8 cmH<sub>2</sub>O during expiration. For NIV to be beneficial in COPD patients, the external positive end-expiratory pressure (PEEPe) provided by the ventilator must match the patients intrinsic PEEP (PEEPi) [279]. The fixed pressures of VitaBreath are in contrast to other commonly used, adjustable, NIV methods, and it is likely that the pressures provided by the pNIV device were excessive for the DH non-responders [280]. A study by Nava and colleagues reported that application of PEEPe greater than PEEPi significantly increased end-expiratory lung volumes [178]. In the present study, 8 patients exhibited greater dynamic hyperinflation, whilst 16 patients experienced less dynamic hyperinflation with pNIV compared to PLB. Although PEEPi was not assessed in this study, the level of PEEPe (8 cmH<sub>2</sub>O) provided by the VitaBreath device was suboptimal compared to the average intrinsic PEEPi (in the range of 2.5-10.0 cmH<sub>2</sub>O) reported in the literature for patients with similar severity of COPD to those in the present study, most likely worsened dynamic hyperinflation in DH non-responders [178, 184, 281, 282]. Furthermore, when intrinsic and extrinsic

PEEP matching is suboptimal, there is increased risk of developing patient-ventilator asynchronies [207], resulting in increased work of breathing, poor alveolar ventilation and insufficient gas exchange [283]. This supports our view that the ability to match PEEPe to the individual patient's needs in future pNIV devices should improve synchrony and lead to a greater reduction in exercise induced DH, thus improving exercise tolerance and breathlessness.

The findings of the present study suggest that pNIV improved exercise tolerance compared to PLB, not only by its direct effect on respiratory mechanics (reducing DH), but also by partial alleviation of the associated adverse hemodynamic responses [20]. Use of pNIV resulted in an increase in cardiac output and systemic oxygen delivery during exercise [20]. This is most likely a result of reduced DH and improved venous return, which is in line with previously published reports following application of PAV [209] and administration of bronchodilators or heliox [144, 284]. This finding confirms that a common basis for enhanced exercise performance in COPD may be associated with improved peripheral muscle oxygen availability and reduced symptoms of leg discomfort, afforded by interventions targeting the abnormal respiratory mechanics in COPD [20].

The delay of on- and off-transient kinetics in central haemodynamic responses during constant-load exercise and the 6MWT has been associated with the disease severity possibly reflecting greater cardiovascular impairment and/or greater physical deconditioning in patients with advanced COPD compared to those patients in early stages [194].

In the present study, the delay in central haemodynamic kinetic responses when pNIV was applied may be for the result of greater CO when using pNIV compared to

PLB (Figure 5.13. a & d). Specifically, the off-transient kinetics analysis revealed that application of pNIV was associated with a delayed response in HR, SV and CO mean response time at the limit of tolerance compared to PLB. These findings suggest that that alleviation of dynamic hyperinflation and associated increase in venous return and stroke volume increased cardiac output more when using pNIV compared to PLB thus leading to a longer recovery time for all central hemodynamic responses.

To the author's knowledge, this is the first study that investigates the effects of NIV application on central haemodynamic off-transient mean response time, following an exercise protocol. However, the application of NIV has previously been found to acutely modify resting heart rate variability in patients with COPD [285]. In fact, there was an increase in sympathetic activity and a decrease in parasympathetic activity when BiPAP (IPAP: 14, EPAP: 5 cmH<sub>2</sub>O), of similar levels to this study, was applied at rest in patients with COPD [285]. This increase in sympathetic activity may partially explain the delay in CO recovery during the recovery periods between consecutive bouts of exercise, mainly due to the delay in the recovery of HR.

Although application of NIV at rest is associated with adverse haemodynamic effects in patients with COPD, a study stratifying patients into responders and non-responders (according to the change in exercise tolerance) when proportional assist ventilation (PAV) was applied compared to normal breathing, reported similar responses in central haemodynamic variables between the two groups [45]. The findings of the present study are in accordance with the existing literature. There were only small, non-significant, differences in stroke volume and heart rate, whilst cardiac output was greater only in the responders group. Additionally, the duration of pNIV application was very brief, and therefore less likely to cause any adverse haemodynamic responses.

In the literature there is conflicting evidence as two studies report no changes in blood pressure when NIV was applied compared to control conditions during exercise [286, 287], whilst one study reported greater diastolic blood pressure when combined NIV and oxygen were applied compared to oxygen alone [288]. The results of the present study showed that in DH responders blood pressure was not different between pNIV and PLB application during exercise, but interestingly, application of pNIV in DH non-responders increased systolic and mean blood pressures compared to PLB. This might be due to greater dynamic hyperinflation in this group when using pNIV, as increased intrathoracic pressure swings are associated with increased pressure in the chest cavity [289].

Increased blood pressure led to greater double product, as heart rate was unchanged in the DH non-responder group when pNIV was applied compared to PLB. Double product is an index assessing the load of the heart during each beat, as it is the product of systolic blood pressure and heart rate [290]. Increased double product is related to a lower ejection fraction in patients with chronic heart failure [291]. Greater arterial blood oxygenation is associated with lower double product values during a 6MWT in patients with CHF [292]. In the present study the greater double product with pNIV application in the DH non-responder group might be associated with the greater degree of resting and exercise-induced dynamic hyperinflation, but also with the slightly higher heart rate reported at iso-time.

VitaBreath provides positive inspiratory pressure support to reduce the work of breathing and positive expiratory pressure to keep the airways open during expiration, thereby reducing air trapping [20, 215]. The mean increase in IC during the recovery periods compared to the end of exercise bouts with pNIV (high-intensity: 140 mL; moderate-intensity: 170 mL) was within the clinically meaningful margin for

bronchodilator trials (138–175 mL) [20, 293], most likely reflecting the improvement in expiratory flow and thus lung emptying [20, 24, 27, 293]. The increase in IC during recovery was matched by a significant reduction in breathlessness that reached the minimal clinically important difference (1.0 unit) [20, 24, 27]. In contrast, PLB was not consistently associated with a clinically meaningful improvement in IC during recovery; this is in keeping with previous work showing that exercise-induced DH normally persists for several minutes following the end of exercise [20, 85]. Furthermore, the mean reduction in breathlessness scores during recovery from exercise did not reach the minimal clinically important difference [20, 24, 27].

Dynamic hyperinflation is an important factor limiting exercise tolerance in patients with COPD [19, 27, 274]. Compared to DH responders, DH non-responders tended to have a lower FEV<sub>1</sub>, thus greater expiratory flow limitation, increased lung volumes and greater lung hyperinflation at rest [19]. These findings are consistent with advanced COPD with emphysema [294]. Moreover, greater resting expiratory flow limitation is associated with smaller improvements in exercise tolerance secondary to increase in end-expiratory lung volume [295]. Although both groups exhibited a reduction in Borg scale breathlessness when using pNIV, only DH responders achieved a clinically meaningful reduction (>1.0 units) [24]. In COPD, dynamic hyperinflation causes inspiratory muscle shortening and tidal volume constraints, effecting ventilatory and central motor output [274, 296] and thus increasing work of breathing and consequent breathlessness.

Only one study in the literature comparing oxygen supplementation and inspiratory pressure support (IPS) has reported data on inspiratory capacity during iso-time exercise [210]. The data revealed greater inspiratory capacity at iso-time with IPS (by 200 ml) compared to oxygen supplementation, secondary to lower minute ventilation [210]. In



contrast, another study reported that application of PEEPe at rest in patients with acute exacerbation of COPD did not cause any change in end expiratory lung volume compared to normal breathing [184]. However, authors suggested that intrinsic PEEP should be assessed and the level of applied PEEPe should be individualised [184].

The reduction in the magnitude of dynamic hyperinflation when using pNIV compared to PLB in DH responders is most likely associated with the greater ability to expand tidal volume during exercise, resulting in improved ventilatory coupling and subsequent reduced breathlessness [274, 296]. Use of pNIV in DH responders was associated with an increase tidal volume with lower breathing frequency, thereby increasing the duty cycle. In contrast, the more tachypnoeic breathing pattern adopted by DH non-responders resulted in less expiratory time and thus increased air trapping and exacerbated breathlessness [18, 27, 274, 275]. The increased fraction of tidal volume to inspiratory capacity ( $V_T/IC$  %) in DH non-responders demonstrates that were more likely to reach the point during exercise where they were unable to further increase tidal volume when using pNIV compared to PLB (Table 5.4) [19]. It is possible that in some patients the fixed EPAP was insufficient to overcome flow limitation thus, failed to facilitate expiration or that excessive pressures directly worsening dynamic hyperinflation. Use of self-adjusting EPAP tailored to the individual patient may lead to better outcomes.

Two intermittent protocols with different duration and intensity characteristics were applied to explore the influence of intermittent pNIV on exercise tolerance in COPD patients with baseline and exercise-induced dynamic hyperinflation [20]. It was expected that the use of pNIV during recovery following successive 2-min exercise bouts at high-intensity would have conferred greater benefit, due to the device being used more frequently compared to 6-min bouts of moderate-intensity exercise [20]. This

hypothesis was not confirmed. The high-intensity protocol elicited greater exercise-induced DH compared to the moderate intensity protocol (Table 5.5), hence the effectiveness of positive pressure ventilation on exercise tolerance, physiological responses and symptoms was highly comparable between the two intermittent modalities [20]. The findings of the study suggest that pNIV could be applied in the pulmonary rehabilitation setting to either prolong endurance at a sustained moderate intensity training load and/or to allow greater training loads, such as the high-intensity protocol used in the present study [20]. Further research is required to confirm this as the present study provides evidence only during acute application of portable NIV; hence these data cannot be extrapolated to give information about the effects during a long period of training [20].

Exercise training is the cornerstone of pulmonary rehabilitation and is associated with significant increases in exercise capacity in patients with COPD [106]. Previous studies have shown that the application of interval exercise during a pulmonary rehabilitation program allows for higher training loads, due to reduced ventilatory requirement, less metabolic acidosis and lower symptoms of breathlessness and leg discomfort compared to continuous exercise [28, 111]. Therefore, interval exercise was the best approach to increase exercise tolerance and simultaneously familiarise patients with the testing procedures.

In the study by Vogiatzis and colleagues [111], following a PR program including 24 training sessions, work load increased by 66% in the interval exercise group. In the present study, work load increased by 86% following 8 exercise sessions, however initial load was lower compared to the study [111]. This was mainly because the primary target of the training sessions was to familiarise the patient with the testing

procedures. The second aim was to ensure that patients would be able to complete the exercise testing without being severely limited by leg discomfort.

### *Study limitations*

This was a single centre study and blinding the patients or investigators to the breathing modality was not possible due to the lack of a sham pNIV device [20]. Thus, the risk of a placebo effect cannot be excluded, especially when considering the effect of the pNIV device on the reduction in breathlessness [20]. Measurements of the work of breathing were not performed directly during the recovery periods from exercise [20]. This would have allowed assessment of the effect of pNIV on respiratory muscle unloading. Use of optoelectronic plethysmography would permit continuous assessment of end-expiratory volumes in the transition from exercise to recovery [20, 85].

Responders and non-responders were defined in terms of dynamic hyperinflation and not the primary outcome of the study. Inspiratory and expiratory positive airway pressures provided by the pNIV device were fixed, therefore adjustment of the aforementioned pressures was not possible. This is distinct to other studies applying NIV in COPD patients given that the level of provided pressure is individualised to maximise the benefit of use. This represents a very important disadvantage of the VitaBreath device, which clearly mitigated the beneficial impact it had on some patients.

### **5.5. Conclusions**

Use of pNIV during the recovery periods interspersing moderate or high intensity exercise bouts enhanced exercise tolerance compared to pursed lip breathing, by lessening the symptoms of breathlessness and enhancing systemic oxygen availability [20]. Future studies should investigate the applicability and benefits of intermittent

application of other available positive pressure ventilation strategies during the recovery periods of high-intensity intermittent exercise in COPD [20].

Application of fixed positive inspiratory and expiratory pressures during the recovery periods between exercise bouts is beneficial for the majority of the COPD patients; however this is not the case in patients with severe resting dynamic hyperinflation and poor lung function. In fact, workload of the myocardium seems to increase in these patients, potentially increasing the risk to cause adverse circulatory effects. Thus, the present dissertation has investigated the cardiovascular and respiratory muscle kinetic response of fixed positive inspiratory and expiratory pressures in a subset of patients with COPD during exercise (Chapter 6).

The findings of the present study suggest that, although pNIV presents with promising results and favourable practical benefits, it is not effective in improving dynamic hyperinflation in all COPD patients. This may be because the fixed pressures were suboptimal in some of the patients. Further studies in auto-adjusted ventilators are warranted in this population.

## **6. Effect of pNIV on thoracoabdominal volumes and circulatory responses during recovery from exercise in patients with COPD**

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### **6.1. Introduction**

This study investigated the acute effect of pNIV application compared to the PLB technique on thoracoabdominal volume regulation, pulmonary rib cage and abdominal kinematics and circulatory responses, during recovery from intermittent exercise in COPD. Chapter 5 investigated the effect of pNIV application compared to the PLB technique on dynamic hyperinflation during recovery from exercise, but not during the acute application of pNIV as it was not possible to perform IC manoeuvres when using pNIV. Accordingly, the present study constitutes an exploratory mechanistic study to appreciate the acute adjustments of ventilation and circulation when using the VitaBreath device compared to the PLB technique in recovery from exercise.

In addition, Chapter 5 presented different patterns of response in terms of the manifestation of dynamic hyperinflation in patients using pNIV compared to the PLB technique during recovery from intermittent exercise. Thus, it was deemed necessary to further investigate the different patterns of dynamic hyperinflation response to pNIV application during exercise in these COPD patients.

Moreover, Chapter 5 assessed the effect of using the VitaBreath device compared to the PLB technique on exercise tolerance in 24 patients with COPD. Use of the VitaBreath device during the recovery periods enhanced exercise tolerance compared to PLB, and reduced symptoms of breathlessness and leg discomfort. Reduced breathlessness was attributed to more rapid recovery from exercise-induced dynamic hyperinflation, assessed by periodic volitional inspiratory capacity manoeuvres performed through a spirometer at the end of exercise bouts and following application

of pNIV or PLB. The actual mechanism by which the VitaBreath device influences the magnitude of dynamic hyperinflation is thought to be the provision of positive end-expiratory pressure, preventing airway collapse and thus facilitating more complete lung emptying [20]. However, in the study of Chapter 5 it was not possible to assess breath-by-breath changes in operational lung volumes during the acute application of pNIV compared to PLB technique. By employing Opto-Electronic Plethysmography (OEP) this chapter investigated breath-by-breath changes in operational thoracoabdominal volumes in the transition from exercise to pNIV or PLB application and subsequently to normal breathing during recovery.

In addition, one technical limitation of the VitaBreath device is that the expiratory and inspiratory positive airway pressures (EPAP and IPAP, respectively) are fixed. Excessive EPAP can worsen hyperinflation and circulatory compromise [50, 51] in some patients. In Chapter 5, the majority of patients (16/24) showed no worsening of dynamic hyperinflation or circulatory compromise whilst using the VitaBreath device during recovery periods (DH responders). However, in six patients (three per group) the improvement in dynamic hyperinflation was greater with PLB than the VitaBreath device [20] (DH non-responders) at the limit of tolerance, thereby suggesting that the fixed pressures were sub-optimal in at least some of the patients in the clinical study. The more detailed analysis presented in Chapter 5, revealed worsening of dynamic hyperinflation in response to pNIV application in terms of manifestation of dynamic hyperinflation in 8/24 patients (DH non-responders) at an identical sub-maximal time point (iso-time) during exercise. Thus, it was deemed necessary to further investigate the different type of thoracoabdominal muscle kinematic response to pNIV application in patients who displayed-worsened dynamic hyperinflation with pNIV. Accordingly, an additional objective of this study was to identify the pattern of dynamic

hyperinflation that worsens with the application of the VitaBreath device, as it is recognised that patients with COPD experience different patterns of dynamic hyperinflation during exercise, categorised as early or late hyperinflators [85] or evolumics [123].

Dynamic hyperinflation can be assessed by either instructing the patient to perform successive inspiratory capacity manoeuvres, which provides a picture of the magnitude of dynamic hyperinflation at a given time point or on a breath-by-breath basis using OEP [18]. In the present study use of OEP allowed continuous assessment of end-inspiratory and end-expiratory volumes of the thoracoabdominal wall and its compartments (rib cage and abdomen). Thus, thoracoabdominal dynamic hyperinflation could be directly assessed, without requiring patients to perform volitional inspiratory capacity manoeuvres. OEP is a valid and reliable method to assess thoracoabdominal wall volumes [245, 247, 248, 250] and has previously been used in patients with COPD during exercise, to assess the rate and pattern of dynamic hyperinflation [85, 86, 297].

Accordingly, the purpose of this study was to use OEP during acute application of the VitaBreath device in recovery from exercise in patients with COPD, in order to: 1) appreciate the acute mechanisms by which the VitaBreath device influences the magnitude and pattern of thoracoabdominal wall dynamic hyperinflation in comparison to the PLB technique, 2) evaluate the relative rib cage and abdominal wall muscle kinematic response, inferred by changes in the volumes of the rib cage and abdominal compartments in patients improving or worsening dynamic hyperinflation with the pNIV device compared to the PLB technique and 3) assess the effect of application of fixed expiratory and inspiratory positive airway pressures (EPAP and IPAP, respectively) on circulatory responses when using the pNIV device.

### **6.1.1. Main outcomes**

#### **6.1.1.1. Primary Outcome**

The primary outcome of the study was the magnitude and pattern of change in end-inspiratory and end-expiratory thoracoabdominal wall dynamic hyperinflation, assessed by OEP when using the pNIV device compared to the PLB technique during recovery from exercise.

#### **6.1.1.2. Secondary Outcomes**

Secondary outcomes included differences in the following variables, when using the pNIV device compared to the PLB technique in recovery from exercise:

- Compartmental thoracoabdominal wall volumes (rib cage and abdominal volumes) assessed by OEP
- Central haemodynamic responses assessed non-invasively by cardio impedance technology:
  - Heart rate
  - Stroke volume
  - Cardiac output

## **6.2. Methods**

### **6.2.1. Study design**

This was an exploratory study investigating the acute effect of the short term (1-min) application of pNIV on thoracoabdominal volumes and circulatory responses compared to the pursed lip breathing technique (PLB), in COPD patients exhibiting different patterns of dynamic hyperinflation. Patients performed two identical exercise tests in a balanced order and the intervention (VitaBreath) was compared to control breathing.



Patients underwent two exercise tests on a cycle ergometer on the same day, using both the VitaBreath device and the pursed-lip breathing technique during recovery from exercise. The investigations were carried out following the rules of the Declaration of Helsinki of 1975 [211], revised in 2013. NHS Research Ethics Committee approval (REC: 19/NE/0091) and Clinical Trials registration (NCT03848819) were obtained (Appendix F).

The study included two visits. During the first visit, patients underwent a clinical assessment including: medical history, physical examination, ECG and full lung function assessment including spirometry, lung volumes and diffusion capacity, to ensure patients were clinically stable. During the second visit, patients performed two intermittent exercise tests lasting 20 minutes each, consisting of 2-min work bouts at 80% of peak work rate (WR<sub>peak</sub>) as determined in the clinical study (REC reference: 17/NE/0085 - IRAS project ID: 221120) (Chapters 4 & 5) with 2-min recovery periods in between work bouts, using either the VitaBreath device or the pursed lip breathing technique during the recovery periods in a balanced order sequence.

### **6.3.Results**

#### **6.3.1. Patient characteristics**

Baseline characteristics of the patients who participated in the study are presented in table 6.1. Patients exhibited moderate to severe airflow limitation and lung hyperinflation at rest without resting hypoxemia (Table 6.1.). In addition, peak exercise capacity and aerobic capacity of the patients assessed by the ramp incremental CPET were reduced (Table 6.2.). Prior to inclusion to the study, all participants were confirmed as previous smokers, had no exacerbations within the last six weeks and no

other uncontrolled comorbidities, in accordance with the study inclusion and exclusion criteria.

Table 6.1 Demographic characteristics of patients at baseline.

<b>Variable</b>	<b>n=7</b>
Gender (M/F)	4/3
Age (years)	64±8
BMI	27.9±5.0
FEV <sub>1</sub> (% predicted)	52±18
FVC (% predicted)	103±13
FEV1/FVC (%)	40±13
IC (litres)	2.11±0.32
IC (% predicted)	85±24
TLC (% predicted)	122±18
FRC (% predicted)	154±34
DLco (% predicted)	43±17

M, male; F, female; BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in the first second; FVC, forced vital capacity; IC, inspiratory capacity; TLC, total lung capacity; FRC, functional residual capacity; DLco, transfer factor of the lung for carbon monoxide; WR, work rate, values presented as mean ± standard deviation (SD).

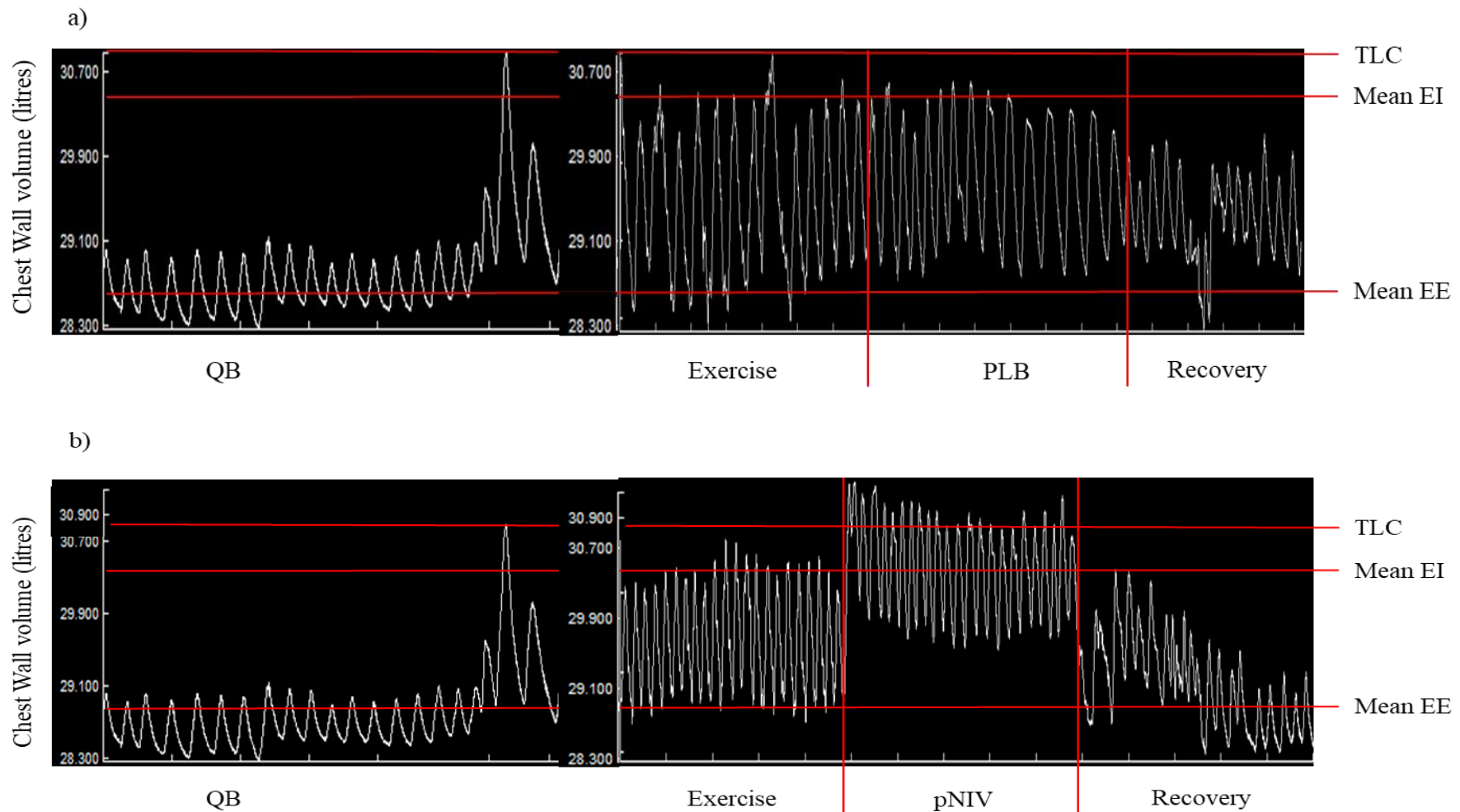
Table 6.2. Peak physiological variables at the limit of tolerance during cardiopulmonary exercise testing (CPET).

<b>Variable</b>	<b>n=7</b>
WR (Watts)	66±29
WR (% predicted)	57±18
VO <sub>2</sub> (ml/kg/min)	16.0±4.3
VO <sub>2</sub> (% predicted)	69±16
VCO <sub>2</sub> (ml/min)	1205.5±495.5
RQ	1.0±0.1
bf (breaths/min)	31±6
V <sub>T</sub> (litres)	1.4±0.4
V <sub>E</sub> (litres/min)	46.6±22.3
V <sub>E</sub> /VO <sub>2</sub> (%)	36.4±4.5
V <sub>E</sub> /VCO <sub>2</sub> (%)	37.8±4.4
V <sub>E</sub> /MVV (%)	1.0±0.3
ΔIC from rest (litres)	-0.6±0.3
V <sub>T</sub> /IC (%)	65±11
SpO <sub>2</sub> (%)	93±3
CO (litres/min)	12.9±3.0
HR (beats/min)	120±17
HR (% predicted)	108±17
SV (ml)	108±17
VO <sub>2</sub> /HR (ml/beat)	80±8
SBP (mmHg)	158±16
DBP (mmHg)	91±7
Dyspnoea (Borg 1–10)	4.0±0.8
Leg discomfort (Borg 1–10)	3.9±1.0

WR, work rate; VO<sub>2</sub>, oxygen uptake; VCO<sub>2</sub>, carbon dioxide expired; RQ, respiratory quotient for oxygen uptake; bf, breathing frequency; V<sub>T</sub>, tidal volume; V<sub>E</sub>, minute ventilation; MVV, Maximum voluntary ventilation; ΔIC, change from rest in inspiratory capacity; SpO<sub>2</sub>, arterial oxygen saturation; CO, cardiac output; HR, heart rate; SV, stroke volume; SBP, systolic blood pressure; DBP, diastolic blood pressure; Values are mean ± SD.

### **6.3.2. Total thoracoabdominal volume acute responses**

Figure 6.1b shows a typical experimental tracing of absolute thoracoabdominal volume measurements at baseline, over the last min of exercise, during the first minute of recovery with pNIV application and during the second minute of recovery breathing quietly. A gradual increase in end-expiratory thoracoabdominal volume took place during exercise, indicating thoracoabdominal dynamic hyperinflation. During acute application of pNIV both end-inspiratory and end-expiratory thoracoabdominal volumes further increased. During quiet breathing in the second minute of recovery, thoracoabdominal volumes regressed towards the levels seen at the end of exercise.



**Figure 6.1.** Pattern of thoracoabdominal kinematic response with a) PLB and b) pNIV at baseline (QB), during exercise, during application of PLB (a) and pNIV (b) and recovery. TLC, total lung capacity assessed by an inspiratory capacity manoeuvre; EI, end-inspiratory volume; EE, end-expiratory volume.

Exercise bouts induced comparable levels of end-expiratory thoracoabdominal dynamic hyperinflation prior to the use of the pNIV method (by:  $0.3 \pm 0.2$  litres) or the PLB technique (by:  $0.3 \pm 0.2$  litres). Figure 6.2a shows the average changes in thoracoabdominal volumes using the pNIV and PLB technique for all patients. During the first minute of recovery both pNIV and PLB application induced further increases in end-expiratory thoracoabdominal volumes, to a similar degree [pNIV: by  $0.3 \pm 0.4$  litres and PLB: by  $0.3 \pm 0.3$  litres ( $p=0.779$ )]. The pattern of change in total end-inspiratory chest wall volume in the first minute of recovery was different between pNIV application and the PLB technique. Application of pNIV further increased end-inspiratory volume (by  $0.3 \pm 0.2$  litres), whilst the PLB technique reduced end-inspiratory volume (by  $0.1 \pm 0.2$  litres) ( $p=0.035$ ) (Figure 6.2a & 6.3a). During the second minute of recovery thoracoabdominal end-inspiratory and end-expiratory volumes were not different after pNIV or PLB application but still significantly elevated compared to baseline (Figure 6.2a), thereby indicating incomplete recovery for both end-inspiratory and end-expiratory dynamic hyperinflation. Thoracoabdominal volumes at TLC were unchanged between baseline and exercise (Figure 6.2a).

### **6.3.3. Rib cage compartment acute responses**

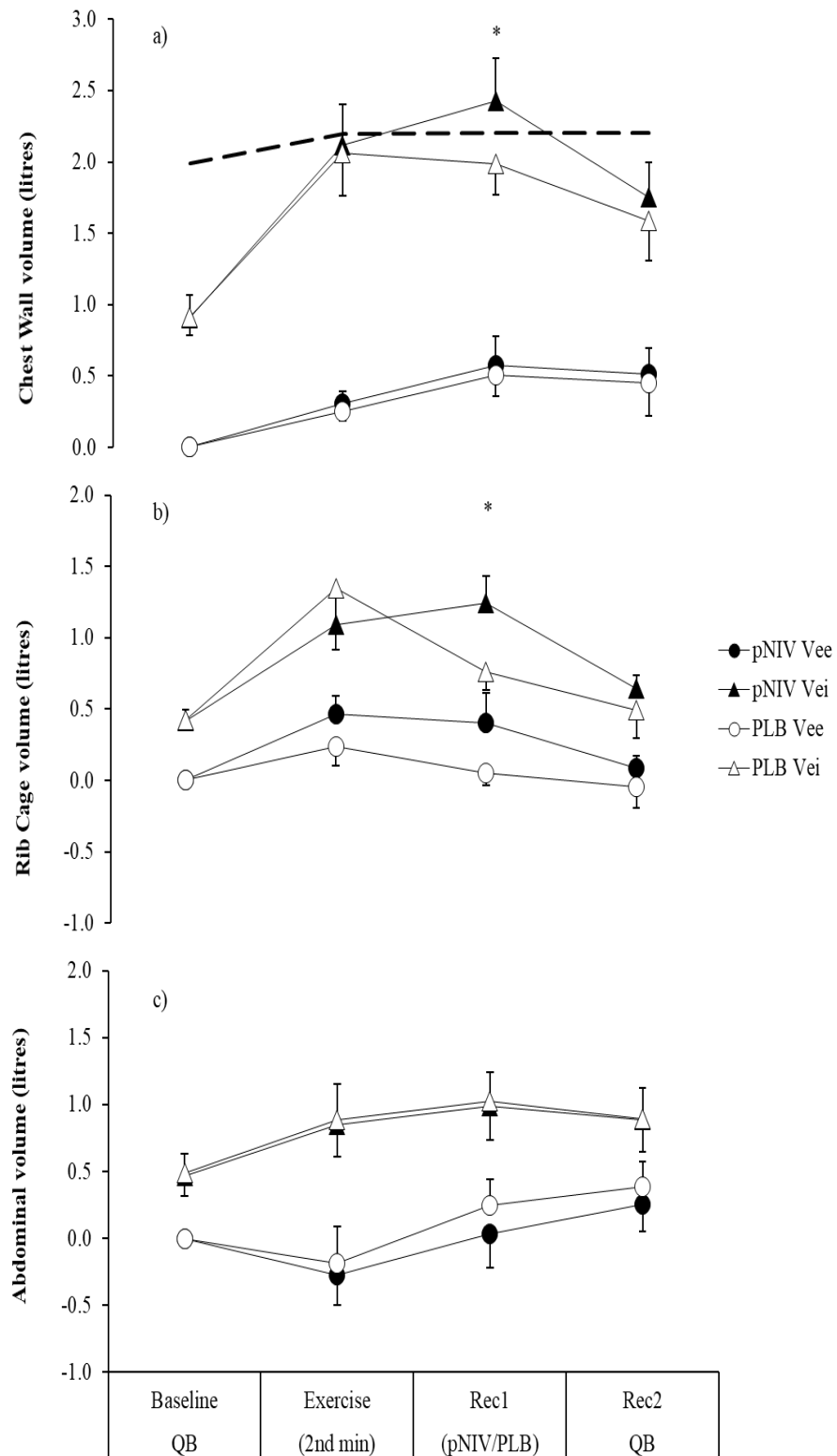
During the first minute of recovery following exercise, pNIV application did not induce any change in end-expiratory rib cage volume, indicating persistent end-expiratory rib cage dynamic hyperinflation. PLB application, however, reduced end-expiratory rib cage volume. In the first minute of recovery end-inspiratory chest wall volume increased with pNIV application (by  $0.2 \pm 0.2$  litres) but it was reduced with the PLB technique (by  $0.6 \pm 1.0$  litres) (Figure 6.2b & 6.3b). During the second minute of recovery rib cage end-inspiratory and end-expiratory volumes regressed towards

baseline but were still greater compared to baseline indicating persistent rib cage wall hyperinflation (Figure 6.3b).

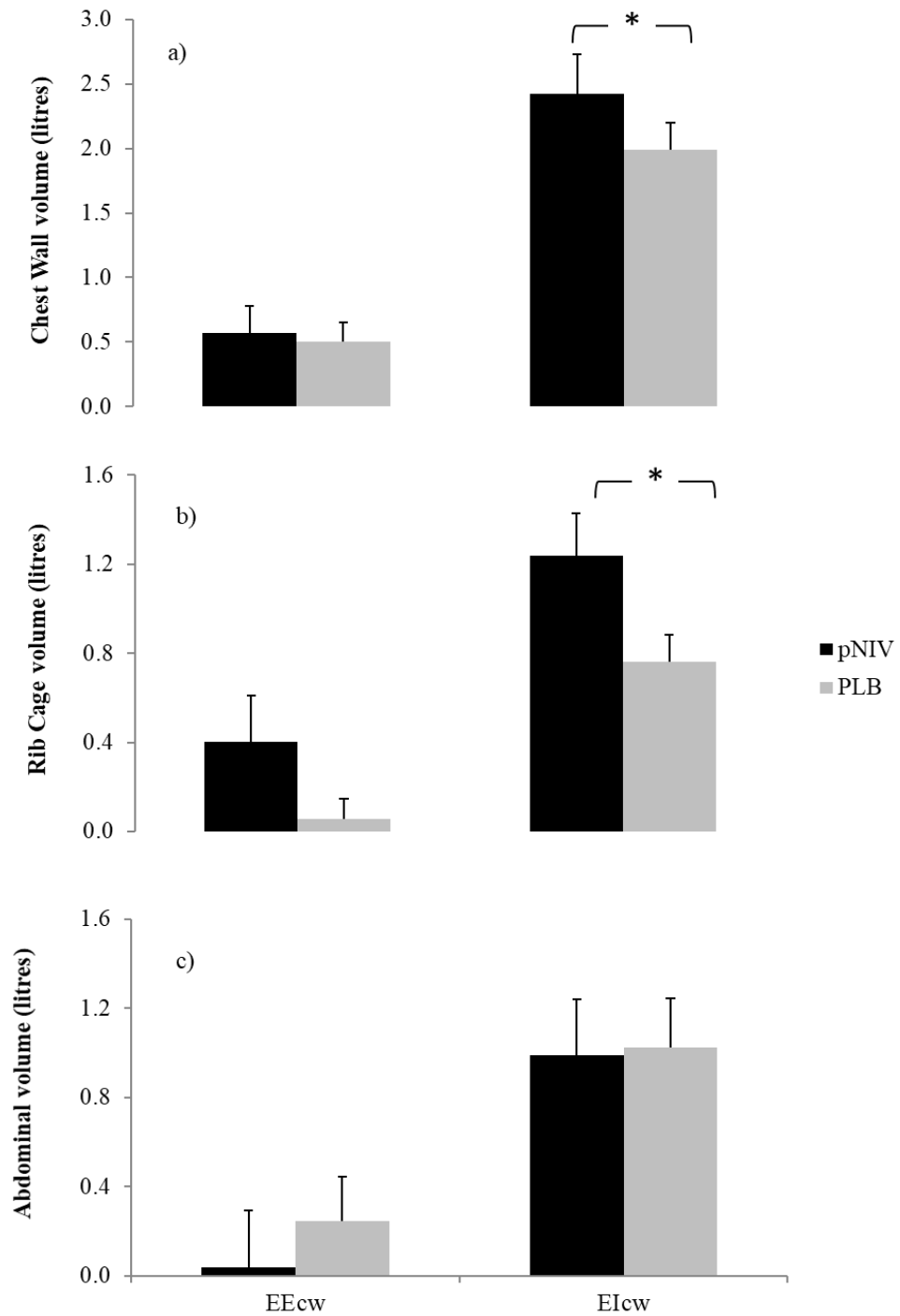
#### **6.3.4. Abdominal compartment volume acute responses**

During the first minute of recovery following exercise, both pNIV and PLB application induced an increase in end-expiratory volume [pNIV: by  $0.3 \pm 0.3$  litres and PLB: by  $0.4 \pm 0.5$  litres ( $p=0.137$ )], whilst the increase in end-inspiratory volume was similar during application of pNIV and PLB [pNIV: by  $0.1 \pm 0.2$  litres and PLB: by  $0.1 \pm 0.2$  litres ( $p=0.668$ )] (Figure 6.2c & 6.3c). During the second minute of recovery abdominal end-inspiratory and end-expiratory volumes were similar after pNIV or PLB but still greater compared to baseline, indicating persistent abdominal wall hyperinflation (Figure 6.2c).

Figure 6.3 shows that nearly identical end-expiratory dynamic hyperinflation with both pNIV and PLB application was due to greater end-expiratory rib cage hyperinflation with pNIV that was, however, compensated by greater end-expiratory abdominal recruitment. In contrast, greater end-inspiratory dynamic hyperinflation with pNIV compared to PLB was due to greater end-inspiratory rib cage dynamic hyperinflation but similar end-inspiratory abdominal volume.



**Figure 6.2.** Effect of the application of pNIV (closed symbols) compared to pursed lip breathing (open symbols) on a) total thoracoabdominal volume, b) rib cage volume and c) abdominal volume. End-expiratory volume (circles), end-inspiratory volume (triangles). Data are presented as mean  $\pm$  standard error of the mean (SEM). Dotted line in figure (a) indicates total lung capacity. \*  $p < 0.05$  pNIV vs pursed lip breathing (PLB).



**Figure 6.3.** Effect of the acute 1-min application of pNIV (black bars) compared to pursed lip breathing (grey bars) on: a) total thoracoabdominal, b) rib cage and c) abdominal end-expiratory (EEcw) and end-inspiratory (EIcw) volumes. Data are presented as mean  $\pm$  standard error of the mean (SEM). \*  $p < 0.05$  pNIV vs pursed lip breathing (PLB).



### **6.3.5. Breathing pattern**

Table 6.3 shows breathing pattern variables during use of the VitaBreath device compared to PLB. Compared to PLB, application of pNIV did not affect either inspiratory (pNIV:  $1.1 \pm 0.2$  seconds and PLB:  $1.0 \pm 0.2$  seconds,  $p=0.801$ ) or expiratory time (pNIV:  $1.7 \pm 0.3$  seconds and PLB:  $1.7 \pm 0.4$  seconds,  $p=0.726$ ), neither total breathing cycle time (pNIV:  $2.8 \pm 0.4$  seconds and PLB:  $2.7 \pm 0.4$  seconds,  $p=0.821$ ). However, application of pNIV compared to PLB induced greater minute ventilation (pNIV:  $43.0 \pm 20.0$  litres/min and PLB:  $37.3 \pm 16.0$  litres/min,  $p=0.049$ ), secondary to increased tidal volume (pNIV:  $1.9 \pm 0.8$  litres and PLB  $1.5 \pm 0.4$  litres,  $p=0.178$ ), whilst breathing frequency was similar between the two breathing modalities (pNIV:  $23 \pm 4$  breaths/min and PLB:  $25 \pm 6$  breaths/min,  $p=0.658$ ). *Interestingly, use of pNIV compared to PLB induced greater inspiratory (pNIV:  $1.9 \pm 0.8$  litres/sec versus PLB:  $1.7 \pm 0.6$  litres/sec,  $p=0.034$ ) and expiratory flow rates (pNIV:  $1.2 \pm 0.6$  litres/sec versus PLB:  $1.0 \pm 0.5$  litres/sec,  $p=0.044$ ).* On average breathlessness scores tended to be lower with pNIV compared to the PLB technique (by:  $0.3 \pm 0.5$ ) and leg discomfort was similar between pNIV ( $2.6 \pm 0.8$  units) and PLB ( $2.5 \pm 0.9$ ).

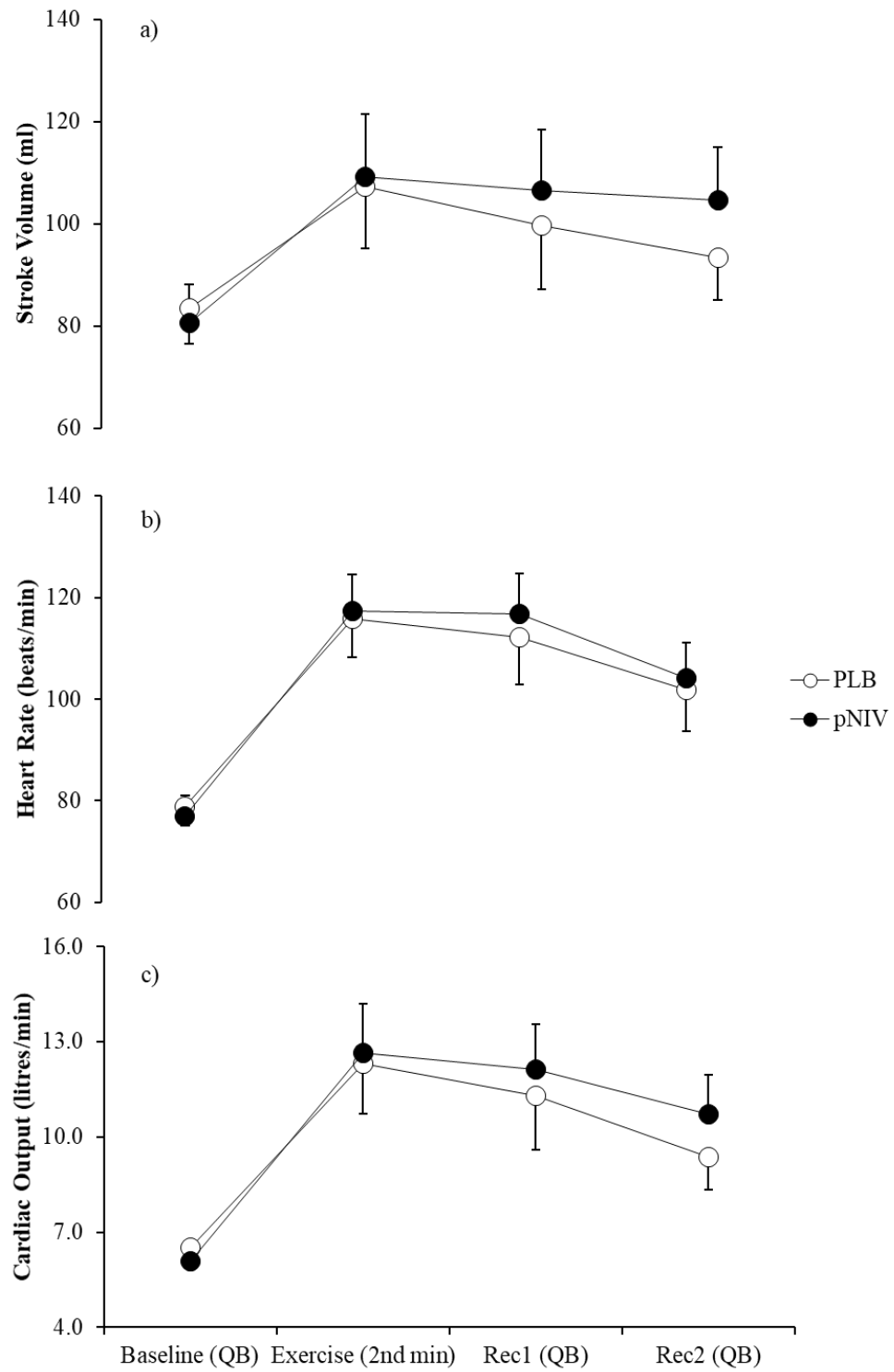
Table 6.3. Effect of 1-min pNIV application following exercise on breathing pattern and circulatory responses

<b>Variable</b>	<b>pNIV</b>	<b>PLB</b>	<b>p</b>
bf (breaths/min)	23±4	25±6	0.658
V <sub>T</sub> (litres)	1.9±0.8	1.5±0.4	0.178
V <sub>E</sub> (litres/min)	43.0±20.0	37.3±16.0	0.059
Ti (seconds)	1.1±0.2	1.0±0.2	0.801
Te (seconds)	1.7±0.3	1.7±0.4	0.726
Ttot (seconds)	2.8±0.4	2.7±0.4	0.821
SV (ml)	107±34	100±36	0.240
HR (beats/min)	117±23	112±27	0.055
CO (litres/min)	12.1±4.1	11.3±4.8	0.204

Data are presented as mean±SD; pNIV, portable non-invasive ventilation; PLB, pursed lip breathing; bf, breathing frequency; V<sub>T</sub>, tidal volume; V<sub>E</sub>, minute ventilation; Ti, inspiratory time; Te, expiratory time; Ttot, total duty cycle; SV, stroke volume; HR, heart rate; CO, cardiac output.

### **6.3.6. Central haemodynamic acute responses**

Compared to pursed lip breathing, 1-min application of pNIV induced greater SV [by 7±14 ml (p=0.240)], HR [by 5±5 beats/min, p=0.055] and CO [by 0.8±1.5 litres/min, p=0.204] (Figure 6.4). Following 1-min application of pNIV SV, HR and CO remained elevated compared to pursed lip breathing [by 11±11 ml (p=0.032)], [by 2±6 beats/min (p=0.343)] and [by 1.3±1.6 litres/min (p=0.069)], respectively (Figure 6.4).

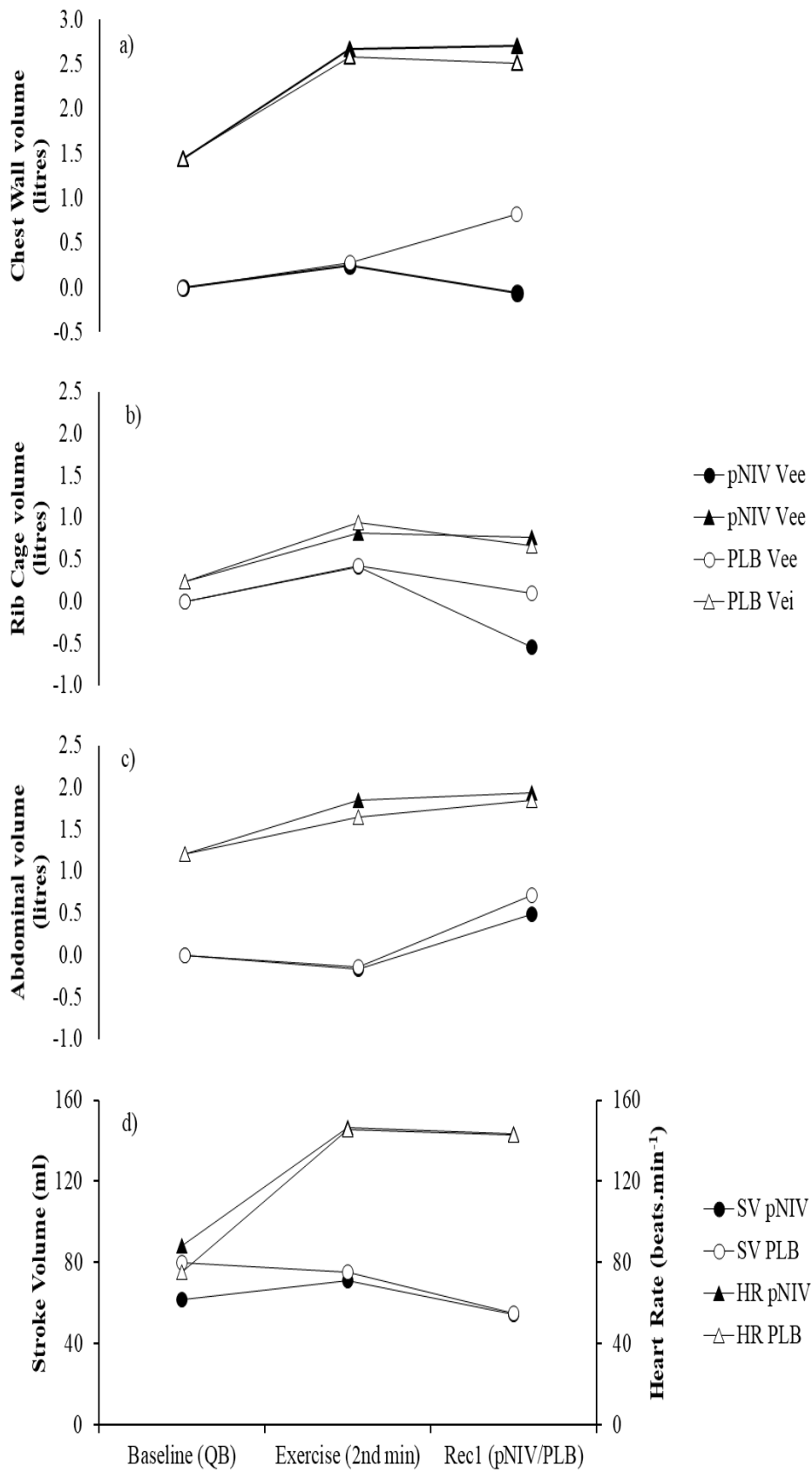


**Figure 6.4.** Effect of 1-min application of pNIV (closed symbols) compared to pursed lip breathing (open symbols) on a) stroke volume, b) heart rate and c) cardiac output. Data are presented as mean  $\pm$  standard error of the mean (SEM). \*  $p < 0.05$  pNIV vs pursed lip breathing (PLB).

### **6.3.7. Different patterns of recovery of dynamic hyperinflation in COPD**

#### **Example A: Improved dynamic hyperinflation with pNIV (responder)**

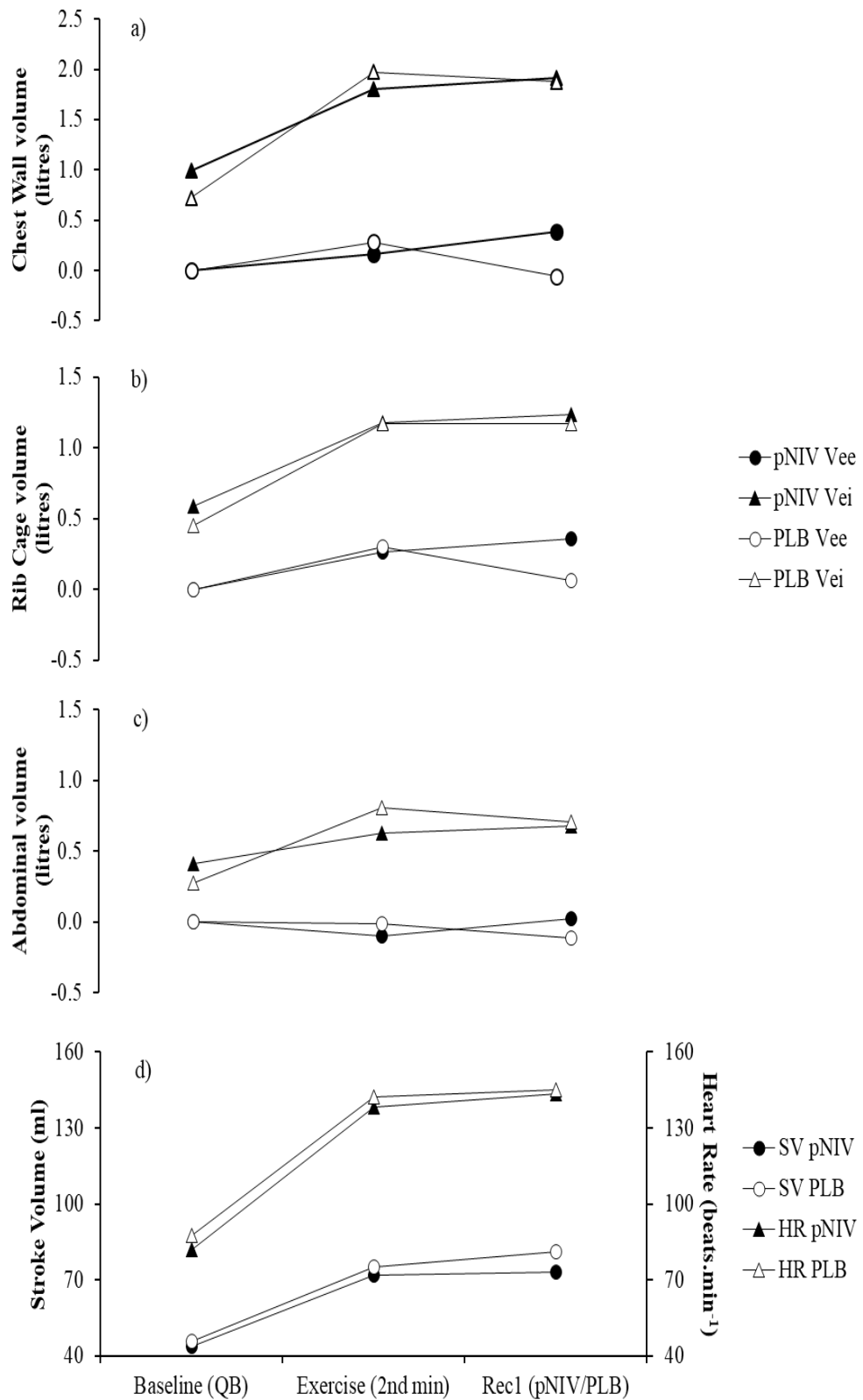
Figure 6.5 presents an example of a patient who reduced the degree of end-expiratory dynamic hyperinflation with the application of pNIV whilst with PLB no improvement was exhibited (Figure 6.5a). This pattern was seen in 2/7 patients identified as responders in Chapter 5. The difference in the pattern of end-expiratory dynamic hyperinflation was due to greater end-expiratory rib cage and abdominal activation (Figure 6.5b & c). Despite the greater reduction of end-expiratory rib cage and abdominal volumes with pNIV, stroke volume and heart rate responses were not different with the application of pNIV or the PLB technique. (Figure 6.5d).



**Figure 6.5.** Effect of 1-min application of pNIV (closed symbols) compared to pursed lip breathing (open symbols) on: a) thoracoabdominal, b) rib cage and c) abdominal end-expiratory volume (circles) and end-inspiratory volume (triangles) of the total thoracoabdominal volume and d) stroke volume (circles) and heart rate (triangles).

Example B: worsening of dynamic hyperinflation with pNIV but not PLB (non-responder)

Figure 6.6 presents an example of a patient who experienced a greater degree of end-expiratory dynamic hyperinflation with application of pNIV, whilst with the PLB technique end-expiratory dynamic hyperinflation was abolished. This pattern was seen in 2/7 patients identified as non-responders in Chapter 5. As presented in figure 6.6b application of pNIV increased end-expiratory rib cage volume and end-expiratory abdominal volume. This pattern differed in comparison to the responders (example A), as both compartments (rib cage and abdominal) were further hyperinflated with pNIV compared to PLB (Figures 6.6b & c). Despite greater compartmental hyperinflation with pNIV, stroke volume and heart rate responses were similar between pNIV and PLB applications (Figure 6.6d).

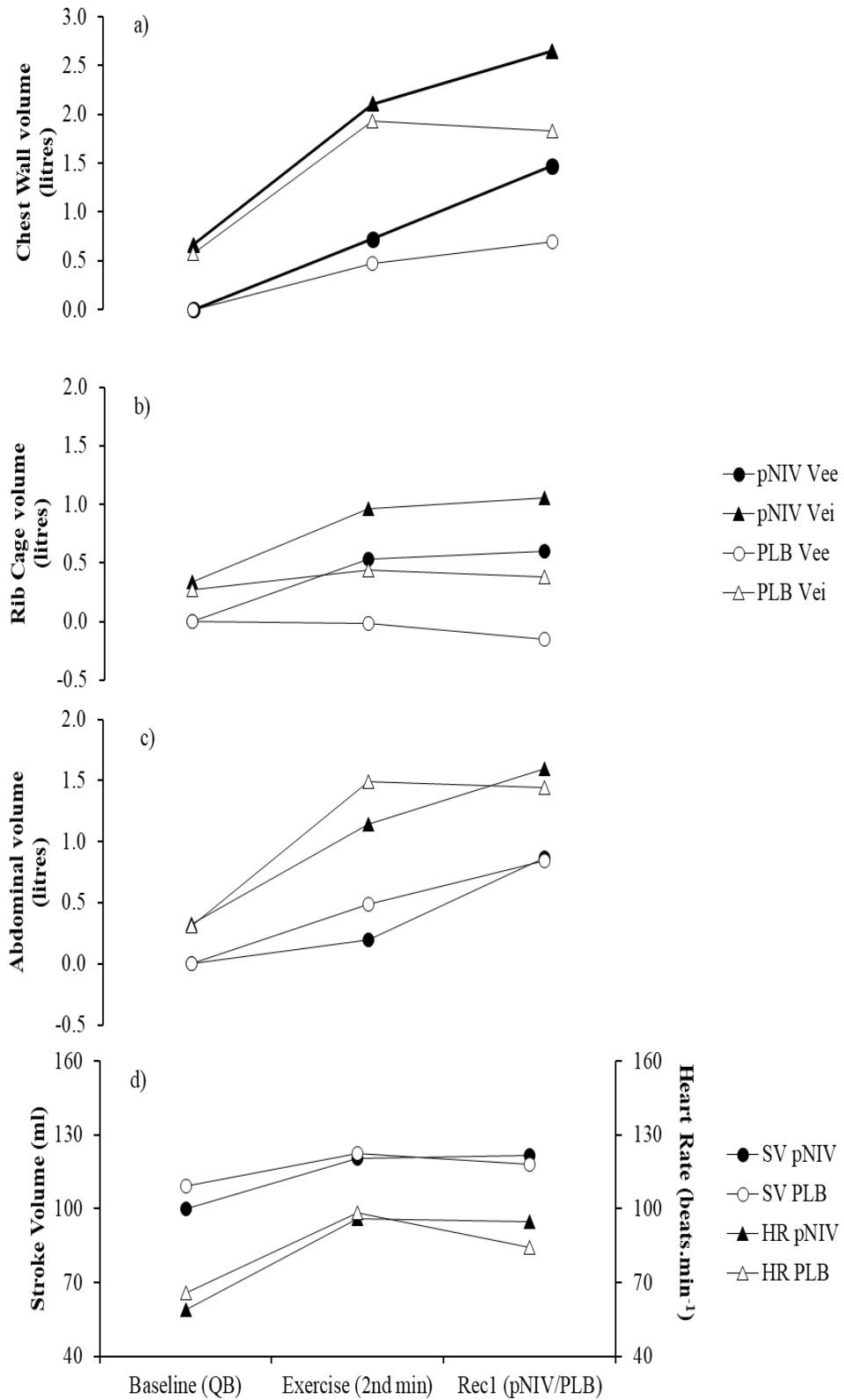


**Figure 6.6.** Effect of 1-min application of pNIV (closed symbols) compared to pursed lip breathing (open symbols) on: a) thoracoabdominal, b) rib cage and c) abdominal end-expiratory volume (circles) and end-inspiratory volume (triangles) of the total thoracoabdominal volume and d) stroke volume (circles) and heart rate (triangles).

### Example C: worsening of DH with both pNIV and PLB

Figure 6.7 presents the results of a patient who experienced a greater degree of end-expiratory and end-inspiratory dynamic hyperinflation with both pNIV and PLB application. However dynamic hyperinflation was greater with pNIV compared to PLB, mainly due to greater end-inspiratory and end-expiratory rib cage hyperinflation (Figures 6.7b & c). This pattern was seen in 3/7 patients, which was not identified as a response pattern in Chapter 5. Stroke volume was similar between the two methods, albeit unchanged from the end of exercise in both cases (Figure 6.7d). In contrast, heart rate recovered to a greater extent with the application of PLB compared to pNIV application, where heart rate remained at similar levels as during exercise (Figure 6.7d).





**Figure 6.7.** Effect of 1-min application of pNIV (closed symbols) compared to pursed lip breathing (open symbols) on: a) thoracoabdominal, b) rib cage and c) abdominal end-expiratory volume (circles) and end-inspiratory volume (triangles) of the total thoracoabdominal volume and d) stroke volume (circles) and heart rate (triangles).

#### **6.4.Discussion**

Compared to the PLB technique, pNIV application in patients with COPD was associated with increased end-inspiratory and end-expiratory thoracoabdominal volumes. This finding is justified by the fixed IPAP and EPAP (18 and 8 cm H<sub>2</sub>O, respectively) provided by the VitaBreath device, which has also been reported with other NIV methods in healthy subjects [242, 298, 299] and in patients with COPD [178, 300, 301]. Furthermore, pNIV application was associated with increased tidal volume, minute ventilation and inspiratory and expiratory flow rates. The VitaBreath device is designed to unload the inspiratory muscles during inspiration and keep the airways open during expiration. Hence, greater expiratory flow rates reported in the present study are indicative of reduced expiratory flow limitation and more adequate lung emptying. Interestingly, breathlessness tended to be lower after pNIV application compared to the PLB technique. However, on average increased expiratory flow rates and reduced breathlessness were not accompanied by reduced end-expiratory thoracoabdominal volumes, when using the pNIV device compared to PLB. The discrepancy is most likely due to the different patterns of hyperinflation response seen in the population studied, but also due to the fact that the optoelectronic plethysmography imaging method captures changes in thoracoabdominal and not only lung volumes, including gas volume, gas compression and blood volumes [125]. In the present study, greater cardiac output was reported with the pNIV device compared to the PLB technique, possibly justifying the increased blood volume within the thoracoabdominal cavity. Furthermore, the effect of pNIV with fixed IPAP and EPAP would be expected to induce greater rates of gas compression compared to PLB, and thus greater thoracoabdominal volumes.

Acute application of pNIV in 7 out of 24 patients originally recruited and presented in Chapter 5, revealed different patterns of response in end-expiratory and end-

inspiratory dynamic hyperinflation, namely improved dynamic hyperinflation with pNIV as in example A (seen in 2/7 patients), and worsened dynamic hyperinflation as in examples B and C that was seen in 5/7 patients. In respect to the latter category two different response patterns were further identified namely: i) worsened dynamic hyperinflation with pNIV compared to PLB as presented in example B and ii) worsened dynamic hyperinflation with both pNIV and PLB as presented in the typical example C. Regardless of the pattern of change in end-expiratory and end-inspiratory thoracoabdominal hyperinflation, no circulatory adverse effects were demonstrated in any of the patients tested. Absence of adverse circulatory effects with the use of the pNIV method is in accordance with the findings in healthy individuals, thereby suggesting that the brief use of pNIV is insufficient to adversely impact on circulation [242].

Furthermore, the findings of the present study confirm the different patterns of end-expiratory dynamic lung hyperinflation reported in Chapter 5 and the findings in healthy individuals, where acute application of pNIV increased both end-expiratory and end-inspiratory thoracoabdominal volumes both during normal breathing and following hyperventilation [242].

The results of the present study are in accordance with the existing literature, as other studies have previously reported that application of non-invasive ventilation with or without additional PEEP increases end-expiratory lung volumes in patients with COPD [178, 300, 301]. The mean average PEEPi from a number of studies was 3.4 cmH<sub>2</sub>O as reported in the review by Kallet and Diaz [175], whilst application of external PEEP of 5 cmH<sub>2</sub>O caused an average reduction of 1.8 cmH<sub>2</sub>O in PEEPi [175]. In contrast, application of IPAP of 15 cmH<sub>2</sub>O and zero PEEPe caused an increase in PEEPi by 1.8 cmH<sub>2</sub>O [302] and thus increased end-expiratory lung volume [178, 300]. Application of

IPAP (18 cmH<sub>2</sub>O) with pNIV, most likely increased PEEPi causing acutely end-expiratory thoracoabdominal hyperinflation in this cohort of patients. The increase in end-expiratory lung volume seems to be the result of mechanical impairment of the respiratory muscles [178, 301]. According to the length-tension relationship, the capacity of the inspiratory muscles to generate power decreases with increased end-expiratory lung volume, owing to the fact that inspiratory muscles become shorter. Furthermore, according to Laplace relationship, the flatter the diaphragm becomes as result of increased lung volume, the less pressure it generates for any given diaphragmatic tension [303, 304]. In contrast to the majority of the literature reporting increased tidal volume and reduced breathing frequency [176-182], application of the VitaBreath device, in the present study, resulted in increased ventilation due to greater tidal volume compared to PLB, whilst breathing frequency was not different to PLB [183, 184, 189, 300]. The breathing pattern adopted during the application of pNIV increased ventilation and thus induced greater end-inspiratory thoracoabdominal dynamic hyperinflation compared to the end of exercise.

Although dynamic hyperinflation is a commonly reported manifestation in patients with COPD, not all patients exhibit a homogenous pattern of hyperinflation during exercise. In fact, a study by Aliverti and colleagues [123] reported two different patterns of end-expiratory chest wall volume regulation during peak exercise in patients with COPD, namely hyperinflators (exhibiting exercise-induced dynamic hyperinflation) and euvolumics (not exhibiting exercise-induced dynamic hyperinflation) [123]. The distinguishing characteristic of the two different patterns of chest wall volume regulation was the greater increase in end-expiratory and end-inspiratory volume of the rib cage compartment in the hyperinflators compared to the euvolumics and the greater reduction of end-expiratory volume of the abdominal compartment in the euvolumics

compared to hyperinflators [123]. However, not all studies agree with these findings as Vogiatzis and colleagues [85] reported that patients with COPD fall into two main categories, namely those who progressively hyperinflate during exercise (early hyperinflators) and those who hyperinflate only during the late stages of exercise (late hyperinflators) [85]. In the present study, all patients hyperinflated progressively during exercise and the majority remained hyperinflated after two minutes of recovery with either pNIV or PLB application. These findings are in agreement with the literature, as it has been reported that end-expiratory chest wall volume takes at least five minutes to recover following exercise in patients with COPD [85]. However, the 3 different dynamic hyperinflation patterns reported in the present study when pNIV was applied suggests that some patients exhibited an evolumic breathing pattern, whilst others demonstrated a hyperinflator pattern during application of pNIV according to Aliverti and colleagues [123]. Moreover, although all patients hyperinflated during exercise, the different patterns of respiratory muscle kinematic response recorded when the VitaBreath device was applied indicate greater recruitment of the expiratory abdominal muscles combating dynamic hyperinflation just like the evolumic pattern described by Aliverti and colleagues [123]. It has been postulated that such a contraction is beneficial because lengthening of the diaphragm results in greater generation of negative pleural pressure (better position of the length-tension relationship) [64, 65]. Thus, adopting such a breathing pattern could assist the patient to fight against the provided inspiratory and expiratory pressures.

The VitaBreath device provides fixed high expiratory pressures. Thus, PEEP generated by the VitaBreath device may be excessive to overcome the emphysematous airway changes observed in some patients. Although the PEEP provided by the device is necessary for preventing airway collapse and subsequently improving expiratory

flow, it will not be beneficial if it is not matching the individual patient's intrinsic PEEP [305]. Thus, the expiratory pressure provided by the VitaBreath device is likely to be suboptimal for some patients not facilitating reduced end-expiratory thoracoabdominal volume, likely due to the inability of the device to individualise the aforementioned pressures. Furthermore, when there is a mismatch between the PEEP<sub>i</sub> and PEEP<sub>e</sub> there is increased risk of patient-ventilatory asynchronies to occur [207], which could lead to increased work of breathing and greater mismatch between alveolar ventilation and perfusion [283]. Thus, the ability of the patient to synchronise with the device might reduce the effectiveness of the ventilator.

Previous studies have reported that application of NIV in patients with COPD at rest reduces cardiac output [198, 200], whilst similar findings are reported in patients with CHF [196, 199, 201, 306]. The short application of pNIV (1-min) may have prevented adverse circulatory effects, as opposed to the existing literature where NIV application exceeded 5 minutes, resulting in adverse circulatory responses [196, 198-201, 306]. Interestingly, the study by Baratz and colleagues in patients with CHF reported that in 7 out of 13 patients a reduction in left ventricular afterload without a change in the systemic arterial pressure and arterial oxygen content resulted in increased cardiac output [199]. In the present study stroke volume and cardiac output were not adversely affected by the application of the VitaBreath device. In fact, cardiac output was slightly greater when pNIV was applied compared to PLB, due to both increased stroke volume and heart rate. The respiratory kinematic findings of this study indicate increased rib cage and abdominal wall muscle recruitment, most likely to accommodate the increased IPAP and EPAP, which could lead to increased circulatory responses.

Moreover, greater activation of the respiratory muscles with pNIV, as inferred by the rib cage and abdominal compartmental analysis in the present study, would be expected

to increase respiratory muscle energy requirement, potentially mitigating the impaired venous return caused by increased IPAP and EPAP. Although a number of studies report a reduction in diaphragmatic and oesophageal pressures with NIV, indicating reduced work of breathing [177-181, 183-186, 302, 307], a recent study that applied high levels of PEEP (10 and 15 cmH<sub>2</sub>O) found an increase in the parasternal and sternocleidomastoid muscle activation, respectively [308]. The VitaBreath device delivers higher inspiratory and expiratory pressures (18 and 8 cm H<sub>2</sub>O, respectively) compared to those usually reported in the literature [24, 33, 42, 44, 49, 128, 175, 177-181, 183-186, 209, 210, 271, 302, 307]. The high pressures further increased dynamic hyperinflation following exercise which justify an increase in respiratory muscle activation as described above, in order to accommodate the increase in breathing volumes; this extra volume regulation would be expected to increase the energy requirement of the respiratory muscles and thus maintain stroke volume and cardiac output at high levels during recovery compared to the end of exercise.

The present study has some limitations. The main limitation as in the previous chapters was that the VitaBreath device provides fixed inspiratory and expiratory pressures and thus it was not possible to individualise the pressures for each patient. In addition, although opto-electronic plethysmography is a more accurate method to detect breath-by-breath changes in thoracoabdominal volumes compared to inspiratory capacity manoeuvres, thoracoabdominal volumes include not only lung volumes but also blood volumes and compressed gas volumes. Thus, the failure to detect differences in end-expiratory thoracoabdominal volumes between the two breathing modalities could be due to differences in blood volume (increased cardiac output) and gas compression with excessive EPAP and IPAP.

Application of pNIV provided by the VitaBreath device acutely worsened end-inspiratory and end-expiratory dynamic hyperinflation following cessation of exercise in a subset of patients with COPD, but conversely lessened end-expiratory dynamic hyperinflation in some patients. This pattern of response was also seen in Chapter 5, which identified DH responders and DH non-responders, however in the present study only 7 out of the original 24 patients agreed to participate. Nevertheless, the clinical implications described in Chapter 5 also apply in this study, as it is apparent that one size does not fit all patients. Therefore, prior to prescription of any NIV device to assist activities of daily living, the health care professional should investigate whether the device improves or worsens the patient symptoms.

### **6.5. Conclusions**

As with any pharmacological or non-pharmacological intervention in COPD, it was shown that the thoracoabdominal response pattern to pNIV application was variable among patients. Patients who could afford expiratory abdominal muscle recruitment, exhibited reduced end-expiratory thoracoabdominal dynamic hyperinflation with the pNIV method without concurrent adverse circulatory effects. Patients not demonstrating expiratory abdominal recruitment exhibited increased thoracoabdominal hyperinflation. Regardless of the thoracoabdominal response pattern identified in the present study, an important limitation of the VitaBreath device is that inspiratory and expiratory pressures were fixed; therefore adjustment of the aforementioned pressures was not possible in patients exhibiting different breathing patterns. This is distinct to other studies applying NIV in COPD, where the level of provided pressure is individualised to maximise the benefit of use. This represents a very important disadvantage of the VitaBreath device, which clearly mitigated the beneficial impact it had on some patients.



The findings of this study suggest that, although the VitaBreath device presents with promising results and favourable practical benefits, it is not effective in improving thoracoabdominal dynamic hyperinflation in all COPD patients. It is therefore important that clinicians investigate whether the VitaBreath or any other NIV device improves or exacerbates symptoms on an individual basis. This will enable the device to be implemented both clinically and cost effectively, to ensure patients are able to reap the desired benefits from the device, and subsequently improve their overall quality of life. Considering the variation in response reported in Chapters 5 and 6, it is important considering that clinicians need to assess the response to pNIV on an individual basis.

Moreover, the VitaBreath device was designed to be used during activities of daily living, in order to relieve breathlessness. Thus, it is important to investigate patient perceptions of the usability and applicability of the device when used during daily physical activities. Accordingly, Chapter 7 reports on usability and applicability of the device, as well as perceived symptoms when COPD patients used the VitaBreath during their daily physical activities.

## **7. Acceptability, comfort and usability of portable non-invasive ventilation during activities of daily life in patients with COPD**

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### **7.1. Introduction**

Patients with COPD exhibit lower exercise capacity and reduced daily physical activity, reflected by lower daily steps and intensity of movement, compared to healthy age matched individuals [265, 309-315]. Interestingly, lower levels of physical activity are associated with a greater risk of exacerbation-related hospitalisations [265, 316-325] and mortality [265, 324-326]. Accordingly, increasing levels of daily physical activity is of great importance in this population.

Reduced exercise capacity and daily physical activity is often the result of intolerable breathlessness when performing different activities [262], secondary to a host of pathophysiological factors, including ventilatory constraints, gas exchange impairment, cardiovascular and metabolic dysfunction [18]. Different strategies have been employed to reduce dynamic hyperinflation, as well as increase exercise tolerance and daily physical activity including bronchodilators, supplemental oxygen, inspiratory muscle training, heliox supplementation, pulmonary rehabilitation and non-invasive ventilation (NIV) [22-24, 28, 128, 327-329]. However, apart from bronchodilators and supplemental oxygen therapy which are commonly used in standard care, non-invasive ventilation and heliox supplementation have poor applicability for ambulatory use, mainly due to the difficulty of using the equipment during activities of daily living [49] and high cost [28], respectively. Moreover, although oxygen supplementation is easy to apply during daily life [330, 331], sometimes it is inadequate to meet the needs of patients with significant ventilatory constraints [332-334].

NIV is domiciliary used mainly to treat obstructive sleep apnoea, central sleep apnoea and hypoventilation in the form of continuous positive airway pressure (CPAP). CPAP is usually applied via a nasal, oral or a combined method (i.e. mask). However, the adherence to commonly used NIV methods is very poor and is associated with the disease severity, the pressure level, the type of interface, and the duration of the treatment which is usually during sleeping hours [335-337].

Nevertheless, due to recent technological developments, devices that are easy to operate during daily physical activities, including portable non-invasive ventilators have been developed [338]. However, there is not enough evidence in the literature investigating the applicability and adherence to these interventions during activities of daily life. In a study investigating ease of use, comfort and preference of a non-invasive open ventilator (NIOV), patients felt less breathless, had more energy when performing tasks and felt more comfortable when using the NIOV device, compared to oxygen supplementation within a five days period [339].

This dissertation has shown that application of pNIV via use of the VitaBreath device increased exercise tolerance in patients with COPD by reducing breathlessness secondary to reduced dynamic hyperinflation[20]. However, given that the main purpose of pNIV is to be easy and comfortable to use during daily life by patients with COPD, it was also important to investigate the adherence with and the applicability of the use of the VitaBreath device during activities of daily life. Thus, in collaboration with Philips Respironics a questionnaire (Appendix E) was developed to assess adherence and applicability of the VitaBreath device when patients used the device during daily activities.

Therefore, the purpose of this study was to investigate patient adherence with pNIV, as well as the effects of pNIV on anxiety, symptom burden and the ability to perform activities of daily living [20]. Accordingly, the frequency and usability of the VitaBreath device, alongside symptom burden and attitudes towards the device in the 12 weeks following completion of the laboratory based study described in Chapter 5 were also assessed within the present dissertation [20].

### **7.1.1. Main outcomes**

#### **7.1.1.1. Primary Outcome**

The primary outcome of the study was to assess patient adherence to using the device during activities of daily living in patients with COPD.

#### **7.1.1.2. Secondary Outcomes**

Secondary outcomes included self-reported anxiety, symptom burden and ability to perform daily physical tasks.

## **7.2. Methods**

### **7.2.1. Study design**

This was a survey research study assessing adherence to pNIV during activities of daily living. Adherence to the device was assessed using a questionnaire provided by Philips (Appendix E), which was administered over the phone. Following completion of the three visits of the study presented in Chapter 5, all 24 patients were given a VitaBreath device to use at home as they wished. Use of, and perceived benefit from, the VitaBreath device was examined at 2 and 12 weeks following completion of the first experimental study of the present thesis [20]. The survey included questions on symptom burden, ability to perform daily tasks and perceived benefit from the device

(Appendix E) [20]. Patients received advice on how to use the device for symptomatic relief during exertion, but the frequency of use was not prescribed [20].

### **7.3.Results**

#### **7.3.1. Patient characteristics**

Baseline characteristics of patients that participated in the follow up study are presented in table 7.1. Patients exhibited severe airway obstruction and lung hyperinflation at rest. Five (20.8%) of the patients were current smokers, with 14 (58.3%) having been admitted to hospital for an exacerbation of COPD (ECOPD) in the past 12 months. The median number of ECOPD (hospital or community managed) in the past 12 months was 2 (1–4.75). The median extended MRC dyspnoea score (eMRCD) was 4 (3–4) [20].

Table 7.1. Demographic characteristics of patients at baseline.

<b>Variable</b>	<b>n=24</b>	<b>DH Non- Responders</b>	<b>DH Responders</b>
Gender (M/F)	10/14	4/4	6/10
Age (years)	67±8	67±3	67±2
BMI	26.3±6.9	24.4±3.1	27.2±1.5
FEV <sub>1</sub> (% predicted)	46±18	40±8	49±4
FVC (% predicted)	89±20	86±7	91±5
FEV1/FVC (%)	38±13	37±5	43±3
IC (litres)	2.00±0.67	1.74±0.26	2.12±0.16
IC (% predicted)	79±22	70±7	84±6
TLC (% predicted)	130±24	135±6	128±7
FRC (% predicted)	173±44	188±14	166±12
DLco (% predicted)	37±21	33±11	40±5

BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in the first second; FVC, forced vital capacity; IC, inspiratory capacity; TLC, total lung capacity; FRC, functional residual capacity; DLco, transfer factor of the lung for carbon monoxide; M, male; F, female; values are mean ± standard error of the mean (SEM) [20].

### **7.3.2. Use and Perceived Benefits of the VitaBreath Device**

#### **7.3.2.1. Adherence and usability of the VitaBreath device**

When comparing responses at 2 and 12 weeks, it became apparent that there was no attrition in the frequency of use of the device in DH responders ( $p=1.000$ ) and DH non-responders ( $p=0.317$ ). At 12 weeks, 23/24 (15/16 DH responders and 8/8 DH non-responders) patients continued to use the device at least once per week, and 16/24 (11/16 DH responders and 5/8 DH non-responders) used the device on a daily basis [20]. Whilst both DH responders and DH non-responders described the VitaBreath as easy to use (good or better), most DH non-responders described its portability as poor or fair (87.5%). In contrast, 50% of DH responders described its portability as poor or fair. Additionally at 12 weeks, DH non-responders and DH responders reported a similar impact of the VitaBreath device on their quality of life, assessed using a 5-point likert scale [3.5 (1.5-4.75); 3.5 (2.25-5),  $p=0.665$ ]. At 12 weeks, the median (IQR) of likelihood to recommend the VitaBreath to others was respectively 9.5 (IQR: 7.5–10) and 10 (6.25-10) in DH non-responders and DH responders. However, the likelihood to purchase the device was respectively 3 (1–4) and 2.5 (1.25-5) on a 10-point likert scale for DH non-responders and DH responders (Table 7.2) [20]. Finally, patients reported that they were unlikely to buy the device online, even if they could afford it [DH non-responders: 1.5 (1-3.75); DH responders 2 (1-3),  $p= 0.803$ ).

Table 7.2. Frequency of use of the VitaBreath device in responders and non-responders.

Question	DH Non-Responders			DH Responders		
	Two weeks of VitaBreath	Twelve weeks of VitaBreath	<i>p</i> -Value	Two weeks of VitaBreath	Twelve weeks of VitaBreath	<i>p</i> -Value
How often do you use VitaBreath?						
Several Times a day	6 (75%)	5 (62.5%)	0.317*	11 (68.8%)	10 (62.5%)	1.000*
Once a day	0 (0%)	0 (0%)		1 (6.3%)	1 (6.3%)	
Couple times a week	1 (12.5%)	1 (12.5%)		2 (12.5%)	4 (25.0%)	
Once a week	1 (12.5%)	1 (12.5%)		1 (6.3%)	1 (6.3%)	
Not at all	0 (0%)	1 (12.5%)		1 (6.3%)	1 (4.2%)	
How would you rate VitaBreath for ease of use?						
Excellent	n/a	2 (25%)	n/a	n/a	6 (37.5%)	0.845 <sup>\$#</sup>
Very Good		4 (50%)			5 (31.3%)	
Good		2 (25%)			5 (31.3%)	
Fair		0			0	
Poor		0			0	
How would you rate VitaBreath for portability?						
Excellent	n/a	0	n/a	n/a	3 (18.8%)	0.028 <sup>\$#</sup>
Very Good		1 (12.5%)			4 (25%)	
Good		0			1 (6.3%)	
Fair		2 (25%)			5 (31.3%)	
Poor		5 (62.5%)			3 (18.8%)	
Would you say that VitaBreath has impacted your quality of life?						
Scale 1 (No difference) to 5 (Tremendous difference)	n/a	Median 3.5 (1.5-4.75)		n/a	Median 3.5 (2.25-5)	0.655 <sup>\$#</sup>

Question	DH Non-Responders			DH Responders		
	Two weeks of VitaBreath	Twelve weeks of VitaBreath	<i>p</i> -Value	Two weeks of VitaBreath	Twelve weeks of VitaBreath	<i>p</i> -Value
Given your recent experience with VitaBreath, how likely is it that you would recommend VitaBreath to a friend or colleague, or other people with COPD? <sup>§</sup>  1 (Not at all likely) to 10 (Extremely likely)	Median 8.5 (7.25-10)	Median 9.5 (7.5-10)	*0.260 3 less likely to recommend 4 more likely to recommend 1 Ties	Median 10 (7-10) §	Median 10 (6.25-10)	*0.150 7 less likely to recommend 2 more likely to recommend 6 Ties
If not given by NHS would you purchase yourself for £499?  Scale 1 (Definitely not) to 5 (Definitely yes)	n/a	Median 3 (1-4)		n/a	Median 2.5 (1.25-5)	0.864 <sup>§#</sup>
If you could buy VitaBreath online, how likely would you be to purchase it online? Scale 1 (Definitely not) to 5 (Definitely yes)	n/a	Median 1.5 (1-3.75)		n/a	Median 2 (1-3)	0.803 <sup>§#</sup>

Data presented as Absolute number (%); \*Wilcoxon Signed-rank test, # Mann-Whitney U test <sup>§</sup> denotes p value for comparison between the two groups, § 1 missing record at 2 weeks.



#### 7.3.2.2. Use of the VitaBreath device during daily physical activity

Patients found improvements in the speed, duration and confidence in which they could undertake activities of daily living, with no loss of these effects at 12 weeks (Table 7.3) [20]. Patients described being more active with the VitaBreath than without it at 2 weeks (DH non-responders: 5/8; DH responders: 8/16) and 12 weeks (DH non-responders: 5/8; DH responders: 9/16) (Table 7.3). Similar improvements were also reported in speed, duration and confidence during activities of daily living when patients were divided into responders and non-responders (Table 7.3) [20]. Moreover, 5 out of 8 (62.5%) and 8 out of 15 (53.3%) patients in the DH non-responders and DH responders group respectively, were more active compared to before using the VitaBreath and this improvement was maintained at 12 weeks in 62.5% and 56.2% in DH non-responders and responders group, respectively (Table 7.3).

Table 7.3. Effect of the VitaBreath device on daily physical activity in DH non-responders and DH responders.

Question	DH Non-Responders			DH Responders		
	Two weeks of VitaBreath	Twelve weeks of VitaBreath	<i>p</i> -Value	Two weeks of VitaBreath	Twelve weeks of VitaBreath	<i>p</i> -Value
Has VitaBreath helped your ability to perform activities?						
Speed <sup>^</sup>						
1 Not at all	3 (37.5%)	2 (25%)	0.414*	7 (50%)	6 (37.5%)	0.670*
2	1 (12.5%)	0 (0%)		0 (0%)	1 (6.3%)	
3	1 (12.5%)	3 (37.5%)	2 improvements	2 (14.3%)	3 (18.8%)	4 improvements
4	2 (25%)	2 (25%)	1 worse	4 (28.6%)	0 (0%)	3 worse
5 Yes, Definitely	1 (12.5%)	1 (12.5%)	5 ties	1 (7.1%)	6 (37.5%)	7 ties
Duration <sup>^</sup>						
1 Not at all	3 (37.5%)	3 (37.5%)	0.705*	5 (35.7%)	3 (18.8%)	0.668*
2	1 (12.5%)	0 (0%)		0 (0%)	3 (18.8%)	
3	1 (12.5%)	4 (50%)	1 improvements	2 (14.3%)	1 (6.3%)	6 improvements
4	2 (25%)	0 (0%)	3 worse	4 (28.6%)	3 (18.8%)	3 worse
5 Yes, Definitely	1 (12.5%)	1 (12.5%)	4 ties	3 (21.4%)	6 (37.5%)	5 ties
Confidence <sup>§</sup>						
1 Not at all	0 (0%)	2 (25%)	0.461*	2 (13.3%)	2 (12.5%)	0.509*
2	1 (12.5%)	0 (0%)		1 (6.7%)	1 (6.3%)	
3	3 (37.5%)	3 (37.5%)	2 improvements	4 (26.7%)	2 (12.5%)	6 improvements
4	2 (25%)	1 (12.5%)	2 worse	4 (26.7%)	4 (25%)	3 worse
5 Yes, Definitely	2 (25%)	2 (25%)	4 ties	4 (26.7%)	7 (43.8%)	6 ties

Question	DH Non-Responders			DH Responders		
	Two weeks of VitaBreath	Twelve weeks of VitaBreath	<i>p</i> -Value	Two weeks of VitaBreath	Twelve weeks of VitaBreath	<i>p</i> -Value
How active have you been since VitaBreath, compared to before?§						
Median (IQR)	6 (5-7)	6 (5-7.75)		6 (5-7)	6 (5-7.75)	
1(Much less active) to 4	1 (12.5%)	1 (12.5%)	0.679*	1 (6.7%)	1 (6.3%)	0.832*
5= The same	2 (25%)	2 (25%)		6 (40%)	6 (37.5%)	
6 to 10 (much more active)	5 (62.5%)	5 (62.5%)		8 (53.3%)	9 (56.2%)	

Data presented as Median (IQR); Absolute number (%); \*Wilcoxon Signed-rank test; § 1 missing record at 2 weeks; ^2 missing records at 2 weeks.

7.3.2.3. Effect of use of the VitaBreath device during daily physical activity on self-reported anxiety and symptom burden

Compared to the pre-VitaBreath period, when patients were divided into DH responders and non-responders, at 12 weeks patients were less anxious about becoming breathless [DH non-responders: pre-VitaBreath = 8.00 (6.00–8.00), 12 weeks = 4.50 (2.25–7.25), (p=0.127); DH responders: pre-VitaBreath = 8.00 (5.25–9.75), 12 weeks = 3.50 (2.00–5.75), (p=0.001)]. In addition, 5 out of 8 DH non-responders (p=0.034) and 11 out of 16 DH responders (p=0.002) perceived a shorter recovery time from breathlessness (Table 7.4).

7.3.2.4. Additional comments and feedback about VitaBreath

A number of patients provided further comments and feedback of their experience using the VitaBreath device during activities of daily living. One DH non-responder patient mentioned that the device was “a bit heavy to carry around” after 2 weeks of use. This was supported by another DH non-responder who stated that the device “does not fit in the pockets” and added that the device “helps with wheeze however, its effect/usefulness varies depending on severity of breathlessness”. Furthermore, two DH non-responders reported a few concerns about the weight of the device as “the device was too heavy to carry outside” and “it should have a carrying case”. Finally, a patient from the same group reported some technical issues such as “the mouthpiece keeps coming out and the screw at the back to clean out the filter is broken”.

In contrast, at 2 weeks only two patients in the DH responders group reported that the device was “bulky and too heavy”. However, 3 patients mentioned that they “would like to be able to buy one but could not afford it”. Finally, two patients reported that “the device is marvellous” and “transformed my life”. Following 12 weeks of using the device at home, four patients reported that they “would buy it but would struggle at that

price” however, the overall feedback was positive as these patients reported that the device “has given my life back”, feel like my whole life has improved, would hate to be without it and my attitude has improved”. Finally one patient reported that the device was “easy to maintain and use”, whilst another patient reported that the device “is not doing much benefit and there is no appreciable difference” following 12 weeks of use during activities of daily living.

Table 7.4. Effect of the use of VitaBreath device on anxiety and recovery from breathlessness in DH non-responders and DH responders.

Question	DH Non-Responders			DH Responders		
	Pre-VitaBreath	Post-VitaBreath	<i>p</i> -Value	Pre-VitaBreath	Post-VitaBreath	<i>p</i> -Value
How anxious are you about becoming short of breath (SOB)?			0.127 *			0.001 *
1 = Not at all anxious	8.00 (6.00–8.00)	4.50 (2.25–7.25)	6 improvements	8.00 (5.25–9.75)	3.50 (2.00–5.75)	15 improvements
10 = Very anxious			1 worse			
			1 ties			1 ties
How long did it take you to recover from SOB?			0.034 *			0.002 *
<1 min	0 (0%)	2 (25%)	5 improvements	1 (6.3%)	4 (25%)	11 improvements
2–3 min	3 (37.5%)	3 (37.5%)		3 (18.8%)	6 (37.5%)	1 worse
4–5 min	1 (12.5%)	1 (12.5%)	3 ties	2 (12.5%)	3 (18.8%)	4 ties
5–7 min	2 (25%)	0 (0%)		2 (12.5%)	1 (6.3%)	
7–10 min	0 (0%)	0 (0%)		6 (37.5%)	2 (12.5%)	
More than 10 min	2 (25%)	2 (25%)		2 (12.5%)	0 (0%)	

Data presented as median (IQR) or absolute number (%); \*Wilcoxon signed-rank test.

#### **7.4.Discussion**

The major finding of the study is that patients' adherence to using the VitaBreath device when performing activities of daily living was satisfactory, mainly due to the simplicity of its operation. Furthermore, use of the VitaBreath device improved anxiety around breathlessness, as well as perceived time of recovery from it during activities of daily living. However, the main drawback of the device was its portability.

All participants were given a device to use in daily life. Data suggests that the VitaBreath device improved anxiety around breathlessness, as well as perceived time to recover from breathlessness [20]. These findings further support the clinically meaningful improvement of inspiratory capacity and breathlessness during recovery from exercise that was reported during the clinical study (Chapter 5) [20]. Patients felt benefits in speed, duration and confidence associated with their activities of daily living, which were maintained at 3 months [20]. The VitaBreath device does not change the underlying disease process and, as expected, there was no change in the frequency of breathlessness, nor the need to plan around, or stop activities due to breathlessness [20]. Patients described the device as easy-to-use, but its portability was unfavourable [20]. However, it is important to note that over 95% of patients continued to use the device regularly, and most would recommend it to another person with COPD [20]. Despite these benefits, few patients would purchase a device [20]. This may, at least in part, reflect the UK National Health Service, which provides treatment free at the point of delivery, and the socioeconomic status of this patient group [20].

Previous studies suggest poor adherence with domiciliary use of other NIV methods. Continuous positive airway pressure which is widely applied to manage patients with obstructive sleep apnoea, central sleep apnoea and hypoventilation often causes discomfort to patients due to the pressure level, the interface type or the duration of the

treatment which is usually during sleeping hours [335]. However, there is limited information about usability and adherence of portable devices in the literature.

One of the first studies that tried to investigate the applicability of non-invasive ventilation during activities simulating those performed in daily life was conducted in 2007 by Dreher and colleagues [288]. Patients covered greater distance and reported lower breathlessness during the 6 minute walk test when NIV was added to oxygen supplementation compared to oxygen supplementation alone [288]. This was the first study [288] suggesting that NIV can be applied during activities of daily living on top of nocturnal application. However, the setup used in this study (patients had to push a wheelchair with the ventilator on it) makes it impractical to use during everyday activities.

Recently a study by Carling and colleagues investigated the effects of a portable non-invasive open ventilation (NIOV) system on activities of daily living in patients with COPD [338]. Patients performed activities under two different conditions (with oxygen supplementation and using NIOV system) for as long as tolerable [338]. In contrast to the present study, patients performed these activities during a single home visit [338]. Authors reported that application of the NIOV system improved endurance time, oxygen saturation, dyspnoea, fatigue and discomfort levels during activities of daily living in patients with COPD [338]. In addition, the NIOV system was well tolerated when patients used it during activities of daily life [338]. However, only the acute effects were assessed, therefore the findings cannot be generalised to long term outcomes. The results of the current study confirm the results of previous studies [338, 339], showing that the use of smaller ventilators that are easier to operate is feasible during activities of daily living in patients with COPD. Devices such as the VitaBreath



and NIOV can increase the adherence to domiciliary NIV application mainly due to the simplicity of their operation.

Although anxiety is a common comorbidity of COPD [340, 341], previous studies have reported conflicting results on the association between disease severity and anxiety levels in patients with COPD, reporting either no correlation [342, 343] or greater levels of anxiety in patients with more severe COPD [344]. This discrepancy is most likely due to the heterogeneous methods used to assess anxiety in these studies. However, in the study by Tsujimura and colleagues anxiety levels were also significantly correlated with poor daily physical activity levels in patients with severe COPD [344]. In the present study, only 63% of DH non-responders reported faster recovery from breathlessness after 12 weeks of using the VitaBreath device compared to 75% of DH responders. Furthermore, only patients in the DH responders group reported significant reductions in anxiety related to breathlessness during activities of daily life. These findings expand the results of the laboratory-based study that pNIV did not improve dynamic hyperinflation and breathlessness in DH non-responders most likely because they exhibited worse baseline lung function (Chapter 5) [344].

In regards to the feedback provided by few patients, it is confirmed that most patients were benefited by using the VitaBreath device during activities of daily living, and that the main disadvantage was its portability and price. However, there were two patients who reported no benefit of using the device. As patients were using the device at home, supervision and feedback on using the device was not available beyond the completion of the two exercise trials reported in Chapter 5. However, patients were encouraged to contact the research team if they had any questions in regards to using the device and a couple of patients contacted the research team during the 12 week follow up to ask for clarifications on the use and the maintenance of the device.

The main limitation of the present study was that the adherence to the use of pNIV, as well as the degree of breathlessness and the levels of daily physical activity were self-reported and no objective measurements were employed in order to assess the aforementioned outcomes. Future studies should use activity monitors in order to capture the effect of the application of pNIV application on daily physical activity outcomes such as steps per day and movement intensity alongside questionnaires.

### **7.5. Conclusions**

Application of pNIV during activities of daily living can be beneficial for reducing anxiety and dyspnoea related to activities in patients with COPD, leading to increased levels of daily physical activity. Future studies should focus on using standardised tools to assess the effect of pNIV on anxiety, dyspnoea and daily physical activity.

## 8. General discussion

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As the VitaBreath device is no longer commercially available, but similar devices may come to market, the present study provides proof of concept on how pNIV can be applied intermittently during exercise in patients with COPD, and how to select patients most likely to respond. This in turn may encourage development of more suitable devices. This concept was tested in patients who demonstrated substantial dynamic hyperinflation and ventilatory constraints to tidal volume expansion during exercise to the limit of tolerance (Table 5.2).

The dominant symptom of exercise intolerance in the majority of patients recruited was breathlessness (Figure 4.5). This was expected as respiratory limitation is a defining characteristic during exercise in patients with COPD, experiencing expiratory flow limitation and dynamic hyperinflation [18, 19, 29, 85, 257]. Furthermore, a significant proportion of patients complained of leg discomfort in addition to breathlessness; this was expected as COPD patients present substantial peripheral muscle dysfunction [18, 263, 264].

Hence, prior to the investigation of the acute effects of intermittent pNIV application on exercise tolerance, it was deemed necessary that all selected COPD patients underwent a number of exercise training sessions on a cyclo-ergometer in order to: i) improve leg muscle stamina, ii) familiarise themselves with the intermittent exercise testing protocols and iii) become accustomed with the correct breathing, technique using the pNIV apparatus or the PLB technique (Figure 5.1).

Previous studies have shown that use of intermittent exercise in COPD is associated with reduced ventilatory requirement, metabolic acidosis and lower symptoms of breathlessness and leg discomfort compared to continuous exercise [28, 111].

Importantly, application of intermittent exercise in the studies presented in this dissertation was essential in order to intermittently apply pNIV or PLB during the recovery periods.

A total of 24 COPD patients were randomised to perform two intermittent exercise protocols sustained at different work intensities (60% and 80% of WR<sub>peak</sub>) and exercise durations (6-min bouts and 2-min bouts, respectively) to resemble exercise training programs adopted during pulmonary rehabilitation in the UK (Figure 3.3 a & c) [165]. Within each intermittent exercise modality, patients performed two identical exercise tests using either the pNIV method or the PLB technique during the recovery phases in a balance order sequence.

The findings of this study showed that with both intermittent protocols endurance time was on average greater when the pNIV method was applied compared to PLB (Figure 5.6), which is in accordance with the existing literature using continuous NIV methods [24, 33, 49, 128]. Improvements in exercise tolerance were in most of the patients due to lower degrees of dynamic hyperinflation and breathlessness with pNIV compared to PLB (Figure 5.9).

VitaBreath provides positive inspiratory pressure support to reduce the work of breathing and positive expiratory pressure to keep the airways open during expiration, thereby reducing air trapping [215]. The mean increase in inspiratory capacity during the recovery periods compared to the end of exercise bouts with pNIV (high-intensity: 140 ml; moderate-intensity: 170 ml) was within the clinically meaningful margin reported in bronchodilator trials (138–175 ml) [293], most likely reflecting the improvement in expiratory flow and thus lung emptying [24, 27, 293] with pNIV. The increase in inspiratory capacity during recovery was matched by a significant reduction

in breathlessness that reached the minimal clinically important difference (1.0 unit) [24, 27]. In contrast, PLB was not consistently associated with a clinically meaningful improvement in inspiratory capacity during recovery; this is in keeping with previous work showing that exercise-induced dynamic hyperinflation normally persists for several minutes following the end of exercise [85]. Furthermore, the mean reduction in breathlessness scores during recovery from exercise did not reach the minimal clinically important difference [24, 27] with PLB.

However, an important observation made with the aforementioned study was that a subgroup of patients worsened dynamic hyperinflation with the pNIV method compared to the PLB technique (Figure 5.10) and thus failed to improve exercise endurance time. It was thus deemed necessary to investigate the characteristics and respiratory pattern responses of these patients not responding to the pNIV method (DH non-responders) in relation to those patients who responded to the pNIV method (DH responders).

Retrospective analysis identified that DH non-responders experienced greater resting hyperinflation (Table 5.3), greater exercise-induced dynamic hyperinflation and breathlessness, as well as reduced endurance time compared to DH responders (Figure 5.8). The greater dynamic hyperinflation and breathlessness during exercise in DH non-responder was the result of the adoption of a more tachypnoeic pattern of breathing when patients used the VitaBreath device. In fact, minute ventilation at exercise iso-time was lower in the DH responders when pNIV was applied compared to PLB, secondary to greater tidal volume and slightly lower breathing frequency. In contrast, in DH non-responders minute ventilation was greater at iso-time when pNIV was applied compared to PLB, secondary to lower tidal volume and greater breathing frequency. Accordingly, inspiratory and expiratory times were slightly increased in the DH responders, but decreased in DH non-responders. These results suggest that the

application of pNIV compared to PLB, improved ventilatory efficiency in DH responders, but worsened ventilatory efficiency in DH non-responders, thus suggesting that one type of pNIV does not benefit all patients.

This dissertation also investigated the acute effects of pNIV application on thoracoabdominal volume regulation, respiratory muscle kinematics and circulatory responses in patients with COPD. It was found that acute application of pNIV, during recovery periods interspersing exercise bouts of high-intensity, increased both end-expiratory and end-inspiratory thoracoabdominal volumes in COPD patients. Thoracoabdominal hyperinflation was mainly attributed to greater rib cage inflation with the pNIV device and in the majority of cases reduced expiratory abdominal recruitment. In fact, the different patterns of dynamic hyperinflation observed in the present dissertation when pNIV was applied suggest that some patients exhibited an evolumic breathing pattern, whilst others exhibited a hyperinflator pattern during application of pNIV [123]. Moreover, although all patients hyperinflated during exercise, the different patterns of respiratory muscle kinematic response recorded when the pNIV device was applied indicate that a subset of patients exhibited greater recruitment of the expiratory abdominal muscles combating end-expiratory dynamic hyperinflation just like the evolumic pattern described by Aliverti and colleagues [123]. It has been postulated that such a contraction is beneficial because of lengthening of the diaphragm resulting in greater generation of negative pleural pressure (better position of the length-tension relationship) [64, 65]. Thus, adopting such a breathing pattern could assist the patient to fight against the provided by pNIV high expiratory pressures.

However in contrast to the existing literature, acute application of pNIV was not associated with any adverse circulatory effects in COPD patients [198, 200], most likely due to the brief duration of pNIV application. In addition, using OEP technology

confirmed the different patterns of response to dynamic hyperinflation in COPD patients that was evident from the original studies namely: there were patients who reduced dynamic hyperinflation acutely with the use of pNIV (DH responders) and patients who worsened dynamic hyperinflation with pNIV (DH non-responders). Small improvements in dynamic hyperinflation with pNIV or in some cases worsening of dynamic hyperinflation with pNIV were attributed to the high fixed IPAP and EPAP applied by this specific pNIV device.

Besides the acute effects of intermittent pNIV application on exercise tolerance, this dissertation investigated the acceptability, comfort and usability of the pNIV method during activities of daily living in those 24 patients that retained the device for three months following the completion of the laboratory exercise assessment. It was shown that with the pNIV device the majority of patients felt less anxious about becoming breathless and felt that their breathlessness recovered faster when using the device at home (Table 7.4). Interestingly, those patients demonstrating worse breathlessness when using the pNIV device during exercise testing (DH non-responders) also reported less benefit from using the device at home in terms of anxiety around breathlessness and recovery time from breathlessness (Table 7.4). This was the first study investigating the effects of a pNIV device on anxiety and recovery of breathlessness during activities of daily life in patients with COPD. In addition, the results of this dissertation confirm the results of previous studies [338, 339], showing that the use of smaller ventilators that are easier to operate are also easier to use during activities of daily living in patients with COPD. Devices such as the VitaBreath and NIOV can increase the adherence to domiciliary NIV application, mainly due to the simplicity of their operation.

Accordingly, this dissertation makes the following two important recommendations: first, the individual COPD patient response to any given pNIV method should be

investigated prior to prescribing pNIV during exercise or daily physical activities, and second, research should focus on developing pNIV methods that automatically adjust IPAP and EPAP according to the individual patient breathing pattern and degree of expiratory flow limitation during exercise. Thus, further studies in auto-adjusted ventilators are warranted.

Importantly, the findings of the present dissertation provide evidence that patients who cannot tolerate continuous NIV methods during exercise, may use the NIV apparatus in recovery from exercise when an intermittent mode of exercise is undertaken. This approach will facilitate the majority of patients to recover from breathlessness faster, thereby increasing the number of intermittent exercise bouts that they can endure in the setting of pulmonary rehabilitation.

### **Future Research**

Future research may act upon the study limitations presented in this dissertation to complete a trial with sufficient number of participants to detect statistically significant differences in thoracoabdominal volumes between ‘DH responders’ and ‘DH non-responders’. This would provide greater clarity into reasons why some COPD patients do not improve thoracoabdominal dynamic hyperinflation when using a pNIV device. Furthermore, future research should investigate how best to identify those patients who may benefit from any pNIV device in everyday life. Additionally, research into new portable NIV devices that allow the adjustment of IPAP and EPAP to the individual should be carried out, to examine the scope of their practical application for those exhibiting severe COPD. Given that there are important developments in auto-adjusted ventilators, future studies may focus on investigating the effects of such ventilators on daily physical tasks in patients with COPD. This in turn may encourage the development of suitable pNIV devices for patients with COPD.



## Appendix A

Table 1. Effect of Pressure Support Ventilation (PSV) compared to spontaneous breathing on the work of breathing at rest

Study	n	NIV method	$\Delta P_{es}$ (cmH <sub>2</sub> O)	$\Delta P_{di}$ (cmH <sub>2</sub> O)	$\Delta P_{ga}$ (cmH <sub>2</sub> O)	WoB (J/L)	$\Delta P_{EEPi}$ (cmH <sub>2</sub> O)	EMG <sub>di</sub>	$\Delta EELV$ (ml)
Nava 1993 [178]	7 COPD patients	PSV (IPAP: 10 cmH <sub>2</sub> O)	-4.29	-4.51	-0.14			-40%	97
Nava 1993 [178]	7 COPD patients	PSV+ PEEP (IPAP: 10 cmH <sub>2</sub> O / PEEP: 5 cmH <sub>2</sub> O)	-5.80	-6.06	-0.23				222
Nava 1993 [178]	7 COPD patients	PSV (IPAP: 20 cmH <sub>2</sub> O)	-6.02	-5.84	0.16				109
Nava 1993 [178]	7 COPD patients	PSV+ PEEP (IPAP: 20 cmH <sub>2</sub> O / PEEP: 5 cmH <sub>2</sub> O)	-7.84	-7.91	-0.06				327
Appendini 1994 [184]	7 COPD patients	PSV (IPAP: 10 cmH <sub>2</sub> O)		-4.50			-0.20		-30
Appendini 1994 [184]	7 COPD patients	PSV+ PEEP (IPAP: 10 cmH <sub>2</sub> O / EPAP: 5 cmH <sub>2</sub> O)		-8.90			-2.50		115
Girault 1997 [177]	15 COPD patients	PSV (IPAP: 15 cmH <sub>2</sub> O)	-11.59			-0.33	0.81	-33%	
Porta 1999 [180]	12 COPD patients	PSV (IPAP: 15 cmH <sub>2</sub> O / EPAP: 4 cmH <sub>2</sub> O)	-7.80				-1.30		
Wysocki 2002 [182]	12 COPD patients	PSV (IPAP: 17 cmH <sub>2</sub> O / EPAP: 5 cmH <sub>2</sub> O)	-8.00			-0.65	0		
Porta 2002 [179]	11 COPD patients / 7 patients with chronic ventilatory failure	PSV (IPAP: 12 cmH <sub>2</sub> O)	-5.80	-6.70			-0.30		
Lellouche 2002 [185]	9 patients with acute respiratory failure	Intermittent PSV (PEEP: 5 cmH <sub>2</sub> O)		-8.85		-0.60	0.050		

Study	n	NIV method	$\Delta P_{es}$ (cmH <sub>2</sub> O)	$\Delta P_{di}$ (cmH <sub>2</sub> O)	$\Delta P_{ga}$ (cmH <sub>2</sub> O)	WoB (J/L)	$\Delta P_{EEPi}$ (cmH <sub>2</sub> O)	EMG <sub>di</sub>	$\Delta EELV$ (ml)
L'Her 2005 [188]	10 patients with acute lung injury	PSV (IPAP: 10 cmH <sub>2</sub> O / EPAP: 10 cmH <sub>2</sub> O)		-6.20		-0.48	-0.50		
L'Her 2005 [188]	10 patients with acute lung injury	PSV (IPAP: 15 cmH <sub>2</sub> O / EPAP: 5 cmH <sub>2</sub> O)		-6.60		-0.49	-0.30		
Prinianakis 2004 [186]	15 COPD patients	PSV (IPAP: 14.2 cmH <sub>2</sub> O / EPAP: 3.5 cmH <sub>2</sub> O) Pressurisation 30 cmH <sub>2</sub> O		-2.30	0.04		-0.44		
Prinianakis 2004 [186]	15 COPD patients	PSV (IPAP: 14.2 cmH <sub>2</sub> O / EPAP: 3.5 cmH <sub>2</sub> O) Pressurisation 80 cmH <sub>2</sub> O		-3.40	-0.46		-0.27		
Prinianakis 2004 [186]	15 COPD patients	PSV (IPAP: 14.2 cmH <sub>2</sub> O / EPAP: 3.5 cmH <sub>2</sub> O) Pressurisation 120 cmH <sub>2</sub> O		-3.60	0.04		-0.71		
Prinianakis 2004 [186]	15 COPD patients	PSV (IPAP: 14.2 cmH <sub>2</sub> O / EPAP: 3.5 cmH <sub>2</sub> O) Pressurisation 200 cmH <sub>2</sub> O		-4.90	-0.36		-0.71		
Wysocki 2004 [43]	7 patients following external thoracic restriction	PSV (IPAP: 9 cmH <sub>2</sub> O)	-2.00			-0.34			
Poggi 2006 [48]	8 COPD patients	PSV (IPAP: 15 cmH <sub>2</sub> O / EPAP: 4 cmH <sub>2</sub> O)					-1.30		
Average		IPAP: 13cmH <sub>2</sub> O / EPAP: 4.5 cmH <sub>2</sub> O	-6.57	-5.73	-0.13	-0.48	-0.55	-0.37	140

PSV: pressure support ventilation; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure

Table 2. Effect of Continuous Positive Airway Pressure, Proportional Assist Ventilation, Inspiratory Positive Airway Pressure and Bi-level Positive Airway Pressure compared to spontaneous breathing on the work of breathing at rest

Study	n	NIV method	$\Delta P_{es}$ (cmH <sub>2</sub> O)	$\Delta P_{di}$ (cmH <sub>2</sub> O)	$\Delta P_{ga}$ (cmH <sub>2</sub> O)	WoB (J/L)	$\Delta P_{EPIP}$ (cmH <sub>2</sub> O)	EMGdi	$\Delta EELV$ (ml)
<b>CPAP</b>									
Appendini 1994 [184]	7 COPD patients	CPAP: 5 cmH <sub>2</sub> O		-2.80			-3.40		110
Elliott 1994 [176]	11 COPD patients	CPAP: 7 cmH <sub>2</sub> O	-2.50		0.60				
L'Her 2005 [188]	10 patients with acute lung injury	CPAP: 10 cmH <sub>2</sub> O		-0.70		-0.23	-0.50		
Average		CPAP: 7 cmH <sub>2</sub> O	-2.50	-1.75	0.60	-0.23	-1.95		110
<b>PAV</b>									
Polese 2000 [183]	15 COPD patients	PAV (Flow assist: 4 cmH <sub>2</sub> O/L/s, Volume assist: 14 cmH <sub>2</sub> O/L) + CPAP: 2 cmH <sub>2</sub> O	-4.00	-6.00			-0.30	-28%	
Polese 2000 [183]	15 COPD patients	PAV (Flow assist: 4 cmH <sub>2</sub> O/L/s, Volume assist: 14 cmH <sub>2</sub> O/L) + CPAP: 5 cmH <sub>2</sub> O	-7.00	-8.00			-1.00	-28%	
Wysocki 2002 [182]	12 COPD patients	PAV (no details provided)	-10.00			-0.71	1.00		
Porta 2002 [179]	11 COPD / 7 chronic ventilatory failure	PAV (Flow assist: 5 cmH <sub>2</sub> O/L/s, Volume assist: 12 cmH <sub>2</sub> O/L)	-4.30	-4.60			-0.10		
Wysocki 2004 [43]	7 patients following external thoracic restriction	PAV (Flow assist: 4 cmH <sub>2</sub> O/L/s, Volume assist: 9 cmH <sub>2</sub> O/L)	-3.00			-0.40			

Study	n	NIV method	$\Delta P_{es}$ (cmH <sub>2</sub> O)	$\Delta P_{di}$ (cmH <sub>2</sub> O)	$\Delta P_{ga}$ (cmH <sub>2</sub> O)	WoB (J/L)	$\Delta P_{EEPi}$ (cmH <sub>2</sub> O)	EMG <sub>di</sub>	$\Delta EELV$ (ml)
Poggi 2006 [48]	8 COPD patients	PAV (Flow assist: 5 cmH <sub>2</sub> O/L/s, Volume assist: 12 cmH <sub>2</sub> O/L)					-0.90		
Average		Flow assist: 4.4 cmH <sub>2</sub> O/L/s, Volume assist: 12 cmH <sub>2</sub> O/L	-5.66	-6.20		-0.56	-0.26	-28%	
<b>IPAP</b>									
Brochard 1990 [187]	13 COPD patients	IPAP: 20 cmH <sub>2</sub> O		-11.20			-0.20	-43%	
Elliott 1994 [176]	11 COPD patients	IPAP: 20 cmH <sub>2</sub> O	-8.8		0.70				
Average		IPAP: 20 cmH <sub>2</sub> O	-8.8	-11.2	0.7		-0.2	-0.43	
<b>Bi-level PAP</b>									
Renston 1994 [191]	17 COPD patients	Bi-level PAP (IPAP 18 cmH <sub>2</sub> O, EPAP 2 cmH <sub>2</sub> O)						-66%	
Thys 2002 [192]	12 COPD patients / 8 patients with acute pulmonary oedema	Bi-level PAP (IPAP: 10 cmH <sub>2</sub> O and EPAP: 4 cmH <sub>2</sub> O)				0.006			
Elliott 1994 [176]	11 COPD patients	Bi-level PAP (IPAP 20 cmH <sub>2</sub> O / EPAP 7 cmH <sub>2</sub> O)	-9.3		0.30				
Average		IPAP: 16 cmH <sub>2</sub> O, EPAP: 4 cmH <sub>2</sub> O	-9.3		0.30	0.006		-66%	

CPAP: Continuous Positive Airway Pressure; PAV: Proportional Assist Ventilation; IPAP: Inspiratory Positive Airway Pressure; BiPAP: Bi-level Positive Airway Pressure; EPAP: expiratory positive airway pressure

Table 3. Effect of Pressure Support Ventilation compared to spontaneous breathing on breathing pattern at rest

<b>Study</b>	<b>n</b>	<b>NIV method</b>	<b>V<sub>E</sub> (L/min)</b>	<b>bf (breaths/min)</b>	<b>V<sub>T</sub> (ml)</b>	<b>Ti (sec)</b>	<b>Te (sec)</b>	<b>Ttot (sec)</b>	<b>Ti/Ttot (%)</b>	<b>V<sub>T</sub>/Ti (L/sec)</b>
Nava 1993 [178]	7 COPD patients	PSV (IPAP: 10 cmH <sub>2</sub> O)	0.9	-6	111		0.7		-0.02	0.032
Nava 1993 [178]	7 COPD patients	PSV+ PEEP (IPAP: 10 cmH <sub>2</sub> O / PEEP: 5 cm H <sub>2</sub> O)	1.5	-6	212		0.7		0.01	0.027
Nava 1993 [178]	7 COPD patients	PSV (IPAP: 20 cmH <sub>2</sub> O)	2.0	-7	321		0.8		0.01	0.09
Nava 1993 [178]	7 COPD patients	PSV+ PEEP (IPAP: 20 cmH <sub>2</sub> O / PEEP: 5 cm H <sub>2</sub> O)	1.9	-8	380		1.0		-0.01	0.145
Appendini 1994 [184]	7 COPD patients	PSV (IPAP: 10 cmH <sub>2</sub> O)	1.2	-2	180	0.20	0.87	1.07	-0.05	0.09
Appendini 1994 [184]	7 COPD patients	PSV+ PEEP (IPAP: 10 / EPAP: 5 cmH <sub>2</sub> O)	1.9	-2	180	0.26	0.43	0.69	-0.01	0.09
Girault 1997 [177]	15 COPD patients	PSV (IPAP: 15 cmH <sub>2</sub> O)	1.6	-3	150	0.16	0.42	0.58	-0.01	0.09
Porta 1999 [180]	12 COPD patients	PSV (IPAP: 15 cmH <sub>2</sub> O / EPAP: 4 cmH <sub>2</sub> O)	2.0	-2	189				-0.01	0.1

Study	n	NIV method	V <sub>E</sub> (L/min)	bf (breaths/min)	V <sub>T</sub> (ml)	Ti (sec)	Te (sec)	Ttot (sec)	Ti/Ttot (%)	V <sub>T</sub> /Ti (L/sec)
Wysocki 2002 [182]	12 COPD patients	PSV (IPAP: 17 cmH <sub>2</sub> O / EPAP: 5 cmH <sub>2</sub> O)		-3	261				0.05	
Porta 2002 [179]	11 COPD patients / 7 patients with chronic ventilatory failure	PSV (IPAP: 12 cmH <sub>2</sub> O)	2.8	-1	169				-0.04	0.19
Lellouche 2002 [185]	9 patients following acute respiratory failure	Intermittent PSV (PEEP: 5 cmH <sub>2</sub> O)	2.8		59	0.04				0.15
L'Her 2005 [188]	10 patients with acute lung injury	PSV (IPAP: 10 cmH <sub>2</sub> O / EPAP: 10 cmH <sub>2</sub> O)	-1.0	-2	-52					
L'Her 2005 [188]	10 patients with acute lung injury	PSV (IPAP: 15 cmH <sub>2</sub> O / EPAP: 5 cmH <sub>2</sub> O)	2.0	-4	56					
Prinianakis 2004 [186]	15 COPD patients	PSV (IPAP: 14.2 cmH <sub>2</sub> O / EPAP: 3.5 cmH <sub>2</sub> O) Pressurisation 30 cmH <sub>2</sub> O		-3	99	0.19	0.16	0.34		
Prinianakis 2004 [186]	15 COPD patients	PSV (IPAP: 14.2 cmH <sub>2</sub> O / EPAP: 3.5 cmH <sub>2</sub> O) Pressurisation 80 cmH <sub>2</sub> O		-3	91	0.20	0.14	0.33		

<b>Study</b>	<b>n</b>	<b>NIV method</b>	<b>V<sub>E</sub> (L/min)</b>	<b>bf (breaths/min)</b>	<b>V<sub>T</sub> (ml)</b>	<b>Ti (sec)</b>	<b>Te (sec)</b>	<b>Ttot (sec)</b>	<b>Ti/Ttot (%)</b>	<b>V<sub>T</sub>/Ti (L/sec)</b>
Prinianakis 2004 [186]	15 COPD patients	PSV (IPAP: 14.2 cmH <sub>2</sub> O / EPAP: 3.5 cmH <sub>2</sub> O) Pressurisation 120 cmH <sub>2</sub> O		2	120	0.11	0.12	0.22		
Prinianakis 2004 [186]	15 COPD patients	PSV (IPAP: 14.2 cmH <sub>2</sub> O / EPAP: 3.5 cmH <sub>2</sub> O) Pressurisation 200 cmH <sub>2</sub> O		-3	103	0.07	0.37	0.43		
Wysocki 2004 [43]	7 patients following external thoracic restriction	PSV (IPAP: 9 cmH <sub>2</sub> O)		2	249				-0.05	
Poggi 2006 [48]	8 COPD patients	PSV (IPAP: 15 cmH <sub>2</sub> O / EPAP: 4 cmH <sub>2</sub> O)	1.8	-4	200	0	0.60		-0.07	
Average		IPAP: 13cmH <sub>2</sub> O / EPAP: 4.5 cmH <sub>2</sub> O	1.7	-3	162	0.14	0.53	0.52	-0.02	0.10

PSV: pressure support ventilation; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure

Table 4. Effect of Continuous Positive Airway Pressure, Proportional Assist Ventilation, Inspiratory Positive Airway Pressure and Bi-level Positive Airway Pressure compared to spontaneous breathing on breathing pattern at rest

Study	n	NIV method	V <sub>E</sub> (Litres/min)	bf (breaths/min)	V <sub>T</sub> (ml)	Ti (sec)	Te (sec)	Ttot (sec)	Ti/Ttot (%)	V <sub>T</sub> /Ti (L/sec)
<b>CPAP</b>										
Appendini 1994 [184]	7 COPD patients	CPAP: 5 cmH <sub>2</sub> O	0.5	2	-10	-0.14	-0.16	-0.3	-0.01	0.03
Elliott 1994 [176]	11 COPD patients	CPAP: 7 cmH <sub>2</sub> O	-0.5	-1	-10					
L'Her 2005 [188]	10 patients with acute lung injury	CPAP: 10 cmH <sub>2</sub> O	-3.3	-2	-141					
Average		CPAP: 7 cmH <sub>2</sub> O	-1.1	0	-54	-0.14	-0.16	-0.30	-0.01	0.03
<b>PAV</b>										
Polese 2000 [183]	15 COPD patients	PAV (Flow assist: 4 cmH <sub>2</sub> O/L/s, Volume assist: 14 cmH <sub>2</sub> O/L) + CPAP: 2 cmH <sub>2</sub> O	2.2	0	160				-0.01	
Polese 2000 [183]	15 COPD patients	PAV (Flow assist: 4 cmH <sub>2</sub> O/L/s, Volume assist: 14 cmH <sub>2</sub> O/L) + CPAP: 5 cmH <sub>2</sub> O	1.7	0	110				0	



Study	n	NIV method	VE (Litres/min)	bf (breaths/min)	VT (ml)	Ti (sec)	Te (sec)	Ttot (sec)	Ti/Ttot (%)	VT/Ti (L/sec)
Wysocki 2002 [182]	12 COPD patients	PAV (no details provided)		-4	208				-0.01	
Porta 2002 [179]	11 COPD patients / 7 patients with chronic ventilatory failure	PAV (Flow assist: 5 cmH <sub>2</sub> O/L/s, Volume assist: 12 cmH <sub>2</sub> O/L)	2.8	0	127				-0.02	0.12
Wysocki 2004 [43]	7 patients following external thoracic restriction	PAV (Flow assist: 4 cmH <sub>2</sub> O/L/s, Volume assist: 9 cmH <sub>2</sub> O/L)		2	180				-0.04	
Poggi 2006 [48]	8 COPD patients	PAV (Flow assist: 5 cmH <sub>2</sub> O/L/s, Volume assist: 12 cmH <sub>2</sub> O/L)	1.7	-1	110	-0.1	0.33		-0.06	
Average		Flow assist: 4.4 cmH <sub>2</sub> O/L/s, Volume assist: 12 cmH <sub>2</sub> O/L	2.10	-1	149	-0.10	0.33		-0.02	0.12
<b>IPAP</b>										
Brochard 1990 [187]	13 COPD patients	IPAP: 20 cmH <sub>2</sub> O	3.0	-16	300					

Study	n	NIV method	V <sub>E</sub> (Litres/min)	bf (breaths/min)	V <sub>T</sub> (ml)	Ti (sec)	Te (sec)	Ttot (sec)	Ti/Ttot (%)	V <sub>T</sub> /Ti (L/sec)
Elliott 1994 [176]	11 COPD patients	IPAP: 20 cmH <sub>2</sub> O	2.0	-7	310					
Average		IPAP: 20 cmH <sub>2</sub> O	2.50	-11	305					
<b>Bi-level PAP</b>										
Renston 1994 [191]	17 COPD patients	Bi-level PAP (IPAP: 18 cmH <sub>2</sub> O, EPAP: 2 cmH <sub>2</sub> O)		0	270					
Thys 2002 [192]	12 COPD patients / 8 patients with acute pulmonary oedema	Bi-level PPV (IPAP: 10 cmH <sub>2</sub> O and EPAP: 4 cmH <sub>2</sub> O)		-15						
Elliott 1994 [176]	11 COPD patients	Bi-level PAP (IPAP 20 cmH <sub>2</sub> O / EPAP 7 cmH <sub>2</sub> O)	1.5	-5	180					
Average		IPAP: 16 cmH <sub>2</sub> O, EPAP: 4 cmH <sub>2</sub> O	1.5	-6	225					

CPAP: Continuous Positive Airway Pressure; PAV: Proportional Assist Ventilation; IPAP: Inspiratory Positive Airway Pressure; BiPAP: Bi-level Positive Airway Pressure; EPAP: expiratory positive airway pressure

Table 5. Studies investigating the effect of the application of non-invasive ventilation on exercise tolerance and dynamic hyperinflation in patients with COPD.

<b>Author/Year</b>	<b>Population</b>	<b>Study protocol</b>	<b>NIV Method</b>
<b>Cyclo-ergometer</b>			
O'Donnell 1988 [35]	6 COPD patients (FEV <sub>1</sub> : 35%)	2 Constant load exercise tests at 50% WRpeak	<b>Control</b> <b>CPAP:</b> 4-5 cmH <sub>2</sub> O
Petrof 1990 [36]	8 COPD patients (FEV <sub>1</sub> : 25%)	2 Constant load exercise tests lasting approximately 3 minutes each	<b>Control</b> <b>CPAP:</b> 7.5-10 cmH <sub>2</sub> O
Dolmage 1997 [46]	10 COPD patients (FEV <sub>1</sub> : 29%)	5 Constant load exercise tests at 60-70% of WRpeak at different days	<b>Sham:</b> CPAP: 0 cmH <sub>2</sub> O, PAV: 0 <b>CPAP:</b> 5 cmH <sub>2</sub> O <b>PAV:</b> Volume Assist: 6 cmH <sub>2</sub> O/L, Flow Assist: 3 cmH <sub>2</sub> O/L <b>CPAP+PAV:</b> 5 cmH <sub>2</sub> O, Volume Assist: 6 cmH <sub>2</sub> O/L, Flow Assist: 3 cmH <sub>2</sub> O/L/s
Bianchi 1998 [44]	15 COPR patients (FEV <sub>1</sub> : 32%)	4 endurance tests at 80% peak in two consecutive days	<b>Control</b> <b>Sham:</b> 1 cmH <sub>2</sub> O <b>CPAP:</b> 6 cmH <sub>2</sub> O <b>PSV:</b> IPAP: 12-16 cmH <sub>2</sub> O, EPAP: 1 cmH <sub>2</sub> O <b>PAV:</b> Volume Assist: 8.6 cmH <sub>2</sub> O/L, Flow Assist: 3 cmH <sub>2</sub> O/L/s

<b>Author/Year</b>	<b>Population</b>	<b>Study protocol</b>	<b>NIV Method</b>
Hernandez 2001 [47]	8 COPD patients (FEV <sub>1</sub> : 25%)	2 Constant load exercise tests at 80% WRpeak	<b>Sham:</b> 1-2 cmH <sub>2</sub> O <b>PAV:</b> Volume Assist: 9.8 cmH <sub>2</sub> O/L Flow Assist: 3.3 cmH <sub>2</sub> O/L/s
van't Hul 2004 [42]	45 COPD patients (FEV <sub>1</sub> : 39%)	<b>Visit 1:</b> pulmonary function test and CPET <b>Visit 2:</b> Constant load exercise test at 75% peak and familiarization with IPS <b>Visit 3:</b> 2 Constant load exercise tests with IPS5 and IPS10	<b>Control</b> <b>Sham:</b> IPS5 cmH <sub>2</sub> O <b>IPS:</b> 10 cmH <sub>2</sub> O
Borghi-Silva 2008 [209]	16 COPD patients (FEV <sub>1</sub> : 42%)	2 Constant load exercise tests at 70-80% WRpeak	<b>Sham:</b> IPS: 5 cmH <sub>2</sub> O, PEEP: 2 cmH <sub>2</sub> O <b>PAV:</b> Volume Assist: 5.8 cmH <sub>2</sub> O/L. Flow Assist 3.5 cmH <sub>2</sub> O/L/s
Carrascossa 2010 [45]	20 COPD patients (FEV <sub>1</sub> : 39%)	2 Constant load exercise tests at 70-80% of WRpeak at the same day with 30 minutes break between the tests	<b>PAV:</b> Volume Assist: 5.1 cmH <sub>2</sub> O/L, Flow Assist: 3.4 cmH <sub>2</sub> O/L/s
Hussain 2011 [210]	10 COPD patients (FEV <sub>1</sub> : 28%)	3 Constant load exercise tests at 80% of WRpeak	<b>O<sub>2</sub>:</b> 30% <b>O<sub>2</sub>:</b> 30% + <b>Helium:</b> 70% (Heliox) <b>O<sub>2</sub>:</b> 30% + <b>IPS:</b> IPAP: 9-19 cmH <sub>2</sub> O

<b>Author/Year</b>	<b>Population</b>	<b>Study protocol</b>	<b>NIV Method</b>
<b>Treadmill</b>			
Keilty 1994* [37]	8 COPD patients (FEV <sub>1</sub> : 0.73 litres)	3 endurance tests on 3 separate days on a treadmill (5 dyspnoea limit)	<b>Control</b> <b>IPS:</b> 12-15 cmH <sub>2</sub> O <b>CPAP-BiPAP:</b> 6 cmH <sub>2</sub> O <b>O<sub>2</sub>:</b> 2L
Kyroussis 2000 <sup>s</sup> [38]	5 COPD patients (FEV <sub>1</sub> : 27%)	6 out of 12 iso distance with PPV 5 out of 6 to the tolerance with PPV Constant speed to exhaustion on treadmill	<b>Control</b> <b>PPV:</b> no details provided

Table 6. Effect of the application of non-invasive ventilation on exercise tolerance and dynamic hyperinflation in patients with COPD.

Author/Year	Exercise tolerance (min)								ΔIC (litres)	ΔIC (litres)
	Control	Sham	CPAP	PSV	PAV	IPS	CPAP+PAV	PPV	Iso-time	Limit of tolerance
O'Donnell 1988 [35]	6.0		8.8						-0.08	-0.02
Petrof 1990 [36]									0.04	
Dolmage 1997 [46]	4.9	6.6	8.3		7.1		12.9			
Bianchi 1998 [44]	7.1	7.2	9.6	10.5	12.5					
Hernandez 2001 [47]	5.4				8.5					
van't Hul 2004 [42]	4.3	4.4				6.3				
Borghi-Silva 2008 [209]	4.6	4.6			5.6					
Carrascossa 2010 [45]	3.7				4.2					
Hussain 2011 [210]	6.9					11.2			0.20	
<b>Average</b>	<b>5.4</b>	<b>5.7</b>	<b>8.9</b>	<b>10.5</b>	<b>7.6</b>	<b>8.8</b>	<b>12.9</b>		<b>0.05</b>	<b>-0.02</b>

<b>Treadmill</b>										
Keilty 1994* [37]	137		121			336				
Kyroussis 2000 <sup>§</sup> [38]	6.8							13.2		

FEV<sub>1</sub>: forced expiratory flow at the first second; CPAP: continuous positive airway pressure; PSV: pressure support ventilation; PAV: proportional assist ventilation; IPS: inspiratory pressure support; PPV: positive pressure ventilation; Δ: change; IC: inspiratory capacity; IPAP: inspiratory positive airway pressure; BiPAP: Bi-level Positive Airway Pressure; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure; WR<sub>peak</sub>: peak work rate \*: data presented as distance covered in metres; <sup>§</sup>: data presented in minutes

## Appendix B

### Consent form for studies presented in chapters 4, 5 and 7.

Influence of the Vitabreath device on exercise tolerance in COPD

Influence of the VitaBreath device on exercise tolerance in patients with chronic obstructive pulmonary disease.  
Consent for patients

PARTICIPANT NAME:
NHS NUMBER:
DATE OF BIRTH:
ADDRESS:

Please initial boxes

1) I have read the information sheet for the above study, and have had the opportunity to ask questions.	
2) I understand that I do not have to take part, and I am free to withdraw at any time, without giving any reason if I do not want to, without my legal rights or the care I receive being affected.	
3) I understand that if I withdraw, the information I have provided will still be used up to when I withdraw, but with my personal information removed so I cannot be identified, unless I state otherwise.	
4) I understand that my medical notes and medical data will be looked at by members of the research team and by regulatory authorities, and give consent for these people to have access to my records.	
5) I understand that the information will be used in future reports, articles or presentations by the research team.	
6) I understand my personal information will not appear in any future reports, articles or presentations by the research team.	
7) I give permission for information to be sent to the GP about my being involved in the study.	
	DD MM YYYY
Participant name (PRINT)	Signature Date
	DD MM YYYY
Researcher taking consent (PRINT)	Signature Date



## **Participant information sheet of the study presented in Chapters 4, 5, and 7**

**Title:** Influence of the VitaBreath device on exercise tolerance in patients with chronic obstructive pulmonary disease.

You are being invited to take part in a research study that will assess whether a new device can help people with chronic obstructive pulmonary disease (COPD) recover from a bout of exercise more quickly, reducing breathlessness, and allow them to exercise for longer. Before you decide if you would like to take part, please take time to read the information, and discuss it with others if you wish. If you would like someone to read through the information with you, please ask.

### **What is the purpose of the study?**

People with COPD have more air in their lungs than other people (this problem with high lung volumes is called “hyperinflation”). Unfortunately this is unhelpful as breathing at higher lung volumes requires more effort and contributes to breathlessness. When anyone exercises, they breathe more quickly. People with COPD have narrowed airways, which makes breathing out difficult. When they breathe more quickly they may not be able to breathe out fully before they need to take the next breath in. This means that the volume of air in their lungs tends to increase further during exercise, which makes breathing even more difficult. This problem is called “dynamic hyperinflation”.

Pulmonary rehabilitation is one of the most helpful interventions for people with COPD and most of the benefit gained is from exercise. Anything that helps people increase the amount of exercise they can perform should lead to further improvements.

Non-invasive positive pressure ventilation is a method of supporting a person’s normal breathing. The ventilator delivers a flow of air at low pressure as you breathe out, which helps you to breathe out more completely. The device also detects when you start to breathe in and delivers a stronger flow of air at a higher pressure, helping you to take a deeper breath in. Previous research studies have shown that when people with COPD use non-invasive ventilation during exercise they are able to exercise for longer and are less breathless. The purpose of this study is to assess whether a new portable non-invasive ventilation device, called the VitaBreath, helps people with COPD recover from breathlessness during the exercise breaks more quickly (by reducing “dynamic hyperinflation”, described above) and to exercise for longer overall. The VitaBreath device is small and light, weighing 0.5 kilograms (just over one pound). It is handheld and battery powered.

### **Why have you been chosen?**

You have been chosen because you have COPD and are keen to improve your ability to exercise by taking part in a pulmonary rehabilitation program. If you

agree to be assessed for the trial, we will verify that you do develop “dynamic hyperinflation” (breathing at progressively higher lung volumes) during exercise.

### **Do I have to take part?**

No, it is your free choice to take part. If you decide to take part you will be asked to sign a consent form. You are free at any time to withdraw from the study, and do not have to give a reason. If you decide to withdraw from the study, we will use the information we have gathered up to that point, but we will not include your personal information unless you give us permission to do so.

If you decide not to take part you will continue to receive the same standard of pulmonary rehabilitation and usual care.

### **What is the VitaBreath device?**

The VitaBreath device is a non-invasive portable ventilator which provides different levels of positive air pressure during inspiration and expiration. This assists normal breathing efforts in a similar way to a conventional non-invasive ventilator. In comparison to conventional noninvasive ventilators, the VitaBreath device is compact, light, battery powered and inexpensive. Consequently it is suitable to use anywhere, including away from your home.

### **What does it mean if I take part in the study?**

If you choose to take part you will attend North Tyneside General Hospital on three occasions over 10 days. You will perform some simple breathing tests in the lung function department, which will take about 30 minutes on your first visit, and undergo an exercise test. The exercise test is called a cardiopulmonary exercise test, and allows us to measure how your breathing, heart and muscles respond to exercise. This will take about 60 minutes.

You should wear cool, comfortable clothing suitable for exercise. You can eat a light meal a few hours before the exercise test, but you should avoid eating a large heavy meal. Adhesive pads will be attached to your skin to monitor your heart and you will wear a blood pressure cuff and oxygen saturation probe. During the test you will breathe through a mouth piece, initially at rest and then while cycling on a fixed bike. After three minutes of measurements at rest, followed by three minutes of pedalling freely without resistance at a steady rate, the amount of resistance you have to pedal against will be increased every minute until it becomes too difficult to continue. This will determine your maximum exercise capacity. During the next two visits you will perform an exercise test with the resistance you have to pedal against will be set between 60% and 80% of this maximum value. You will be asked to cycle for a short period of time (either two or six minutes) followed by a two minute rest period, and repeat this sequence of exercise and rest as often as you can. On one visit you will use the VitaBreath device during rest periods and on the other visit you will perform a simple

technique called pursed lip breathing (similar to blowing out a candle) to aid recovery. A computer will decide how long you exercise for during each cycling bout (two or six minutes) and whether you use the VitaBreath device or pursed lip breathing first; you will not be able to choose. This is avoid any potential bias favouring one technique over the other as there may be a “learning effect”, and you may perform better on the second exercise test.

After the tests you will receive information about your exercise capacity and the factors limiting your exercise tolerance.

### **What are the possible disadvantages and risks to taking part?**

You should expect to feel breathless and/or muscle discomfort during and after the exercise test. This is not harmful, but rather a normal part of exercise. You will soon return to your original state. The risks are no different to similar levels of exercise in other settings, and overall exercise is beneficial. About 1 in 1000 patients develops complications such as abnormal blood pressure, fainting, problems with heart rate or rhythm. In exceptional circumstances there can be more serious complications such as angina (chest pain) or a heart attack.

### **What are the advantages to taking part?**

You will have the chance to experience the effect of using the device following exercise. This may help you recover more quickly. You will be allowed to keep the device, which will be supplied with a charger. Your results will help us determine whether routine use of this device during pulmonary rehabilitation is helpful, and thus will be of benefit to other people with COPD.

### **Payment**

Travel expenses will be reimbursed.

### **Will my personal information be kept confidential?**

During the study we will collect information from you about your health and well-being. Your personal information such as your name and date of birth will be kept confidential and only available to the research team. The information given will only be used in a way that cannot be traced back to you, and any personal information will be stored securely. With your permission, we will write to your GP to let him/her know that you are taking part in the study. No one outside the research team will know if you decide not to take part.

### **What if there is a problem or I need more information?**

If you wish to complain, or have any concerns about the study, please ask to speak to the researcher who will do their best to answer your questions. If you are still unhappy, you can complain formally using the normal NHS complaints channels.

### **What will happen with the results of the study?**

The results will be discussed at scientific medical meetings, and also will be published in medical journals so that others can learn from our findings. You can receive a copy of the results by contacting Dr Stephen Bourke (whose details are at the end of this document).

#### **Contact details:**

Dr. Stephen Bourke

Consultant Respiratory Physician

North Tyneside General Hospital

Rake Lane

North Shields

NE29 8NH

Tel: 0191 2934026

Email: [stephen.bourke@NHCT.nhs.uk](mailto:stephen.bourke@NHCT.nhs.uk)

Ioannis Vogiatzis

Professor of Rehabilitation Sciences

Faculty of Health and Life Sciences

Department of Sport, Exercise and Rehabilitation

Northumbria University

Contact Number: 01913395446

## Letter to GP for studies presented in chapters 4, 5 and 7.

Influence of the Vitabreath device on exercise tolerance in COPD

GP

Northumbria Healthcare NHS Foundation Trust

North Tyneside General Hospital

PATIENT DETAILS

Rake Lane

North Shields

NE29 8NH

DATE

Dear General Practitioner,

Your patient has agreed to take part in a research project entitled:

**Influence of the VitaBreath device on exercise tolerance in patients with chronic obstructive pulmonary disease.**

Ethical approval has been obtained. Reference: REC.....

We are comparing the effects of a small handheld non-invasive ventilatory support device (Vitabreath) to pursed lip breathing (a breathing technique commonly used by COPD patients) on exercise tolerance and dynamic hyperinflation in stable patients with COPD. Participants will be randomly allocated to perform either continuous or interval exercise during assessments. The trial will be conducted in North Tyneside General Hospital and all aspects of the trial, including transport, will be arranged by the research team.

The intervention includes 3 visits. During the first visit a medical history will be recorded and the patient will undergo a respiratory function assessment (spirometry, lung volumes and diffusion capacity measurements) and a cardiopulmonary exercise test. During visits 2 and 3 the patient will undergo a continuous or interval exercise test to the limit of exercise tolerance. The duration of the trial will be approximately 10 days from the date of the first visit and it is important no change in medication of the patient occurs during this period, unless there is an important reason (i.e. exacerbation).

Please contact us if you would like any further information about the study,

Kind regards,

Stephen Bourke

Consultant respiratory physician

Version 1.1 7<sup>th</sup> Feb 2017

## Letter of support from Philips Respironics



February 13, 2017

Dr. Stephen Bourke  
Consultant Respiratory Physician  
Northumbria Healthcare NHS Foundation Trust  
North Tyneside General Hospital  
Rake Lane North Shields  
Tyne and Wear  
NE29 8NH.

Dr. Ioannis Vogiatzis  
Professor of Rehabilitation Sciences  
Faculty of Health and Life Sciences  
Department of Sport, Exercise and Rehabilitation

Northumbria University Newcastle  
Newcastle upon Tyne  
NE1 8ST

Re: Letter of Support for your study titled: **Influence of the VitaBreath device on exercise tolerance in patients with chronic obstructive pulmonary disease.**

Dear Drs. Bourke and Vogiatzis

Philips-Respironics Inc., a Philips Healthcare company, is a world leader in manufacturing respiratory, diagnostic and ventilation devices used for the treatment of various conditions, such as sleep disordered breathing, respiratory insufficiency and respiratory failure. As a medical device manufacturer of these types of products, we are deeply interested in the promotion of clinical research and education in these areas and welcome formal applications for support from clinicians. Requests are reviewed on a quarterly basis and we encourage clinicians to submit applications to the clinical department throughout the year using our standard template which is available upon request ([clinical.research@philips.com](mailto:clinical.research@philips.com)). Consistent with our history of support, your application has been reviewed competitively by our central review committee and I am pleased to inform you that we are happy and excited to commit our support to the above proposed study (Grant Reference #:HRC-GRA-17030-VBREATH-SH).

As part of this support, Philips-Respironics, intends to provide you with approximately £7,500 (Seven Thousand Five Hundred Pounds) and approximately 24 VitaBreath devices, with the anticipation that that this funding will start in 2017 and that you will secure any additional funding required support from alternative sources (NHS, Pharma, other...). This support is solely intended to facilitate the execution of the research outlined

[www.philips.com/respironics](http://www.philips.com/respironics)





above. The proposed timetable of payments is included in this letter for your review and will appear in the final study agreement, subject to change as mutually agreed upon.

**Proposed Deliverables/Payment timetable.**

Deliverable	Due Date	Responsible Party
Upon execution of agreement (signatures) (£5,000) and delivery of equipment.	Q2 2017	PI/Philips
Data Analysis, draft publication submitted to Philips (£2,500)	Q1 2018	PI
Quarterly report to include recruitment update and review of any issues encountered	Quarterly	PI

PI= Principle Investigator; Philips= Gary Lotz

Should you have any questions, please don't hesitate to contact me

Sincerely,

Gary W. Lotz  
Director, Global Clinical & Scientific Affairs  
Philips HealthTech  
Sleep and Respiratory Care (SRC)  
1010 Murry Ridge Lane  
Murrysville, PA 15146  
Phone: +1-724-733-5812  
Cell: +1-724-882-5812  
Fax: +1-724-387-4469

[www.philips.com/respironics](http://www.philips.com/respironics)



## Appendix C

### Consent form of the study presented in Chapter 6.

#### Effect of the VitaBreath device on chest wall dynamic hyperinflation and respiratory muscle activation during recovery from exercise in patients with Chronic Obstructive Pulmonary Disease.

PARTICIPANT NAME:
Year of birth:
IRAS No: 259201

Please initial boxes

1) I have read the information sheet for the above study, version 1.5 dated 24 <sup>th</sup> of August 2019, and have had the opportunity to ask questions.	
2) I understand that I do not have to take part, and I am free to withdraw at any time, without giving any reason if I do not want to, without my legal rights or the care I receive being affected.	
3) I understand that if I withdraw, the information I have provided will still be used up to when I withdraw, but with my personal information removed so I cannot be identified, unless I state otherwise.	
4) I understand that relevant sections of my medical records and data collected during the study may be looked at by responsible individuals from the NHS Trust or regulatory authorities where it is relevant to taking part in this research. I give permission for these individuals to have access to my records	
5) I understand that the information will be used in future reports, articles or presentations by the research team.	
6) I understand my personal information will not appear in any future reports, articles or presentations by the research team.	
7) I give permission for information to be sent to the GP about my being involved in the study.	
8) I agree to participate to the study	
	DD MM YYYY
<b>Participant name (PRINT)</b>	<b>Signature</b> <b>Date</b>
	DD MM YYYY
<b>Researcher taking consent (PRINT)</b>	<b>Signature</b> <b>Date</b>



## **Participant information sheet of the study presented in Chapter 6.**

**Title:** Effect of the VitaBreath device on chest wall dynamic hyperinflation and respiratory muscle activation during recovery from exercise in patients with Chronic Obstructive Pulmonary Disease.

**IRAS No: 259201**

You are being invited to take part in a research study that will assess the effect of a CE marked device which has been used since 2015 (VitaBreath) on your breathing pattern and its effect on the operation of your respiratory muscles. The study is part of a Ph.D. project. Before you decide if you would like to take part, please take time to read the information, and discuss it with others if you wish. If you would like someone to read through the information with you, please ask.

### **What is the purpose of the study?**

People with COPD have more air in their lungs than other people (this problem with high lung volumes is called “hyperinflation”). Unfortunately this is unhelpful as breathing at higher lung volumes requires more effort and contributes to breathlessness. When anyone exercises, they breathe more quickly. People with COPD have narrowed airways, which makes breathing out difficult. When they breathe more quickly they may not be able to breathe out fully before they need to take the next breath in. This means that the volume of air in their lungs tends to increase further during exercise, which makes breathing even more difficult. This problem is called “dynamic hyperinflation”. Today there are available ventilation assist devices that can help people with COPD to breathe easier even during exercise or activities of daily living such as the VitaBreath device.

Data from a previous study we conducted comparing use of the VitaBreath device during recovery periods between bouts of exercise to pursed lip breathing (normal breathing strategy recommended to COPD patients) showed that patients using the VitaBreath device were able to exercise longer and also reported less breathlessness. However, during the first study we weren’t able to investigate the actual mechanism by which the device impacts on your breathing capacity because specialised technology to monitor your breathing pattern was not available.

The purpose of this study is to investigate the mechanism by which the VitaBreath device influences your breathing pattern and better understand how breathing through the device influences the activation of your respiratory muscles and your sensation of breathlessness.

### **Why have you been chosen?**

You have been chosen because you have COPD and you have experienced breathlessness during moderate exercise. If you agree to be assessed for the trial, you will attend North Tyneside General Hospital to ensure that you meet all of the criteria required to participate, including that you are clinically stable and safe to

exercise. If you are suitable for the trial and agree to take part you will attend Northumbria University and perform two exercise tests each lasting for 20 minutes each on the same day.

### **Do I have to take part?**

No, it is your free choice to take part. If you decide to take part you will be asked to sign a consent form. You are free at any time to withdraw from the study, and do not have to give a reason. If you decide to withdraw from the study, we will use the information we have gathered up to that point, but we will not include your personal information unless you give us permission to do so.

If you decide not to take part you will continue to receive the same standard usual care.

### **What is the VitaBreath device?**

The VitaBreath device is a non-invasive portable ventilator which provides different levels of positive air pressure during inspiration and expiration. This assists normal breathing efforts in a similar way to a conventional non-invasive ventilator. In comparison to conventional non-invasive ventilators, the VitaBreath device is compact, light, battery powered and inexpensive. Consequently it is suitable to use anywhere, including away from your home. If you participated in the previous study you will have experience using the VitaBreath device, if not you will be trained how to use the device properly.

### **What does it mean if I take part in the study?**

If you choose to take part you will attend North Tyneside General Hospital once to perform some simple breathing tests, including spirometry, lung volumes and diffusion capacity assessment, in the lung function department, and have an ECG (tracing of your heart rhythm). One of the respiratory doctors will speak to you about your COPD and any other problems, and perform a physical examination. This will take about 90 minutes in total. If you have not your exercise capacity assessed before you will undergo an exercise test on a bicycle ergometer. The exercise test is called cardiopulmonary exercise test, and allows us to measure how your breathing, heart and muscles respond to exercise. This will take about 60 minutes. On your second visit (which will be conducted within a period of 5 days following the first visit) you will attend Northumbria University for approximately 2 hours. Adhesive skin markers and optodes (simple sensors) will be attached on the skin of your chest to record chest wall volumes, activation and oxygenation requirements of the respiratory muscles. This will take about 20 minutes. Following your preparation you will perform two exercise tests lasting 20 minutes each. Between the two tests there will be a break in order to allow complete recovery from exercise.

**You should wear cool, comfortable clothing suitable for exercise. You can eat a light meal a few hours before the exercise test, but you should avoid eating a large heavy meal.** Adhesive pads will be attached to your skin to monitor your heart and you will wear a blood pressure cuff and oxygen saturation probe. After

three minutes of measurements at rest, followed by three minutes of pedalling freely without resistance at a steady rate, you will be asked to cycle for two minutes followed by a two minute recovery period, and repeat this sequence of exercise and recovery for 20 minutes in total. During the first minute of each recovery you will breathe either through the VitaBreath device or using the pursed lip breathing technique.

After the tests you will receive information about the effect of the VitaBreath device on the way you breathe.

### **What are the possible disadvantages and risks to taking part?**

You should expect to feel breathless and/or muscle discomfort during and after the exercise test. This is not harmful, but rather a normal part of exercise. You will soon return to your original state. The risks are no different to similar levels of exercise in other settings, and overall exercise is beneficial. About 1 in 1000 patients develops complications such as abnormal blood pressure, fainting, problems with heart rate or rhythm. In *exceptional circumstances* there can be more serious complications such as angina (chest pain) or a heart attack.

### **What are the advantages to taking part?**

One of the conclusions of the original study is that patients retaining the device for use at home found the device helpful to their breathing, so it is likely that they would like to test their breathing capacity again during exercise and compare their old results with the ones of this study. The results of the trial will inform clinical services in the future. This may be of benefit to participants during future pulmonary rehabilitation courses, as well as other patients. If you do not have your own device we will provide you with a new device to use during the study, which you can keep after you have completed the study.

### **Payment**

Travel expenses to Northumbria University will be reimbursed.

### **Will my personal information be kept confidential?**

During the study we will collect information from you about your health and well-being. Your personal information such as your name and date of birth will be kept confidential and only available to the research team. The information given will only be used in a way that cannot be traced back to you, and any personal information will be stored securely. With your permission, we will write to your GP to let him/her know that you are taking part in the study. No one outside the research team will know if you decide not to take part.

### **What if there is a problem or I need more information?**

If you wish to complain, or have any concerns about the study, please ask to speak to the researchers who will do their best to answer your questions. If you are still unhappy, you can complain formally using the normal NHS complaints channels.

### **What will happen with the results of the study?**

The results will be discussed at scientific medical meetings, and also will be published in medical journals so that others can learn from our findings. You can receive a copy of the results by contacting Dr Stephen Bourke (whose details are at the end of this document).

***This study has been reviewed and approved by REC.***

Northumbria Healthcare trust is the sponsor for this study based in the United Kingdom / England. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Northumbria Healthcare trust will keep identifiable information about you for 12 months after the study has finished.

Your rights to access change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by contacting Professor Stephen Bourke.

North Tyneside General Hospital will collect information from you and your medical records for this research study in accordance with our instructions. North Tyneside General Hospital will use your name, and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Northumbria Healthcare trust and regulatory organisations may look at your medical and research records to check the accuracy of the research study. North Tyneside General Hospital will pass these details to Northumbria Healthcare trust along with the information collected from you and/or your medical records. The only people in Northumbria Healthcare trust who will have access to information that identifies you will be people who need to contact you to about the research study or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

Northumbria Healthcare trust will collect information about you for this research study from your medical records. This information will include your name, NHS number, contact details and health information, which is regarded as a special category of information. We will use this information to contact you in regards to your involvement to the study.

You can find out more about how we use your information by contacting the Respiratory Nurse Consultant in charge of this study, who's contact details can be found below:

**Contact details:**

Prof. Stephen Bourke  
Consultant Respiratory Physician  
North Tyneside General Hospital  
Rake Lane  
North Shields  
NE29 8NH  
Tel: 0191 2934026  
Email: [stephen.bourke@nhct.nhs.uk](mailto:stephen.bourke@nhct.nhs.uk)

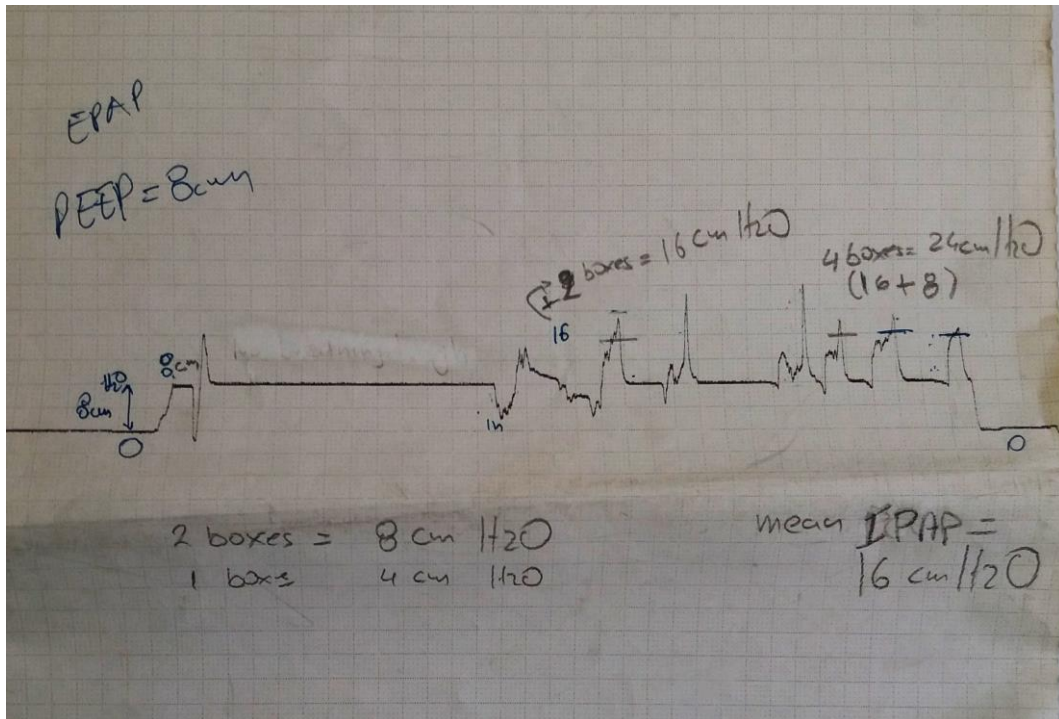
Ioannis Vogiatzis  
Professor of Rehabilitation Sciences  
Faculty of Health and Life Sciences  
Department of Sport, Exercise and Rehabilitation  
Northumbria University  
Contact Number: 01913395446

**Independent contact:**

Dr. John Steer  
Consultant Respiratory Physician  
North Tyneside General Hospital  
Rake Lane  
North Shields  
NE29 8NH  
Email: [john.steer@nhct.nhs.uk](mailto:john.steer@nhct.nhs.uk)

## Appendix D

### Assessment of inspiratory and expiratory pressures provided by the VitaBreath device



Breathing through the VitaBreath device whilst connected to a pressure transducer to record inspiratory and expiratory positive airway pressures.

# Appendix E

## Questionnaire



### VitaBreath: Patient questionnaire

Please kindly complete this questionnaire after using VitaBreath for 2-3 weeks and return it to your clinician.

1. What is your gender?  
Male  Female
  
2. Which hospital do you attend for the management of your COPD?  
\_\_\_\_\_
  
3. What is your age group?  
30-40  41-50  51-60  61-70  71-80  +80 years
  
4. Do you know how severe your COPD is?  
Mild (stage 1)   
Moderate (stage 2)   
Severe (stage 3)   
Very severe (stage 4)   
I don't know
  
5. When were you first diagnosed with COPD?  
Less than 1 year ago  2-3 years  4-5 years  5-7 years  8-10 years  +10 years
  
6. How often do you become breathless because of your COPD?  
Several times a day   
Once a day   
Couple of times a week   
Once a week   
Less than once a week
  
7. Have you (or someone on your behalf) called the 999 emergency services because of your breathlessness? Yes  No
  
8. Have you been taken by ambulance to hospital because of your breathlessness? Yes  No
  
9. Have you stayed in hospital for one day or longer because of your breathlessness? Yes  No
  
10. Have you attended a pulmonary rehabilitation programme?  
I am currently attending   
I have attended in the last year   
I attended 2-3 years ago   
I attended over 3 years ago   
I have not attended
  
11. a) Are you a member of a local patient support group? (e.g. BLF Breathe Easy) Yes  No   
If yes, which one? \_\_\_\_\_

b) Do you participate in an online patient support group or forum? Yes  No

If yes, which one? \_\_\_\_\_

12. Does breathlessness stop you from doing certain activities? Yes  No

If yes, what activities? \_\_\_\_\_

13. Do you plan activities based on the potential to become short of breath? Yes  No

If yes, what activities? \_\_\_\_\_

14. Before you were given VitaBreath, how anxious were you about becoming breathless?

Not at all anxious  1  2  3  4  5  6  7  8  9  10  Very anxious

15. Before you were given VitaBreath, how did you normally recover from your breathlessness?

Breathing techniques  Rescue inhaler  Oxygen  Rest

Other \_\_\_\_\_

16. Before you were given VitaBreath, how long did it take you to recover from your breathlessness?

Less than one minute

2-3 minutes

4-5 minutes

5-7 minutes

7-10 minutes

Longer than 10 minutes

17. How adequate was your answer to question 15 at relieving your breathlessness?

Not at all adequate  1  2  3  4  5  6  7  8  9  10  Very adequate

18. How often did you use VitaBreath?

Several times a day

Once a day

Couple of times a week

Once a week

Not at all

19. During or after what activities did you use VitaBreath? (tick all that apply)

Walking in the home

Walking outside

Climbing stairs

Carrying groceries

Playing with family

Physical activity

Other \_\_\_\_\_



20. How long did it take you to recover from your breathlessness with VitaBreath?
- Less than one minute
- 2-3 minutes
- 4-5 minutes
- 5-7 minutes
- 7-10 minutes
- Longer than 10 minutes
21. How adequate was VitaBreath at relieving your breathlessness?
- Not at all adequate            Very adequate
22. Has VitaBreath improved your ability to perform activities...
- Quicker (e.g. climbing the stairs)? Not at all      Yes, definitely
- For longer (e.g. walking)? Not at all      Yes, definitely
- More confidently? Not at all      Yes, definitely
23. How would you rate VitaBreath for...
- Ease of use? Excellent  Very good  Good  Fair  Poor
- Portability? Excellent  Very good  Good  Fair  Poor
24. Now that you have VitaBreath, how anxious are you about becoming breathless?
- Not at all anxious            Very anxious
25. How active have you been since you have had VitaBreath, compared to before?
- Much less active            Much more active
26. Would you say that VitaBreath has impacted your quality of life?
- No difference      Tremendous difference
27. If VitaBreath could not be given to you by the NHS, would you purchase it yourself for £499?
- Definitely would not      Definitely would
28. If you could buy VitaBreath online, how likely would you be to purchase it online?
- Definitely would not      Definitely would
29. Given your recent experience with VitaBreath, how likely is it that you would recommend VitaBreath to a friend or colleague, or other people with COPD?
- Not at all likely            Extremely likely
30. Other comments and feedback about VitaBreath
- 
- 
- 
-

31. a) Do you actively research information on COPD, or the care of your condition? Yes  No   
If yes, where do you research most frequently? \_\_\_\_\_

b) If you search online about COPD, what are the top sites that you use?

- 1 \_\_\_\_\_  
2 \_\_\_\_\_  
3 \_\_\_\_\_

32. Please rank your order of preference when accessing information and support (write 1 – 8)

- \_\_\_\_ Brochure  
\_\_\_\_ Health magazine  
\_\_\_\_ Medical website  
\_\_\_\_ Manufacturer's website  
\_\_\_\_ Web search  
\_\_\_\_ Peer-to-peer support group (e.g. patient association)  
\_\_\_\_ Physician office / Respiratory therapist  
\_\_\_\_ Social media

If you would be happy to be contacted by Philips to discuss further your experience with VitaBreath and possible involvement in a case study, please write your name and contact details below (optional):

Name \_\_\_\_\_

Telephone \_\_\_\_\_

Email \_\_\_\_\_

Thank you for taking the time to complete this questionnaire – your feedback is greatly appreciated

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