

**Acute and Chronic Adaptations To Intermittent and Continuous
Exercise in Chronic Obstructive Pulmonary Disease Patients**

Author

Sabapathy, Surendran

Published

2006

Thesis Type

Thesis (PhD Doctorate)

School

School of Physiotherapy and Exercise Science

DOI

[10.25904/1912/979](https://doi.org/10.25904/1912/979)

Rights statement

The author owns the copyright in this thesis, unless stated otherwise.

Downloaded from

<http://hdl.handle.net/10072/366117>

Griffith Research Online

<https://research-repository.griffith.edu.au>

**ACUTE RESPONSES AND CHRONIC ADAPTATIONS TO
INTERMITTENT AND CONTINUOUS EXERCISE IN
CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS**

A thesis submitted in fulfilment of the requirements
for the award of the degree
Doctor of Philosophy

by

SURENDRAN SABAPATHY
BExSc(Hons)



Griffith Health
School of Physiotherapy & Exercise Science
Gold Coast, Australia

February 2006

[Blank Page]

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Surendran Sabapathy

ACKNOWLEDGEMENTS

This story begins late in the year 2000... sitting under the brilliant Gold Coast summer sun, in what was called “Don’s Café”, just outside the Health Sciences building that then housed the School of Physiotherapy and Exercise Science. The question put to me by the ‘owner-proprietor’, Dr Donald Schneider, was simple, “Have you thought about getting into research, maybe do an Honours Degree?” – A question that stopped a then newly-graduate in my tracks. Well, here I am at the end-beginning with an answer, “I suppose I’ll give it a go.” Don, what can I say but that “you learnt me good”. As my principal Honours supervisor and then PhD co-supervisor, my education through you has been on-going and will continue to be so. I cannot thank you enough for what has not only been a fruitful collaboration, but for teaching me the trade and respect for the craft. More than just a teacher and mentor, also a friend. Associate Professor Norman Morris, my Honours co-supervisor and principal PhD supervisor, what a ride it’s been! Doc, you have kept the engine firing and done more for me, professionally and personally, than the job-description (if there is one) would have required of you. You have always challenged and pushed my boundaries of experience and I am only the better person/scientist/academic for it. Here’s to many more projects and collaborations down the road. While the cover of this thesis bears my name only, this undertaking has been a team effort. Including my supervisors, foremost in the team must be Rebecca Kingsley, research assistant extraordinaire. You were there right from the beginning and saw this project through most of its way with your amazing organisational skills. It has been an absolute pleasure working with you on these and the many other projects thrown our way from time to time, and I hope you are pleased with the outcome.

These were studies in integrative physiology and would not have been possible without the voluntary participation of all the individuals who formed the study

population. Their enthusiasm and support has been tremendous and I cannot thank them enough for their contributions. The staff and fellow grad students in the School cannot be denied a significant acknowledgement for providing a great atmosphere to work in. A few need to be named: Dr Clare Minahan, great friend and colleague; Justin Kavanagh, you among all others know the ups and downs of this journey since our paths have paralleled each other so closely; Danielle Loveless (Bling!) for keeping me sane – you are an absolute champion! Luke DeBeus for putting up with me in the grad office; Professor Greg Gass, former Head of School, and Dr Lewis Adams, current Head, for their belief and support.

At home – Perry, Sheila, Liam and Ashley Canning who are my family here on the Coast. I hope you share my pride in this.

This work could not have been possible without a generous scholarship and research funding from the Breathlessness Research Charitable Trust, the United Kingdom.

This story meets a qualitative end in this work, but it resides within a larger one. One that, particular to this story, has provided me with the courage, confidence and support (and so much of it!) to see this through. Stars in this greater story are my parents, Kanaga and Dori Sabapathy. Dad, art historian and the greatest academic I know, your love and enthusiasm for education and the processes of constructive thought and query have inspired and guided me every step of the way. Mum, who is an oasis of steadfast, calm support; there is no way to thank you enough. If this can be considered a labour of love, then it is of and for you both.

A handwritten signature in black ink, consisting of stylized, overlapping loops and curves, likely representing the author's name.

PUBLICATIONS

Publications arising from this thesis (to date):

Sabapathy, S., Kingsley, R. A., Schneider, D. A., Adams, L., Morris, N. R. (2004).

Continuous and intermittent exercise responses in individuals with chronic obstructive pulmonary disease. *Thorax*. 59: 1026-1031.

Sabapathy, S., Awater, M. F., Schneider, D. A., Kingsley, R. A., Hopman, M. T.

E., Morris, N. R. (2006). Lower limb vasodilatory capacity is not reduced in patients with moderate COPD. *Int J COPD*. 1: 73-81.

Publications contributing to this thesis:

Sabapathy, S., Schneider, D.A., Comadira, G., Johnston, I., Morris, N.R. (2004).

Oxygen uptake kinetics during severe exercise: a comparison between young and older men. *Respir Physiol Neurobiol*. 139: 203-213.

ABSTRACT

The primary aim of this thesis was to develop a better understanding of the physiology and perceptual responses associated with the performance of continuous (CE) and intermittent exercise (IE) in patients with moderate chronic obstructive pulmonary disease (COPD). A secondary aim was to examine factors that could potentially limit exercise tolerance in COPD patients, particularly in relation to the dynamics of the cardiovascular system and muscle metabolism. The results of the four studies conducted to achieve these aims are presented in this thesis.

In Study 1, the physiological, metabolic and perceptual responses to an acute bout of IE and CE were examined in 10 individuals with moderate COPD. Each subject completed an incremental exercise test to exhaustion on a cycle ergometer. Subjects then performed IE (1 min exercise: 1 min rest ratio) and CE tests at 70% of peak power in random order on separate days. Gas exchange, heart rate, plasma lactate concentration, ratings of breathlessness, inspiratory capacity and the total amount of work completed were measured during each exercise test. Subjects were able to complete a significantly greater amount of work during IE (71 ± 32 kJ) compared with CE (31 ± 24 kJ). Intermittent exercise was associated with significantly lower values for oxygen uptake, expired ventilation and plasma lactate concentration when compared with CE. Subjects also reported a significantly lower rating of breathlessness during IE compared to CE. The degree of dynamic lung hyperinflation (change in end-expiratory lung volume) was lower during IE (0.23 ± 0.07 L) than during CE (0.52 ± 0.13 L). The results suggest that IE may be superior to CE as a mode of training for patients with COPD. The greater amount of total work performed and the lower measured physiological responses attained with intermittent exercise could potentially allow greater training adaptations to be achieved in individuals with more limited lung function.

The purpose of Study 2 was to compare the adaptations to 8 wk of supervised intermittent and continuous cycle ergometry training, performed at the same relative intensity and matched for total work completed, in patients with COPD. Nineteen subjects with moderate COPD were stratified according to age, gender, and pulmonary function, and then randomly assigned to either an IE (1 min exercise: 1 min rest ratio) or CE training group. Subjects trained 3 d per week for 8 wk and completed 30 min of exercise. Initial training intensity, i.e., the power output applied during the CE bouts and during the exercise interval of the IE bouts, was determined as 50% of the peak power output achieved during incremental exercise and was increased by 5% each week after 2 wk of training. The total amount of work performed was not significantly different ($P=0.74$) between the CE (750 ± 90 kJ) and IE (707 ± 92 kJ) groups. The subjects who performed IE ($N=9$) experienced significantly lower levels of perceived breathlessness and lower limb fatigue during the exercise-training bouts than the group who performed CE ($N=10$). However, exercise capacity (peak oxygen uptake) and exercise tolerance (peak power output and 6-min walk distance) improved to a similar extent in both training groups. During submaximal constant-load exercise, the improved (faster) phase II oxygen uptake kinetic response with training was independent of exercise mode. Furthermore, training-induced reductions in submaximal exercise heart rate, carbon dioxide output, expired ventilation and blood lactate concentrations were not different between the two training modes. Exercise training also resulted in an equivalent reduction for both training modes in the degree of dynamic hyperinflation observed during incremental exercise. Thus, when total work performed and relative intensity were the same for both training modes, 8 wk of CE or IE training resulted in similar functional improvements and physiological adaptations in patients with moderate COPD.

Study 3 examined the relationship between exercise capacity (peak oxygen uptake) and lower limb vasodilatory capacity in 9 patients with moderate COPD and 9 healthy age-matched control subjects. While peak oxygen uptake was significantly lower in the COPD patients ($15.8 \pm 3.5 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$) compared to the control subjects ($25.2 \pm 3.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), there were no significant differences between groups in peak calf blood flow or peak calf conductance measured 7 s post-ischemia. Peak oxygen uptake was significantly correlated with peak calf blood flow and peak conductance in the control group, whereas there was no significant relationship found between these variables in the COPD group. However, the rate of decay in blood flow following ischemia was significantly slower ($p < 0.05$) for the COPD group ($-0.036 \pm 0.005 \text{ mL}\cdot 100 \text{ mL}^{-1}\cdot\text{min}^{-1}\cdot\text{s}^{-1}$) when compared to the control group ($-0.048 \pm 0.015 \text{ mL}\cdot 100 \text{ mL}^{-1}\cdot\text{min}^{-1}\cdot\text{s}^{-1}$). The results of this study suggest that the lower peak exercise capacity in patients with moderate COPD is not related to a loss in leg vasodilatory capacity.

Study 4 examined the dynamics of oxygen uptake kinetics during high-intensity constant-load cycling performed at 70% of the peak power attained during an incremental exercise test in 7 patients with moderate COPD and 7 healthy age-matched controls. The time constant of the primary component (phase II) of oxygen uptake was significantly slower in the COPD patients ($82 \pm 8 \text{ s}$) when compared to healthy control subjects ($44 \pm 4 \text{ s}$). Moreover, the oxygen cost per unit increment in power output for the primary component and the overall response were significantly higher in patients with COPD than in healthy control subjects. A slow component was observed in 5 of the 7 patients with COPD ($49 \pm 11 \text{ mL}\cdot\text{min}^{-1}$), whereas all of the control subjects demonstrated a slow component of oxygen uptake ($213 \pm 35 \text{ mL}\cdot\text{min}^{-1}$). The slow component comprised a significantly greater proportion of the total oxygen uptake response in the healthy control group ($18 \pm 2\%$) than in the COPD group ($10 \pm 2\%$). In the COPD patients, the slow component amplitude was significantly correlated with the decrease in inspiratory capacity ($r = -0.88$, $P < 0.05$; $N=5$), indicating that the magnitude of the slow component was larger in individuals

who experienced a greater degree of dynamic hyperinflation. This study demonstrated that most patients with moderate COPD are able to exercise at intensities high enough to elicit a slow component of oxygen uptake during constant-load exercise. The significant correlation observed between the slow component amplitude and the degree of dynamic hyperinflation suggests that the work of breathing may contribute to the slow component in patients with COPD.

CONTENTS

DECLARATION	i
ACKNOWLEDGMENTS	ii
PUBLICATIONS	iv
ABSTRACT	v
Table of CONTENTS	ix
CHAPTER 1	
Introduction – An Overview of the Literature and Statement of Purpose	1
Emphysema	3
Chronic Bronchitis	4
Risk factors contributing to the development of COPD	5
The Burden of COPD	7
Diagnosis and classification of severity and treatment	7
Exercise intolerance and disability in COPD	8
<i>Ventilatory limitation in COPD</i>	8
<i>Skeletal muscle dysfunction in COPD</i>	10
Exercise training as a component of pulmonary rehabilitation ...	12
Aims	18
REFERENCES	20
ABBREVIATED TERMS	31

CHAPTER 2	Study 1 – Acute Responses to Continuous and Intermittent Exercise in Chronic Obstructive Pulmonary Disease Patients ...	33
	INTRODUCTION	35
	METHODS	37
	Subjects and experimental design	37
	Experimental procedures	38
	<i>Pulmonary function assessment</i>	38
	<i>Incremental exercise test</i>	38
	<i>Continuous and intermittent exercise tests</i>	39
	<i>The effect of \dot{V}_{O_2} kinetics on the intermittent exercise response</i>	40
	<i>Determination of plasma lactate concentration</i>	43
	<i>Measurement of inspiratory capacity and end-expiratory lung volume</i>	43
	<i>Ratings of breathlessness</i>	44
	Statistical Analysis	44
	RESULTS	45
	DISCUSSION	51
	REFERENCES	57
	ABBREVIATED TERMS	60
CHAPTER 3	Study 2 – Continuous and Intermittent Exercise Training in Chronic Obstructive Pulmonary Disease Patients	63
	INTRODUCTION	65
	METHODS	67

	Subjects and experimental design	67
	Pre-training and post-training procedures	68
	<i>Pulmonary function assessment</i>	68
	<i>Incremental exercise test</i>	69
	<i>Submaximal exercise test and \dot{V}_{O_2} kinetics</i>	71
	<i>Six-minute walk test</i>	73
	<i>Assessment of Quality of Life</i>	74
	Training Protocol	75
	Statistical Analysis	75
	RESULTS	76
	DISCUSSION	89
	REFERENCES	99
	ABBREVIATED TERMS	105
CHAPTER 4	Study 3 – Lower Limb Vasodilatory Capacity in Patients with Chronic Obstructive Pulmonary Disease	109
	INTRODUCTION	111
	METHODS	113
	Subjects and experimental design	113
	Experimental procedures	114
	<i>Pulmonary function assessment and anthropometry</i>	114
	<i>Incremental exercise test</i>	115
	<i>Calf blood flow and conductance</i>	115

	Statistical analysis	119
	RESULTS	120
	DISCUSSION	125
	REFERENCES	131
	ABBREVIATED TERMS	136
CHAPTER 5	Study 4 – Oxygen Uptake Kinetics during ‘Heavy’ Exercise in Patients with Chronic Obstructive Pulmonary Disease.....	137
	Preface	139
	INTRODUCTION	140
	METHODS	142
	Subjects and experimental design	142
	Experimental procedures	143
	<i>Pulmonary function assessment</i>	143
	<i>Incremental exercise test</i>	143
	<i>Constant-load exercise test and \dot{V}_{O_2} kinetics</i>	144
	Statistical analysis	147
	RESULTS	147
	DISCUSSION	153
	REFERENCES	164
	ABBREVIATED TERMS	171
CHAPTER 6	Conclusion	173

APPENDIX A	Sample Information Sheet and Consent Form	183
APPENDIX B	Medical History Questionnaire	193
APPENDIX C	St. George's Hospital Respiratory Questionnaire (SGRQ)	197

[Blank Page]

**C
H
A
P
T
E
R

1**

Introduction

An Overview of the Literature and Statement of Purpose

CONTENTS

Introduction
3

Aims & Outline
18

References
20

**Abbreviated
Terms**
31

[Blank Page]

Chronic Obstructive Pulmonary Disease (COPD) can be defined as a disease state characterised by airflow obstruction - impairment of lung function is generally slow and progressive, and may only be partially reversed by bronchodilator or other therapies (Burrows et al., 1979; British Thoracic Society 1997; O'Donnell et al., 2001). The disease encompasses a spectrum of pathology including emphysema, chronic bronchitis, bronchiectasis and asthma. However the term COPD, as defined above (and for the patients described in this thesis), generally refers to individuals with emphysema and/or chronic bronchitis (American Thoracic Society, 1995).

Emphysema

Emphysema is characterised by dilatation or enlargement of the terminal air spaces of the lung distal to the terminal bronchiole, accompanied by destruction of their walls. Bronchioles and small bronchi depend on the attachment of adjacent alveolar walls to the superficial aspect of their airway walls in order to maintain support and tubular integrity (radial traction). The destruction of alveolar walls and their attachments could compromise the patency of the airways, leading to airflow obstruction and limitation. Figure 1.1 shows the typical histological appearance of an emphysematous lung (panel B) where the loss of alveolar walls and portions of the capillary bed, and narrowing and reduction in the number of small airways can be observed. Consequently, there is an enlargement of the air spaces with a corresponding reduction in the area available for gas exchange (increased physiological dead space).

Two main patterns of emphysema are recognised: 1) centriacinar or centrilobular emphysema involves damage to the central lobule of the lung (i.e. the respiratory bronchioles), while the more distal alveolar ducts and alveoli may be unaffected;

2) panacinar or panlobular emphysema results in the destruction and distension of the entire lobule, and commonly affects the lower half of the lungs. It is thought that an imbalance of endogenous proteinases and anti-proteinases in the lung, brought about by the action of inflammatory cells and mediators and/or genetic factors (α_1 -antitrypsin deficiency) are the major mechanisms causing emphysema (British Thoracic Society, 1997).

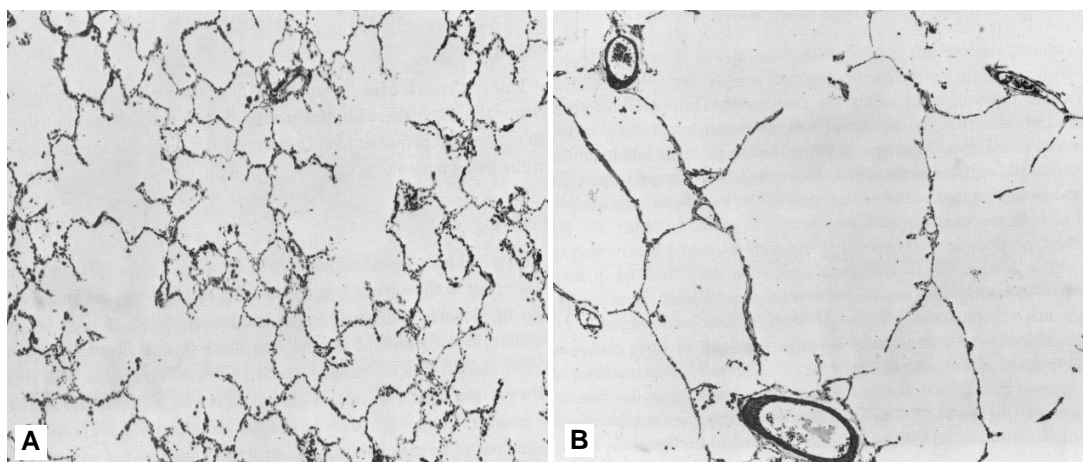


Figure 1.1. Microscopic section (x 90) of A) normal lung, and B) emphysematous lung (Heard, 1969). Note the loss of alveolar walls and enlargement of air spaces.

Chronic bronchitis

Chronic bronchitis refers to a hyper-secretory disorder characterised by excessive production and secretion of mucus within the bronchial tree. It is defined as the presence of cough with the production of sputum on most days for at least 3 months of 2 successive years (Bourke and Brewis, 1998), provided other causes of chronic cough have been excluded. The mucus hyper-secretion is the result of enlarged mucus-secreting glands and an increase in the number of goblet cells (Figure 1.2). Additionally, chronic inflammation in the small airways (small bronchi and bronchioles with an internal diameter of less than 2 mm) leads to injury of the airway wall. The injury-repair cycle then results in structural

remodelling of airway walls, increased scar tissue and collagen formation, thus narrowing the airway lumen and causing “fixed” airway obstruction (West, 2003).

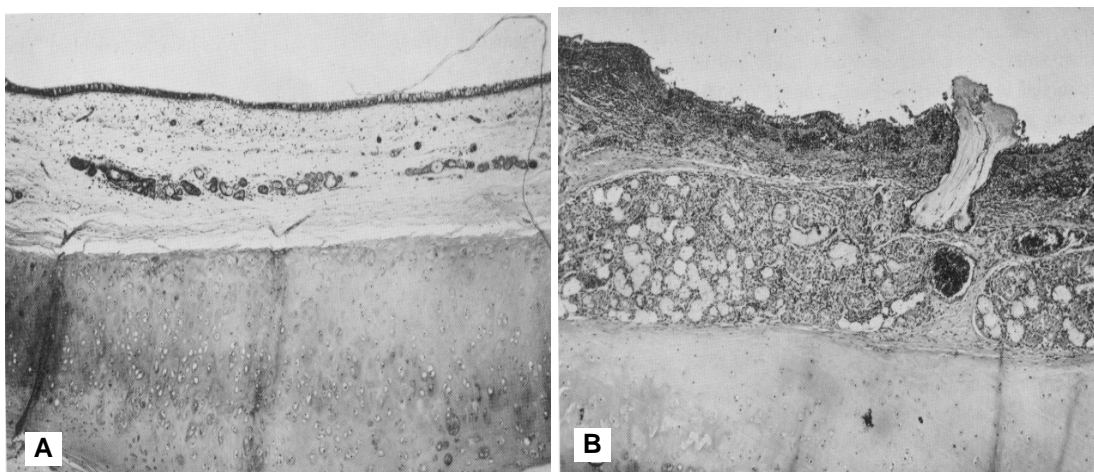


Figure 1.2. Microscopic section (x 60) of A) normal bronchial wall and B) bronchial wall of a patient with chronic bronchitis (Thurlbeck, 1976). The mucous glands are hypertrophied and submucosa thickened in the chronic bronchitis specimen compared to the normal specimen.

Risk factors contributing to the development of COPD

The risk factors for COPD encompass host factors and environmental exposures, and development of the disease is usually a combination of both. Probably the best documented genetic risk factor is a hereditary deficiency of α_1 -antitrypsin (Pauwels et al., 2001). α_1 -antitrypsin is a major inhibitor of proteolytic enzymes with a strong affinity for neutrophil elastase (Ohlsson, 1971), an enzyme that has been shown to produce emphysema in animal models (Janoff et al., 1977). While this hereditary deficiency is rare and accounts for less than 1% of all cases of COPD (Bourke and Brewis, 1998), cigarette smoking, for example, in combination with α_1 -antitrypsin deficiency greatly increases the risk of developing emphysema (Pauwels et al., 2001).

One of the primary causes of COPD is cigarette smoking (British Thoracic Society, 1997). It has previously been reported that 15-20% of smokers develop

COPD (American Thoracic Society, 1995), although the proportion increases with age (Lundbäck et al., 2003). Indeed, a recent study by Lundbäck et al. (2003) suggests that the proportion of elderly smokers who develop COPD approaches 50%. In this study, increasing age and smoking were the predominant risk factors; family history also increased the possibility of developing COPD, while gender did not emerge as a contributing factor (Lundbäck et al., 2003). The risk of developing COPD also appears dependent on the severity of smoking habit (Figure 1.3) – the greater the tobacco exposure, the greater the risk (Burrows et al., 1979). Cigarette smoke is a lung irritant that induces lung inflammation which can manifest as bronchitis and probably underlies the pathogenesis of emphysema in smokers (Stockley, 1995). It has consistently been demonstrated that inflammatory cells (macrophages and neutrophils) are increased in the lungs of smokers (Hunninghake and Crystal, 1983; Morrison et al., 1999; Maestrelli et al., 2001).

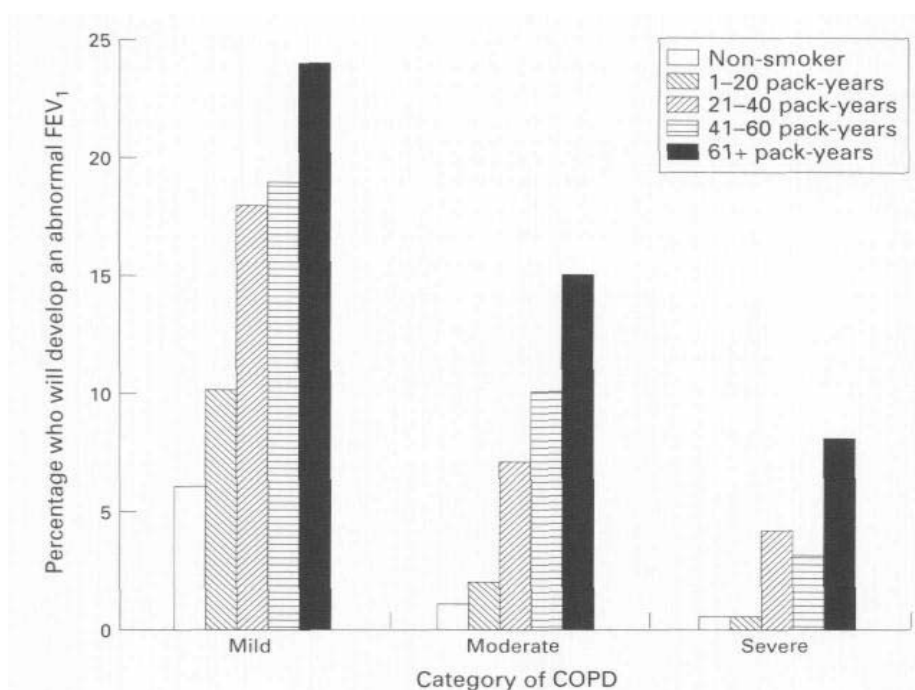


Figure 1.3. Proportion of individuals who will develop a particular grade of COPD for five different levels of cigarette consumption (Burrows et al., 1979; O'Donnell et al., 2001). FEV₁: forced expiratory volume in 1 s.

Intense, long-term exposure to occupational dust and chemicals, and air pollution have also been recognised as risk factors for COPD. Occupational dust and chemicals, in the form of vapours, fumes and airborne irritants have been shown to cause COPD, with the risk increased in concurrent smokers (Pauwels et al., 2001). High concentrations of out- and in-door urban pollution have also been implicated in causing COPD (for a review, see Pauwels et al., 2001). Other factors contributing to the development of COPD include history of childhood infections causing reduced lung function and respiratory symptoms in adulthood (Tager et al., 1988), pre-existing bronchial hyper-responsiveness (O'Connor et al., 1989), and poor *in utero* nutrition (Barker et al., 1991).

The Burden of COPD

The 2002 World Health Organisation's World Health Report cites COPD as the fourth leading cause of death in the world (World Health Organisation, 2002). In Australia, COPD is currently the fourth most common cause of death in males and the sixth most common cause in females (Australian Institute of Health and Welfare, 2002). Encouragingly, since 1995 there has been an annual decline in the death rate from COPD of 5.2% and 4.2% in males and females, respectively (Australian Institute of Health and Welfare, 2002). The prevalence of COPD is highest in countries where tobacco consumption is high, and the disease is responsible for a significant proportion of physician visits and hospitalisations (British Thoracic Society, 1997).

Diagnosis and classification of severity and treatment

A preliminary diagnosis of COPD is usually made in a patient who presents with symptoms of cough, sputum production, dyspnoea, and/or a history of exposure to risk factors for the disease (Bourke and Brewis, 1998). Confirmation of the

diagnosis is usually dependent upon spirometric assessment of airways obstruction. Table 1.1 lists the severity classifications of COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (Pauwels et al., 2001). In accordance with the GOLD guidelines, the presence of a post-bronchodilator forced expiratory volume in 1 s (FEV_1) less than 80% of the predicted value combined with an FEV_1 /forced vital capacity (FVC) ratio less than 70% confirms the presence of airflow limitation that is not fully reversible.

Table 1.1. Severity classification of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Guideline	Criteria
Stage 0 (at risk)	Normal lung function
Stage I (mild)	$FEV_1 > 80\%$ predicted, $FEV_1/FVC < 70\%$
Stage II (moderate)	$30\% \leq FEV_1 < 80\%$ predicted, $FEV_1/FVC < 70\%$
Stage III (severe)	$FEV_1 < 30\%$ predicted, $FEV_1/FVC < 70\%$

FEV_1 : forced expiratory volume in 1 s; FVC: forced vital capacity.

Exercise intolerance and disability in COPD

Patients with COPD are often disabled by their inability to perform many of the activities of daily living (Steiner and Morgan, 2001). The primary factors that contribute to exercise intolerance include ventilatory limitation and skeletal muscle dysfunction (Casaburi, 2001; O'Donnell, 2001); with cardiovascular limitations, nutritional deficiencies, and psychological factors also playing a part (Kaplan et al., 1993; Rochester, 2003).

Ventilatory limitation in COPD

Ventilatory limitation during exercise in patients with COPD may occur for a number of reasons. Progressive damage to lung tissue and bronchoconstriction increase airways resistance, resulting in expiratory flow limitation. During exercise, airflow obstruction can lead to incomplete lung emptying, raising end-

expiratory lung volume (dynamic hyperinflation) (Johnson et al., 1999). Dynamic hyperinflation (DH), in turn, limits tidal volume expansion in response to increases in ventilatory demand (O'Donnell et al., 2001). Breathing at higher operational lung volumes increases the elastic load to the inspiratory muscles, and coupled with an increase in breathing frequency to meet rising ventilatory demands, also serves to elevate the work of breathing (Bauerle et al., 1998; O'Donnell et al., 2001). Figure 1.4 illustrates the constraint imposed upon tidal volume expansion as a result of DH in a COPD patient.

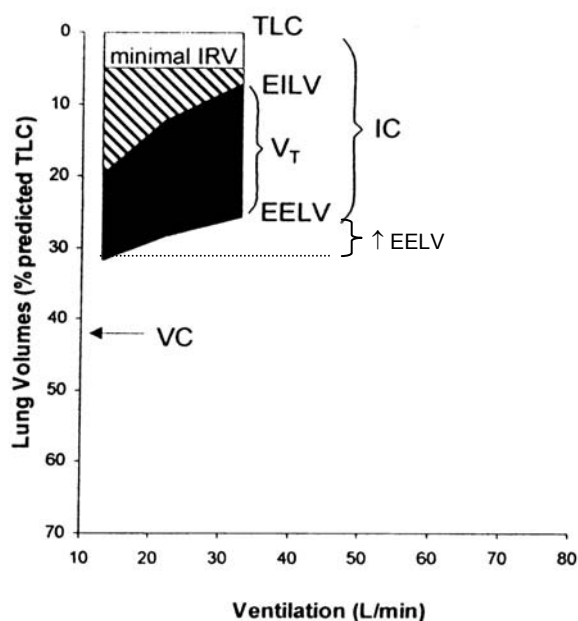


Figure 1.4. Lung volume changes with respect to increasing ventilation during exercise in a patient with COPD (adapted from O'Donnell et al., 2001). Dynamic hyperinflation (increase in end-expiratory lung volume, EELV) constrains tidal volume expansion (solid area), consequently restricting breathing to higher operational lung volumes. TLC: total lung capacity; VC: vital capacity; IRV: inspiratory reserve volume; EILV: end-inspiratory lung volume; IC: inspiratory capacity; V_T: tidal volume.

Gas exchange abnormalities can also contribute to ventilatory limitation. Excess physiological dead space (increased dead space to tidal volume ratio), intrapulmonary shunting, ventilation to perfusion mismatch and impaired lung diffusion capacity contribute to hypoxaemia, hypercapnia, and an increased ventilatory demand for a given level of physical activity (West, 2003). In conjunction with ventilatory limitations, hypoxic vasoconstriction and structural remodelling of the pulmonary vasculature could also increase pulmonary vascular

resistance, while DH may impair right ventricular preload and limit cardiac output during exercise (Stewart and Lewis, 1986; Bogaard et al., 1998).

A recent review by Aliverti and Macklem (2001) provides evidence to support the suggestion that the increased work of breathing may compromise oxygen (O_2) delivery to the locomotor muscles through competition for blood flow. These researchers demonstrated that in a patient with COPD exercising maximally, the O_2 consumption of the respiratory muscles could comprise a “whopping 48% of \dot{V}_{O_2} max [maximal oxygen consumption]” (Aliverti and Macklem, 2001, p235)! This finding agrees with other researchers who have shown that the work of breathing accounts for a significant proportion of whole body O_2 uptake (\dot{V}_{O_2}) at very high exercise intensities in both healthy and patient populations (Evison and Cherniack, 1968; Aaron et al., 1992; Harms et al., 1997). Ultimately, reduced blood flow would compromise O_2 and substrate delivery and possibly metabolic by-product removal to and from the exercising muscles, thereby contributing to limb fatigue.

Skeletal muscle dysfunction in COPD

Although the progressive damage to lung tissue and abnormal ventilatory mechanics in COPD are associated with dyspnoea (Grazzini et al., 2005), and represents one of the primary complaints of patients with lung disease (Carrieri-Kohlman et al., 1996), changes in peripheral skeletal muscle function are increasingly recognised as a significant contributing factor to the disability associated with the disease (American Thoracic Society/European Respiratory Society, 1999). Indeed, lower limb fatigue and discomfort are important contributing factors to exercise intolerance in patients with COPD (Killian et al., 1992).

There is a growing body of literature suggesting that skeletal muscles of COPD patients do not function normally and that this dysfunction contributes to poor exercise tolerance (American Thoracic Society/European Respiratory Society, 1999). Studies have shown muscle fibre atrophy (Hughes et al., 1983), changes in fibre composition with a selective loss of type I fibres (Jakobsson et al., 1990; Whittom et al., 1998), reduced capillary to fibre ratio (Whittom et al., 1998), and a reduction in oxidative enzyme capacity (Maltais et al., 1996) of the vastus lateralis and various other muscles in COPD patients compared to healthy controls. Cachexia (loss of muscle mass and strength) is associated with diminished exercise capacity (Gosselink et al., 1996), and is also a strong predictor of mortality in patients with COPD (Marquis et al., 2002).

Magnetic resonance spectroscopy of skeletal muscle in COPD patients performing exercise have demonstrated a greater rate of phosphocreatine (PCr) breakdown and slower PCr recovery kinetics (Tada et al., 1992; Kutsuzawa et al., 1995). Casaburi et al. (1991) and others (Maltais et al., 1996) have also reported that lactate is released at lower power outputs during exercise in COPD patients compared to healthy controls. These findings suggest an impairment of oxidative phosphorylation and greater dependence on anaerobic glycolysis during exercise in COPD patients. The increased reliance on anaerobic metabolism could lead to greater cellular and metabolic perturbations, speeding the onset of muscle fatigue, while metabolic acidosis would further increase ventilatory requirements during exercise.

Recently, systemic inflammation and oxidative stress have been proposed as a mechanism contributing to some of the skeletal muscle abnormalities observed in patients with COPD (Agusti et al., 2002; Couillard et al., 2002; Agusti et al., 2003;

Couillard et al., 2003). Agusti et al. (2002) showed that skeletal muscle apoptosis (cell death) was greater in patients with COPD than in healthy controls and that body mass index was inversely related the degree of apoptosis and correlated positively with exercise capacity. Couillard and colleagues (2002) demonstrated that markers of oxidative stress (via the measurement of plasma levels of thiobarbituric reactive substances and superoxide anion) were elevated, while plasma levels of the anti-oxidant vitamin E were lower in patients with COPD compared to healthy controls following exercise. Lipofuscin, another marker of oxidant damage, has also been reported to be elevated in the vastus lateralis muscle of COPD patients after exercise, suggesting that the contracting muscles are a source of oxidative stress in this population (Allaire et al., 2002). Finally, antioxidant (N-acetylcysteine) administration increases knee-extensor exercise endurance time and decreases superoxide anion and lipid peroxidation levels in patients with COPD (Koechlin et al., 2004). These findings implicate oxidative stress as a mechanism contributing to lower limb fatigue in COPD patients.

Exercise training as a component of pulmonary rehabilitation

Whether the observed skeletal muscle dysfunction is related to the disease pathology itself, or is a function of inactivity, is an important consideration. The ability to reverse the deleterious changes within the skeletal muscles of COPD patients with exercise training could provide an important intervention for improving exercise tolerance. It is likely that the exertional dyspnoea and lower limb fatigue/discomfort experienced by patients with COPD leads to a decline in their physical activity levels so as to avoid these unpleasant sensations. A reduction in physical activity produces a “vicious cycle” of progressive deconditioning that exacerbates the respiratory and peripheral muscular discomfort associated with a given level of exertion, further diminishing activity

levels. The gradual deterioration in physical capacity also leads to psychosocial issues such as social isolation, depression, anxiety, and loss of independence, that exert an increasingly deleterious effect upon a patient's quality of life (Dudley et al., 1980; Karajgi et al., 1990). Oga and colleagues (Oga et al., 2003) have shown that physical capacity and health status are predictors of mortality in patients with COPD.

There are numerous studies demonstrating improvements in peripheral muscle function in COPD patients following endurance exercise training (Casaburi et al., 1991; Maltais et al., 1996; Casaburi et al., 1997; Maltais et al., 1997; Serres et al., 1997; O'Donnell et al., 1998; Coppoolse et al., 1999; Vogiatzis et al., 2002; Puente-Maestu et al., 2003). Indirect evidence indicating peripheral muscle adaptations to endurance training in subjects with COPD include faster oxygen uptake and muscle oxygenation onset- and recovery-kinetics (Casaburi et al., 1997; Otsuka et al., 1997; Puente-Maestu et al., 2003), and reduced lactate and carbon dioxide (CO_2) output (\dot{V}_{CO_2}) during incremental as well as during constant-load exercise (Casaburi et al., 1991). More direct proof of skeletal muscle adaptations to exercise training have been demonstrated by Maltais et al. (1996) and Puente-Maestu et al. (2003), who reported increases in mitochondrial enzymes (citrate synthase and 3-hydroxyacyl CoA dehydrogenase) following 12- and 6-wk of endurance training, respectively, in COPD patients. Muscle antioxidant capacity has also been shown to be improved with endurance training in COPD patients, although the degree of improvement was lower in patients compared to healthy controls (Rabinovich et al., 2001).

Improvements in clinical and functional outcome measures such as increases in peak O_2 uptake ($\dot{V}_{\text{O}_2 \text{ peak}}$), peak exercise work rate, the duration of constant-

load exercise and 6-min walk distance (Casaburi et al., 1997; Coppoolse et al., 1999; Vogiatzis et al., 2002) have also been demonstrated in COPD patients following exercise training. Additionally, exercise training also results in improvements in health related quality of life (Wijkstra et al., 1994; Vogiatzis et al., 2002), and a reduction in dyspnoea (O'Donnell et al., 1995; Carrieri-Kohlman et al., 1996) during laboratory based exercise tests as well as while performing activities of daily living (Carrieri-Kohlman et al., 1996). Psychosocial improvements with endurance training in COPD patients have been documented (Emery et al., 1998; Koroza et al., 2002). These varied benefits of exercise training in individuals with COPD culminate in the fact that improvements in functional capacity enhance survival in these patients (Bowen et al., 2000).

There is currently no cure for COPD. As such, treatment is aimed at managing the progression and acute exacerbations of the disease, as well as improving quality of life. An effective management strategy generally comprises four components: 1) assessment and monitoring of the disease; 2) reduction of risk factors (e.g. smoking cessation); 3) management of stable COPD through a combination of education, pharmacological interventions, pulmonary rehabilitation and oxygen therapy; and 4) management of acute exacerbations (British Thoracic Society, 1997; Pauwels et al., 2001). The principal goals of pulmonary rehabilitation are to reduce the symptoms associated with COPD, and improve quality of life through increased participation in, and enhanced ability to perform, the activities of daily living (American Thoracic Society, 1995). An increasingly recognised and valued component of pulmonary rehabilitation programmes is exercise training.

While the evidence presented clearly supports the role of exercise training within the pulmonary rehabilitation setting, there are currently no clear guidelines with respect to training prescription for individuals with COPD. Training prescription for COPD patients is generally based on the exercise prescription principles used in healthy populations: continuous dynamic exercise such as walking or cycling (exercise mode) of 20 to 40 min duration (exercise duration), three to five times a week (exercise frequency) (American Thoracic Society/European Respiratory Society, 1999; Cooper, 2001). In patients with COPD, training intensities (for continuous exercise) ranging from as low as 30% up to 80% of \dot{V}_{O_2} peak or the peak power output achieved during symptom limited incremental exercise have demonstrated functional and physiological benefits (Ries and Archibald, 1987; Casaburi et al., 1991; Maltais et al., 1996; Maltais et al., 1997; Puente-Maestu et al., 2000; Normandin et al., 2002).

It is argued by some that the training intensity required to elicit physiological adaptations should be high, ranging from 60% to 80% of peak power output (Ambrosino and Strambi, 2004; Troosters et al., 2005). Certainly, the magnitude of physiological adaptations and improvement in exercise tolerance has been shown to be greater when exercise training is performed at higher compared to lower intensities (Casaburi et al., 1991; Puente-Maestu et al., 2000; Normandin et al., 2002). Casaburi et al. (1991) reported that although both high (80% of peak power output) and low intensity (40% of peak power output) endurance training resulted in an increase in endurance time during constant-load exercise, and reductions in lactate production and ventilation at identical power outputs, the magnitude of improvement was greater for high compared to lower intensity training. However, many patients, particularly those with severe COPD, may not be able to achieve high training intensity targets or exercise for the prescribed

duration at these relatively high intensities. Maltais and colleagues (1997) demonstrated that patients with severe COPD ($FEV_1 = 38 \pm 13\%$) were unable to achieve the target intensity of 80% of peak power output at the onset of 12 wk of cycle ergometer training (average training intensity at the end of 2 wk of training was $24.5 \pm 12.6\%$ of peak power output). Training intensity was adjusted in a progressive manner such that the patients were training at approximately 60% of peak power output after 10 wk of training. These results suggest that while some patients with COPD may not be able to achieve high intensity training targets at the onset of training programs, progressive increments in intensity over the course of the program will enable them to attain training intensities that will elicit physiological adaptations and functional improvement.

There is no consensus over the duration of training, but exercise training programs as short as 2-3 wk have resulted in improvements in exercise tolerance in COPD patients (Clini et al., 2001). While functional and physiological changes may be achieved during short-term training programs, maintenance of these adaptations and behavioural changes (which are important goals in pulmonary rehabilitation) probably require longer duration interventions (Kaplan et al., 1993; Troosters et al., 2000). Troosters et al. (2005) suggest that a minimum of 8 wk of exercise training as part of pulmonary rehabilitation is required to gain substantial benefits, with longer duration programs enhancing the beneficial outcome. Ultimately, interactions between training program costs, program adherence, and the degree of functional or physiological gain are likely to be the key determinants of program duration (Rochester, 2003).

Recently, the use of intermittent exercise (IE) as an alternative training modality to continuous exercise (CE) in COPD patients has been suggested (Cappoose et

al., 1999; Vogiatzis et al., 2002). Intermittent exercise is typically characterised by repeated short periods of exercise separated by periods of lower intensity exercise (Figure 1.5, panel B) or rest (Figure 1.5, panel C). In healthy subjects, IE is associated with a significant increase in exercise tolerance (Åstrand et al., 1960) and is accompanied by a lower degree of metabolic perturbation (Saltin et al., 1976; Morris et al., 2003), when the exercise intervals are performed at the same absolute intensity as that used during CE. Thus, IE may be a preferred mode of exercise training in COPD patients, particularly for individuals who cannot sustain extended periods of CE. Moreover, IE more closely resembles the physical output required for most activities of daily living and therefore confers greater specificity to a rehabilitation program when used as a training mode.

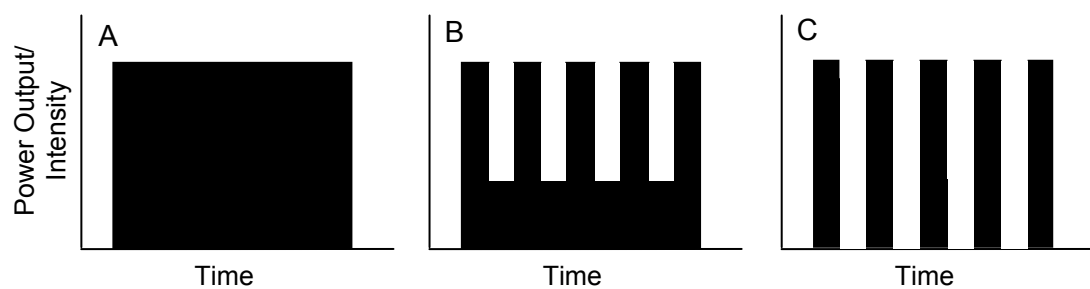


Figure 1.5. Schematic comparing continuous exercise (panel A) and two intermittent exercise (panels B and C) protocols. During continuous exercise, the power output or exercise intensity is held constant for the duration of the exercise bout. Intermittent exercise can comprise bouts of high intensity exercise interspersed with lower intensity exercise (panel B) or rest (panel C). The duration of the intervals can vary, as can the ratio of the intervals – for example, panel C suggests an equal exercise to rest interval ratio (i.e., 1:1), where the duration of each interval may be as short as 15 s, or up to 3 min and longer.

Morris and colleagues (2002) recently demonstrated that the adaptations to endurance exercise in healthy older individuals may be independent of exercise mode (i.e. CE v IE) when the same total amount of work is completed. This

finding raises the possibility that the total amount of work completed in a training study, rather than exercise intensity or even training mode *per se*, is the important determinant of the adaptations to endurance exercise. The results of Vogiatzis et al. (2002) lend some validity to this statement since these researchers demonstrated that the adaptations to 12 wk of CE and IE training were similar in patients with moderate to severe COPD. While the total work performed during training was similar between the CE and IE groups, IE was performed at a higher intensity relative to CE (Vogiatzis et al., 2002). Thus, it is not clear if the similar degree of functional improvement was due to the similar amount of total work performed or because IE training was relatively more intense than CE. Other studies that have not controlled for total work performed, or training intensity between CE and IE, have reported significant differences in the adaptations to these exercise modalities (Henriksson and Reitman, 1976; Gorostiaga et al., 1991). It would certainly be useful to compare the training adaptations to CE and IE when exercise intensity and total work performed are equal for both exercise training modes. Under these experimental conditions, differences between the outcome measures can only be attributed to exercise mode.

Aims

The primary aim of this thesis is to provide a deeper understanding of the physiology distinguishing CE and IE in patients with COPD. Studies One and Two will directly address this aim by firstly characterising the physiological responses to acute bouts of IE and CE in this patient population (Chapter Two), and then examining the adaptations to an 8-wk training program involving IE and CE (Chapter Three). In these studies, measures of exercise tolerance, gas exchange, muscle metabolism, ventilatory mechanics, and perceptual indices will

be used to assess and compare IE and CE. Additionally, aspects of \dot{V}_{O_2} kinetics (i.e., the time course change in oxygen uptake at the onset of exercise) will be examined as they relate to the exercise modes. Study Three (Chapter Four) examines aspects of lower limb blood flow and its potential as a factor limiting exercise tolerance in patients with COPD. This study represents a collaboration with researchers from the Department of Physiology, University of Nijmegen, the Netherlands. Study Four (Chapter Five) will focus exclusively on \dot{V}_{O_2} kinetics at the onset of exercise, comparing and discussing the physiological implications of the kinetic responses to 'heavy' intensity exercise in patients with COPD and age-matched healthy control subjects.

Each experimental chapter will include an introduction placing the study within the context of the relevant scientific literature, a statement and justification of the aims and hypotheses, describe the methods used, state the results, and provide a discussion of the findings. This thesis will conclude with a summary of the major findings of these experiments (Chapter Six). It is my hope and intention that the outcomes from this work will contribute significantly to the improvement of exercise prescription and practice principles for pulmonary rehabilitation programs as well as expand upon the body of knowledge addressing the physical function of individuals with COPD.

REFERENCES

- Aaron, E.A., Seow, C.K., Johnson, B.D., Dempsey, J.A. (1992). Oxygen cost of exercise hyperpnea: implications for performance. *J Appl Physiol.* 72.
- Agusti, A.G., Noguera, A., Sauleda, J., Sala, E., Pons, J., Busquets, X. (2003). Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J.* 21: 347-360.
- Agusti, A.G., Sauleda, J., Miralles, C., Gomez, C., Togoeres, B., Sala, E., Batle, S., Busquets, X. (2002). Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 166: 485-489.
- Aliverti, A., Macklem, P.T. (2001). How and why exercise is impaired in COPD. *Respiration.* 68: 229-239.
- Allaire, J., Maltais, F., LeBlanc, P., Simard, P.M., Whittom, F., Doyon, J.F., Simard, C., Jobin, J. (2002). Lipofuscin accumulation in the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Muscle Nerve.* 25: 383-389.
- Ambrosino, N., Strambi, S. (2004). New strategies to improve exercise tolerance in chronic obstructive pulmonary disease. *Eur Respir J.* 24: 313-363.
- Åstrand, I., Åstrand, P.-O., Christensen, E.H., Hedman, R. (1960). Intermittent muscular work. *Acta Physiol Scand.* 48: 448-453.
- American Thoracic Society. (1995). Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 152: S77-S120.

- American Thoracic Society/European Respiratory Society. (1999). Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 159: S1-S40.
- Australian Institute of Health and Welfare. (2002). Australia's Health 2002: The Eighth Biennial Health Report of the Australian Institute of Health and Welfare. Canberra, Australian Institute of Health and Welfare.
- Barker, D.J.P., Godfrey, K.M., Fall, C., Osmond, C., Winter, P.D., Shaheen, S.O. (1991). Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive lung disease. *BMJ.* 303: 671-675.
- Bauerle, O., Chrusch, C.A., Younes, M. (1998). Mechanisms by which COPD affects exercise tolerance. *Am J Respir Crit Care Med.* 157: 57-68.
- Bogaard, H.J., Dekker, B.M., Arntzen, B.W.G.J., Woltjer, H.H., van Keimpema, A.R.J., Postmus, P.E., de Vries, P.M.J.M. (1998). The haemodynamic response to exercise in chronic obstructive pulmonary disease: assessment by impedance cardiography. *Eur Respir J.* 12: 374-379.
- Bourke, S.J., Brewis, R.A.L. (1998). *Lecture Notes on Respiratory Medicine.* Blackwell Science, London.
- Bowen, J.B., Votto, J.J., Thrall, R.S., Haggerty, M.C., Stockdale-Woolley, R., Bandyopadhyay, T., Zu Wallack, R.L. (2000). Functional status and survival following pulmonary rehabilitation. *Chest.* 118: 679-703.
- British Thoracic Society, COPD Guidelines Group of the Standards of Care Committee. (1997). BTS Guidelines for the management of chronic obstructive pulmonary disease. *Thorax.* 52 (Suppl 5): S1-S28.

- Burrows, B., Knudson, R.J., Cline, M.G., Lebowitz, M.D. (1979). Quantitative relationships between cigarette smoking and ventilatory function. *Am Rev Respir Dis.* 115: 195-205.
- Cappoose, R., Schols, A.M.W.J., Baarends, E.M., Mostert, R., Akkermans, M.A., Janssen, P.P., Wouters, E.F.M. (1999). Interval versus continuous training in patients with severe COPD: a randomized clinical trial. *Eur Respir J.* 14: 258-263.
- Carrieri-Kohlman, V., Gormley, J.M., Douglas, M.K., Paul, S.M., Stulbarg, M.S. (1996). Exercise training decreases dyspnea and the distress and anxiety associated with it. *Chest.* 110: 1526-1535.
- Casaburi, R. (2001). Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Med Sci Sports Exerc.* 33: S662-670.
- Casaburi, R., Patessio, A., Ioli, F., Zanaboni, S., Donner, C.F., Wasserman, K. (1991). Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis.* 143: 9-18.
- Casaburi, R., Pórszász, J., Burns, M.R., Carithers, E.R., Chang, R.S.Y., Cooper, C.B. (1997). Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 155: 1541-1551.
- Clini, E., Foglio, K., Bianchi, L., Porta, R., Vitacca, M., Ambrosino, N. (2001). In-hospital short-term training program for patients with chronic airway obstruction. *Chest.* 120: 1500-1505.
- Cooper, C.B. (2001). Exercise in chronic pulmonary disease: aerobic exercise prescription. *Med Sci Sports Exerc.* 33: S671-S679.

- Coppoolse, R., Schols, A.M.W.J., Baarends, E.M., Mostert, R., Akkermans, M.A., Janssen, P.P., Wouters, E.F.M. (1999). Interval versus continuous training in patients with severe COPD: a randomized clinical trial. *Eur Respir J.* 14: 258-263.
- Couillard, A., Koechlin, C., Cristol, J.P., Varray, A., Prefaut, C. (2002). Evidence of local exercise-induced systemic oxidative stress in chronic obstructive pulmonary disease patients. *Eur Respir J.* 20: 1123-1129.
- Couillard, A., Maltais, F., Saey, D., Debigare, R., Michaud, A., Koechlin, C., LeBlanc, P., Prefaut, C. (2003). Exercise-induced quadriceps oxidative stress and peripheral muscle dysfunction in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 167: 1664-1669.
- Dudley, D.L., Glaser, E.M., Jorgensen, B.N., Logan, D.L. (1980). Psychosocial concomitants to rehabilitation in chronic obstructive pulmonary disease. Part I: Psychosocial and psychological considerations. *Chest.* 77: 413-420.
- Emery, C.F., Schein, R.L., Hauck, E.R., MacIntyre, N.R. (1998). Psychological and cognitive outcomes of a randomized trial of exercise among patients with chronic obstructive pulmonary disease. *Health Psychol.* 17: 232-240.
- Evison, H., Cherniack, R.M. (1968). Ventilatory cost of exercise in chronic obstructive pulmonary disease. *J Appl Physiol.* 25: 21-27.
- Gorostiaga, E.M., Walter, C.M., Foster, C., Hickson, R.C. (1991). Uniqueness of interval and continuous training at the same maintained exercise intensity. *Eur J Appl Physiol.* 63: 101-107.

- Gosselink, R., Troosters, T., Decramer, M. (1996). Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med.* 153: 976-980.
- Grazzini, M., Stendardi, L., Gigliotti, F., Scano, G. (2005). Pathophysiology of exercise dyspnea in healthy subjects and in patients with chronic obstructive pulmonary disease (COPD). *Respir Med.* 99: 1403-1412.
- Harms, C.A., Babcock, M.A., McClaran, S.R., Pegelow, D.F., Nickele, G.A., Nelson, W.B., Dempsey, J.A. (1997). Respiratory muscle work compromises leg blood flow during maximal exercise. *J Appl Physiol.* 82: 1573-1583.
- Heard, B.E. (1969). *Pathology of Chronic Bronchitis and Emphysema.* Churchill, London.
- Henriksson, J., Reitman, J.S. (1976). Quantitative measures of enzyme activities in type I and type II muscle fibres of man after endurance training. *Acta Physiol Scand.* 97: 392-397.
- Hughes, R.L., Katz, H., Sahgal, V., Campbell, J.A., Hartz, R., Shields, T.W. (1983). Fiber size and energy metabolites in five separate muscles from patients with chronic obstructive lung disease. *Respiration.* 44: 321-328.
- Hunninghake, G.W., Crystal, R.G. (1983). Cigarette smoking and lung destruction. Accumulation of neutrophils in the lungs of cigarette smokers. *Am Rev Respir Dis.* 128: 833.
- Jakobsson, P., Jorfeldt, L., Brundin, A. (1990). Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD), with and without chronic respiratory failure. *Eur J Appl Physiol.* 3: 192-196.

- Janoff, A., Sloan, B., Weinbaum, G., Damiano, V., Sandhaus, R.A., Elias, J., Kimbel, P. (1977). Experimental emphysema induced with purified human neutrophil elastase: tissue localization of the instilled protease. *Am Rev Respir Dis.* 109: 502-509.
- Johnson, B.D., Weisman, I.M., Zeballos, R.J., Beck, K.C. (1999). Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. *Chest.* 116: 488-503.
- Kaplan, R.M., Eakin, E.G., Ries, A.L., 1993. Psychosocial issues in the rehabilitation of patients with chronic obstructive pulmonary disease. In: *Principles and Practice of Pulmonary Rehabilitation.* Casaburi, R., Petty, T.L. (Eds.). W. B. Saunders Co., Philadelphia, pp. 351-365.
- Karajgi, B., Rifkin, A., Doddi, S., Kolli, R. (1990). The prevalence of anxiety disorders in patients with chronic obstructive pulmonary disease. *Am J Psychiatry.* 147: 200-201.
- Killian, K.J., LeBlanc, P., Martin, D.H., Summers, E., Jones, N.L., Campbell, E.J.M. (1992). Exercise capacity and ventilatory, circulatory and symptom limitation inpatients with chronic airflow limitation. *Am Rev Respir Dis.* 146: 935 - 940.
- Koechlin, C., Couillard, A., Simar, D., Cristol, J.P., Bellet, H., Hayot, M., Prefaut, C. (2004). Does oxidative stress alter quadriceps endurance in Chronic Obstructive Pulmonary Disease? *Am J Respir Crit Care Med.* 169: 1-6.
- Koroza, E., vu Tran, Z., Make, B. (2002). Neurobehavioural improvement after brief rehabilitation in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil.* 22: 426-430.
- Kutsuzawa, T., Shioya, S., Kurita, D., Haida, M., Ohta, Y., Yamabayashi, M. (1995). Muscle energy metabolism and nutritional status in patients with

chronic obstructive pulmonary disease: A ^{31}P magnetic resonance study. *Am J Respir Crit Care Med.* 152: 647-652.

Lundbäck, B., Lindberg, A., Lindström, M., Rönmark, E., Jönsson, A.C., Jönsson, E., Larsson, L.-G., Andersson, S., Sandström, T., Larsson, K. (2003). Not 15 but 50% of smokers develop COPD? - Report from the Obstructive Lung Disease in Northern Sweden Studies. *Respir Med.* 97: 115-122.

Maestrelli, P., Saetta, M., Mapp, C.E., Fabbri, L.M. (2001). Remodelling in response to infection and injury. Airway inflammation and hypersecretion of mucus in smoking subjects with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 164: S76-S80.

Maltais, F., LeBlanc, P., Jobin, J., Bérubé, C., Bruneau, J., Carrier, L., Breton, M.J., Falardeau, G., Belleau, R. (1997). Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 155: 555-561.

Maltais, F., LeBlanc, P., Simard, C., Jobin, J., Bérubé, C., Bruneau, J., Carrier, L., Belleau, R. (1996). Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 154: 442-447.

Maltais, F., Simard, A.-A., Simard, C., Jobin, J., Desgagnés, P., LeBlanc, P. (1996). Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med.* 153: 288-293.

Marquis, K., Debigare, R., Lacasse, Y., LeBlanc, P., Jobin, J., Carrier, G., Maltais, F. (2002). Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 166: 809-813.

- Morris, N., Gass, G., Thompson, M., Bennett, G., Basic, D., Moreton, H. (2002). Rate and amplitude of adaptation to intermittent and continuous exercise in older men. *Med Sci Sports Exerc.* 34: 471-477.
- Morris, N., Gass, G., Thompson, M., Conforti, D. (2003). Physiological responses to intermittent and continuous exercise at the same relative intensity in older men. *Eur J Appl Physiol.* 90: 620-625.
- Morrison, D., Rahman, I., Lannan, S., MacNee, W. (1999). Epithelial permeability, inflammation, and oxidant stress in the air spaces of smokers. *Am J Respir Crit Care Med.* 159: 473-479.
- Normandin, E.A., McCusker, C., Connors, M.L., Vale, F., Gerardi, D., Zu Wallack, R.L. (2002). An evaluation of two approaches to exercise conditioning in pulmonary rehabilitation. *Chest.* 121: 1085-1091.
- O'Connor, G.T., Sparrow, D., Weiss, S.T. (1989). The role of allergy and non-specific airway hyper-responsiveness in the pathogenesis of chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 140: 225-252.
- O'Donnell, D.E. (2001). Ventilatory limitations in chronic obstructive pulmonary disease. *Med Sci Sports Exerc.* 33: S647-S655.
- O'Donnell, D.E., McGuire, M., Samis, L., Webb, K.A. (1995). Impact of exercise reconditioning on breathlessness in severe chronic airflow limitation. *Am J Respir Crit Care Med.* 152: 2005-2013.
- O'Donnell, D.E., McGuire, M., Samis, L., Webb, K.A. (1998). General exercise training improves ventilatory and peripheral muscle strength and endurance in chronic airflow limitation. *Am J Respir Crit Care Med.* 157: 1489-1497.

- O'Donnell, D.E., Revill, S.M., Webb, K.A. (2001). Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 164: 770-777.
- Oga, T., Nishimura, K., Tsukino, M., Sato, S., Hajiro, T. (2003). Analysis of factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med.* 167: 544-549.
- Ohlsson, K. (1971). Neutral leukocyte proteases and elastase inhibited by plasma alpha1-antitrypsin. *Scand J Clin Lab Invest.* 28: 251-253.
- Otsuka, T., Kurihara, N., Fuji, T., Fujimoto, S., Yoshikawa, J. (1997). Effect of exercise training and detraining on gas exchange kinetics in patients with chronic obstructive pulmonary disease. *Clin Physiol.* 17: 287-297.
- Pauwels, R.A., Buist, A.S., Calverley, P.M.A., Jenkins, C.R., Hurd, S.S. (2001). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. *Am J Respir Crit Care Med.* 163: 1256-1276.
- Puente-Maetsu, L., Sanz, M.L., Sanz, P., Ruiz de Ona, J.M., Rodriguez-Hermosa, J.L., Whipp, B.J. (2000). Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. *Eur Respir J.* 15: 1026-1032.
- Puente-Maestu, L., Tena, T., Trascasa, C., Pérez-Parra, J., Godoy, R., García, M.J., Stringer, W.M. (2003). Training improves muscle oxidative capacity and oxygenation recovery kinetics in patients with chronic obstructive pulmonary disease. *Eur J Appl Physiol.* 88: 580-587.

- Rabinovich, R.A., Ardite, E., Troosters, T., Carbo, N., Alonso, J., Gonzalez-de-Suso, J.M., Vilaro, J., Barbera, J.A., Polo, M.F., Argiles, J.M., Fernandez-Checa, J.C., Roca, J. (2001). Reduced muscle redox capacity after endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 164: 1114-1118.
- Ries, A.L., Archibald, C.J. (1987). Endurance exercise training at maximal targets in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil.* 7: 594-601.
- Rochester, C.L. (2003). Exercise training in chronic obstructive pulmonary disease. *J Rehabil Res Dev.* 40: 59-80.
- Saltin, B., Essén, B., Pederson, P.K., 1976. Intermittent exercise: its physiology and some practical applications. In: Jokl, E. (Eds.). *Medicine and Sport*. Karger, Basel, pp. 23-51.
- Serres, I., Varray, A., Vallet, G., Micallef, J.P., Prefaut, C. (1997). Improved skeletal muscle performance after individualized exercise training in patients with severe chronic obstructive pulmonary disease. *J Cardiopulm Rehabil.* 17: 232-238.
- Steiner, M.C., Morgan, M.D.L. (2001). Enhancing physical performance in chronic obstructive lung disease. *Thorax.* 56: 73-77.
- Stewart, R.I., Lewis, C.M. (1986). Cardiac output during exercise in patients with COPD. *Chest.* 89: 199-205.
- Stockley, R.A., 1995. Biochemical and cellular mechanisms. In: *Chronic Obstructive Pulmonary Disease*. Calverley, P., Pride, N. (Eds.). Chapman and Hall, London, pp. 93-134.
- Tada, H., Kato, H., Misawa, T., Sasaki, F., Hayashi, S., Takahashi, H., Kutsumi, Y., Ishizaki, T., Nakai, T., Miyabo, S. (1992). ³¹P-Nuclear magnetic

resonance evidence of abnormal skeletal muscle metabolism in patients with chronic lung disease and congestive heart failure. *Eur Respir J.* 5: 163-169.

Tager, I.B., Segal, M.R., Speizer, F.E., Weiss, S.T. (1988). The natural history of forced expiratory volumes: effect of cigarette smoking and respiratory symptoms. *Am Rev Respir Dis.* 138: 837-849.

Thurlbeck, W.M. (1976). *Chronic Airflow Obstruction in Lung Disease.* W. B. Saunders, Philadelphia.

Troosters, T., Casaburi, R., Gosselink, R., Decramer, D. (2005). Pulmonary rehabilitation in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 172: 19-38.

Troosters, T., Gosselink, R., Decramer, M. (2000). Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Am J Med.* 109: 207-212.

Vogiatzis, I., Nanas, S., Roussos, C. (2002). Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J.* 20: 12-19.

West, J.B. (2003). *Pulmonary Pathophysiology: The Essentials.* Lippincott Williams and Wilkins, Philadelphia.

Whittom, F., Jobin, J., Simard, P.-M., LeBlanc, P., Simard, C., Bernard, S., Belleau, R., Matais, F. (1998). Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc.* 30: 1467-1474.

World Health Organization. (2002). World Health Report. World Health Organization, Geneva. 2002. Available from URL: <http://www.who.int/whr/2002/en/>.

Wijkstra, P.J., Van Altena, R., Kraan, J., Otten, V., Postma, D.S., Koeter, G.H. (1994). Quality of life in patients with chronic obstructive pulmonary disease improves after rehabilitation at home. *Eur Respir J*. 7: 269-273.

ABBREVIATED TERMS

CE	Continuous exercise
CO ₂	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
DH	Dynamic hyperinflation
EELV	End-expiratory lung volume
EILV	End-inspiratory lung volume
FEV ₁	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GOLD	Global Initiative of Chronic Obstructive Lung Disease
IC	Inspiratory capacity
IE	Intermittent exercise
IRV	Inspiratory reserve volume
O ₂	Oxygen
PCr	Phosphocreatine
TLC	Total lung capacity
VC	Vital capacity
\dot{V}_{CO_2}	Carbon dioxide output

Chapter 1

\dot{V}_{O_2} Oxygen uptake

V_T Tidal volume

**C
H
A
P
T
E
R

2**

Study 1

Acute Responses to Continuous and Intermittent Exercise in Chronic Obstructive Pulmonary Disease Patients

CONTENTS

Introduction
35

Methods
37

Results
45

Discussion
51

References
57

**Abbreviated
Terms**
60

[Blank Page]

INTRODUCTION

Endurance training has been shown to reduce ventilatory demand during exercise and improve peripheral muscle function in chronic obstructive pulmonary disease (COPD) patients (for a review, see American Thoracic Society/European Respiratory Society, 1999, and O'Donnell, 2001). While these results are encouraging, individuals with moderate to severe COPD are often unable to sustain prolonged periods of exercise at intensities that could maximise peripheral muscle and central cardiovascular adaptations (Maltais et al., 1997). Consequently, intermittent exercise (IE) has been suggested as an alternative training modality that may be better tolerated in COPD patients (Cappoose et al., 1999; Vogiatzis et al., 2002). IE is characterised by repeated bouts of short exercise separated by periods of rest and may be more suited to COPD patients, whose daily activities typically require short bursts of exertion interspersed with periods of recovery (Smolaka and Adamovich, 1974).

In healthy individuals, IE is associated with lower values for heart rate, oxygen uptake (\dot{V}_{O_2}), expired ventilation (\dot{V}_E) and blood lactate concentration when compared to continuous exercise (CE) (Åstrand et al., 1960; Morris et al., 2003). An important functional outcome is that total work performed is greatly increased during IE when the exercise intervals are performed at the same absolute intensity as that used during CE (Åstrand et al., 1960). These results suggest that in IE, the lower degree of metabolic perturbation within the active muscles during the exercise period and ability to recover during the rest intervals may delay the onset of fatigue and increase the total duration of exercise. Moreover, Morris and colleagues (2003) demonstrated that the lower \dot{V}_{O_2} response associated with IE compared to CE performed at 70% of peak power output (W_{peak}) was primarily due to the exponential \dot{V}_{O_2} kinetic response typical to a step change in activity

level (on-transient \dot{V}_{O_2} kinetics). At the onset of constant-load exercise, a transient exponential increase in \dot{V}_{O_2} is observed, attaining a new steady-state level within 2-3 min during light- to moderate-intensity exercise (Whipp and Casaburi, 1982). Even during higher-intensity exercise that engenders a slow component of increasing \dot{V}_{O_2} , the on-transient kinetic response remains exponential (Barstow, 1994). Thus, for exercise intervals longer than 2 min, the \dot{V}_{O_2} attained at the end of each exercise interval approaches that reached during CE performed at the same exercise intensity. This suggests that the duration of the exercise period is an important factor in determining the IE response, with longer exercise intervals reducing the differences observed between CE and IE.

To date, there have been no studies examining the acute response to IE in individuals with COPD. However, Vogiatzis et al. (2002) reported that the perception of dyspnoea was systematically lower during IE training compared to CE training in patients with moderate to severe COPD, despite IE being performed at a greater relative intensity than CE. A reduced ventilatory demand and lower degree of dynamic lung hyperinflation (DH) during IE could contribute to a reduction in dyspnoea and an improvement in exercise tolerance, independent of the metabolic demand for this mode of exercise. Studies in COPD patients have also demonstrated slowed on-transient \dot{V}_{O_2} kinetics (measured as the time constant, i.e. the time taken to attain 63% of the asymptotic amplitude) when compared to healthy control subjects during submaximal exercise (Nery et al., 1982; Palange et al., 1995). Slower kinetics may in turn result in a relatively lower \dot{V}_{O_2} amplitude during IE.

Severe deconditioning and dyspnoea with exertion are major deterrents to physical activity in COPD patients and could reduce compliance to exercise rehabilitation programs (Kaplan et al., 1993). If total work performed and/or time to exhaustion are increased and perceived intensity of breathlessness reduced during IE compared to CE, then IE may be a useful training mode in the pulmonary rehabilitation setting. Therefore, the purpose of the present study was to compare the physiological responses to IE using 1 min exercise and 1 min rest intervals, and CE performed at the same absolute power output in a group of COPD patients with moderate airflow obstruction. Performing IE and CE at the same absolute intensity will normalise the metabolic demand and allow for a comparison of the physiological responses between the two exercise modes. It is hypothesised that 1) exercise tolerance (total work performed) will be greater during IE than during CE, 2) IE will be associated with a lower degree of physiological perturbation (\dot{V}_{O_2} , \dot{V}_E , blood lactate concentration, dyspnoea), 3) the degree of DH will be lower in IE than in CE, and 4) DH will be positively correlated with breathlessness.

METHODS

Subjects and experimental design

Five male and 5 female patients with COPD participated in this study. Inclusion criteria for the study were 1) patients classified as having moderate COPD (Pauwels et al., 2001), 2) shortness of breath on exertion, and 3) no documented history of substantial co-morbidity. All testing was performed in the Physiology of Exercise Research Laboratory, Gold Coast campus, Griffith University, Australia. Subjects visited the laboratory on four separate occasions with each visit separated by at least 48 hr. During the first visit, the subjects performed pulmonary function tests, were familiarised with the exercise testing procedures,

and provided written informed consent. The second visit was used to determine each subject's maximal exercise capacity. During the subsequent two visits, the subjects performed CE or IE on a cycle ergometer. The order of the CE and IE tests was randomised, and the subjects performed only a single bout of exercise on either test day. The experimental protocol was approved by the Griffith University Human Research Ethics Committee.

Experimental procedures

Pulmonary function assessment

Pulmonary function was measured and assessed using standard techniques (American Thoracic Society, 1994). Spirometry, static lung volumes, lung diffusion capacity (DL_{CO}), and inspiratory capacity (IC) during exercise were measured using a closed-circuit pulmonary function testing system (Collins GS Modular PFT, Warren E. Collins, Inc, Braintree, MA, USA). Total lung capacity (TLC) was measured using the helium dilution method, while DL_{CO} was assessed by the single-breath carbon monoxide test.

Incremental exercise test

The incremental exercise test used to measure peak \dot{V}_{O_2} was performed on a Lode (Excalibur Sport, Gronigen, Netherlands) cycle ergometer. Subjects commenced unloaded cycling for 3 min and then the power output was increased by $4 \text{ W} \cdot 30 \text{ s}^{-1}$ for the male subjects and by $3 \text{ W} \cdot 30 \text{ s}^{-1}$ for the female subjects until volitional termination of the test.

During the incremental cycling test, subjects breathed through a mouthpiece and wore a nose-clip. Throughout exercise, \dot{V}_{O_2} , carbon dioxide output (\dot{V}_{CO_2}) and \dot{V}_E were measured breath-by-breath and averaged over 30-s intervals using a

metabolic measuring system (MedGraphics CardiO₂, Cardiopulmonary Diagnostic Systems, St. Paul, MN, USA). A 12-lead electrocardiograph (ECG) configuration was used to monitor cardiac rhythm and to determine heart rate (MedGraphics CardiO₂, Cardiopulmonary Diagnostic Systems, St. Paul, MN, USA). Peak exercise values for incremental cycling were calculated as the average of the two highest consecutive 30-s values obtained prior to termination of exercise.

Continuous and intermittent exercise tests

The power output for the CE and IE tests was calculated as 70% of W_{peak} . Each of the CE and IE tests were preceded by 3 min of unloaded cycling. The IE test consisted of 1 min of exercise interspersed with 1 min of rest (i.e. 1:1 exercise to rest ratio). The subjects were encouraged to cycle until the limit of tolerance during both exercise tests. The tests were terminated if subjects were able to complete 30 min of CE and/or 60 min of IE. Gas exchange indices were measured as described for the incremental test. The breath-by-breath data were smoothed using a middle 5 of 7 breath averaging procedure. Heart rate and rhythm were monitored during the tests with the ECG electrodes placed in a CM5 configuration (Lohmeier M607, Munich, Germany). Gas exchange and heart rate values are reported as the peak value attained within a 10-s bin at the end of every minute of exercise (for example, the value at the end of the first minute of exercise for both modes would represent the peak value attained between 0:50 and 1:00 min). Total work completed was calculated as the product of exercise time and external power output.

The effect of \dot{V}_{O_2} kinetics on the intermittent exercise response

In order to determine if any differences in \dot{V}_{O_2} between the exercise modes were caused by the on-transient kinetics of \dot{V}_{O_2} , the time constant (τ) of the initial rise in \dot{V}_{O_2} (the phase II or primary component) during the CE bout was calculated. In addition to the CE and IE bouts, 7 subjects performed one to two additional constant-load transitions to 70% of W_{peak} . The protocol for these additional exercise bouts involved 3 min of unloaded cycling followed by an abrupt application of the pre-determined power output for 7 min. The breath-by-breath \dot{V}_{O_2} data from each trial (including the first 7 min of the CE bout) were inspected for aberrant breaths. Values exceeding 3 standard deviations from the local mean were removed. The \dot{V}_{O_2} data from the repeated trials were then interpolated to 1-s values, time aligned and averaged, effectively smoothing the data and enhancing the underlying kinetic response. A four-compartment model with three exponential terms was used to describe the time course of the \dot{V}_{O_2} response:

$$\dot{V}_{O_2}(t) = A_B + A_C(1 - e^{-(t-TD_C)/\tau_C}) + A_P(1 - e^{-(t-TD_P)/\tau_P}) + A_S(1 - e^{-(t-TD_S)/\tau_S})$$

Equation 2.1

where $\dot{V}_{O_2}(t)$ is the \dot{V}_{O_2} at time t ; A_B is the baseline \dot{V}_{O_2} during unloaded cycling, while A_C , A_P and A_S represent the cardio-dynamic (phase I), primary (phase II) and slow component amplitudes, respectively; TD_C , TD_P and TD_S , and τ_C , τ_P and τ_S are the time delays and time constants of phase I and the primary and slow components, respectively. Since A_S represents an asymptotic amplitude and could therefore constitute an extrapolated value, the measured slow component at the end of 7 min of constant-load exercise (A'_S) was calculated using the model equation:

$$A'_S = A_S(1 - e^{-(t_e - TD_S)/\tau_S}) \quad \text{Equation 2.2}$$

where t_e is 420 s (or 7 min) and represents the end of exercise. If the amplitude of the slow component (A_S) was not significantly different from 0, the model was reduced to three compartments with exponential terms describing phase I and phase II:

$$\dot{V}_{O_2}(t) = A_B + A_C(1 - e^{-(t - TD_C)/\tau_C}) + A_P(1 - e^{-(t - TD_P)/\tau_P}) \quad \text{Equation 2.3}$$

Figure 2.1 provides an example of the \dot{V}_{O_2} response and model fit for a representative subject and Table 2.1 provides the individual and group mean values for selected model parameters.

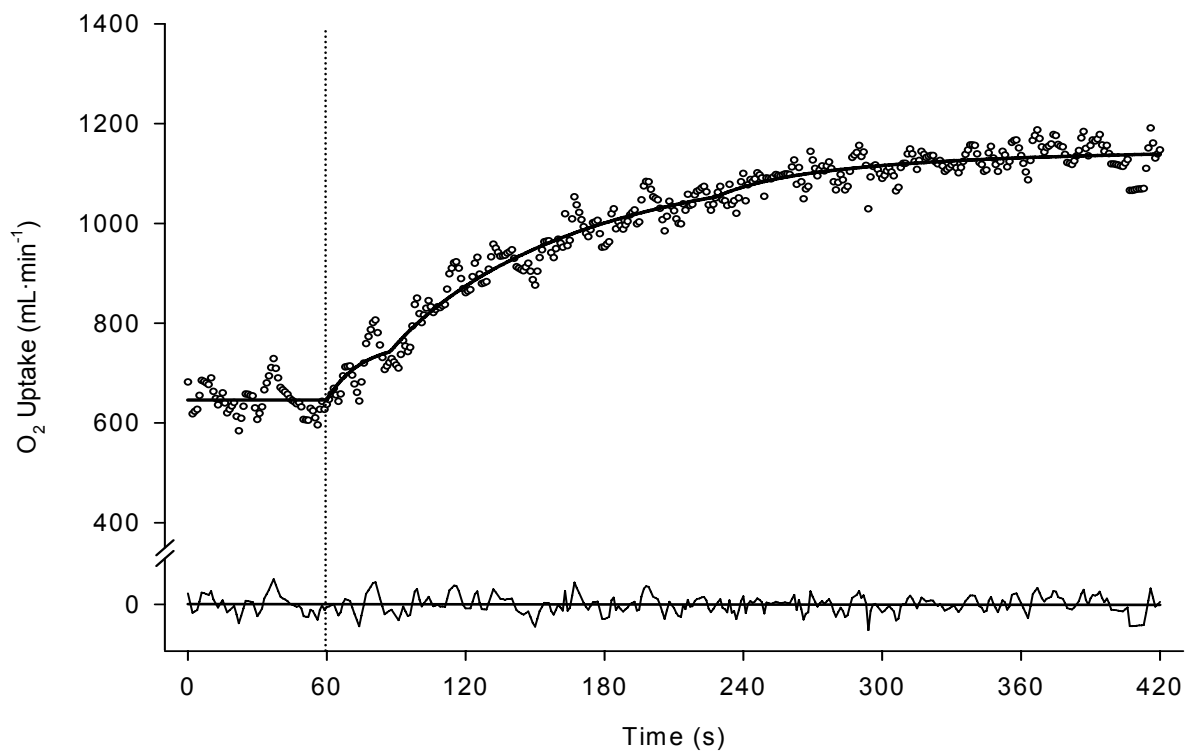


Figure 2.1. The O_2 uptake response to constant-load exercise in a representative subject. Data points represent mean second-by-second values for 2 transitions from unloaded cycling to 70% of peak power. The solid line indicates the model fit, with the residuals shown at the bottom. The pre-determined power output was applied at 60 s. The O_2 uptake values from 0 to 60 s are for unloaded cycling.

Table 2.1. Oxygen uptake kinetics in the transition to constant-load exercise performed at 70% of peak power.

Subjects	A_B (mL·min ⁻¹)	A_C (mL·min ⁻¹)	A_P (mL·min ⁻¹)	A'_S (mL·min ⁻¹)	τ_P (s)	TD_P (s)	TD_S (s)
1	555	24	310	59	86	9	217
2	580	53	324	55	64	25	224
3	477	19	146	--	97	32	--
4	646	115	361	24	85	27	141
5	551	47	352	26	74	26	229
6	714	127	581	--	115	22	--
7	747	158	663	80	55	8	174
Mean ± SEM	610 ± 37	78 ± 21	391 ± 66	49 ± 11	82 ± 8	21 ± 3	197 ± 17

A_B : baseline oxygen uptake amplitude; A_C : phase I amplitude; A_P : phase II amplitude; A'_S : slow component amplitude; τ_P : phase II time constant; TD_P : phase II onset time; TD_S : slow component onset time.

To determine if the lower \dot{V}_{O_2} response observed during IE compared to CE was primarily the result of the exponential shape of the on-kinetic response, a similar methodology to that recently described by Morris and colleagues (2003) was used. Briefly, the \dot{V}_{O_2} amplitude at 60 s of CE was calculated and compared with the measured IE response. The \dot{V}_{O_2} amplitude for IE was determined as the average \dot{V}_{O_2} measured during the final 10 s of each 60-s exercise interval over the duration of the entire IE bout. The predicted \dot{V}_{O_2} value was calculated using a single exponential term, omitting the Phase I response:

$$\dot{V}_{O_2}(t) = A_B + A_P(1 - e^{-(t-TD_P)/\tau_P}) \quad \text{Equation 2.3}$$

The predicted \dot{V}_{O_2} amplitude at 60 s was also re-calculated using a time constant (τ_P) value of 42 s. This value is the mean phase II τ for healthy older individuals performing constant-load cycling at approximately 70% of W_{peak} (Sabapathy et al., 2004). The purpose of using a τ_P derived from healthy older individuals was to examine the affect of “speeding” the on-transient response on the predicted \dot{V}_{O_2} amplitude during IE.

Determination of plasma lactate concentration

Before commencement of the CE and IE tests, an indwelling catheter was placed into an antecubital vein of the subject. Plasma lactate concentration was determined (Ciba-Corning Blood Gas Analyser) for blood samples obtained at rest, at the end of 3 min of unloaded cycling, after 3 and 6 min of CE and IE, and at the end of the exercise bouts.

Measurement of inspiratory capacity and end-expiratory lung volume

End expiratory lung volume (EELV) was calculated by subtracting IC from TLC. Inspiratory capacity was measured at rest (while seated on the cycle ergometer), following 7 min of exercise and at the end of CE and IE (Figure 2.2). An investigator demonstrated the IC manoeuvre before each test. At each measurement point, the subjects were prompted and encouraged to inspire maximally to TLC. Inspiratory capacity was quantified as the change in volume from end-expiration during a normal tidal breath and end-inspiration during the maximal inspiratory manoeuvre. The sampling lines to the pulmonary function system, and the pneumotachograph and gas-sampling lines to the metabolic cart were interfaced through a single mouthpiece which the subject wore throughout the duration of the CE and IE tests.

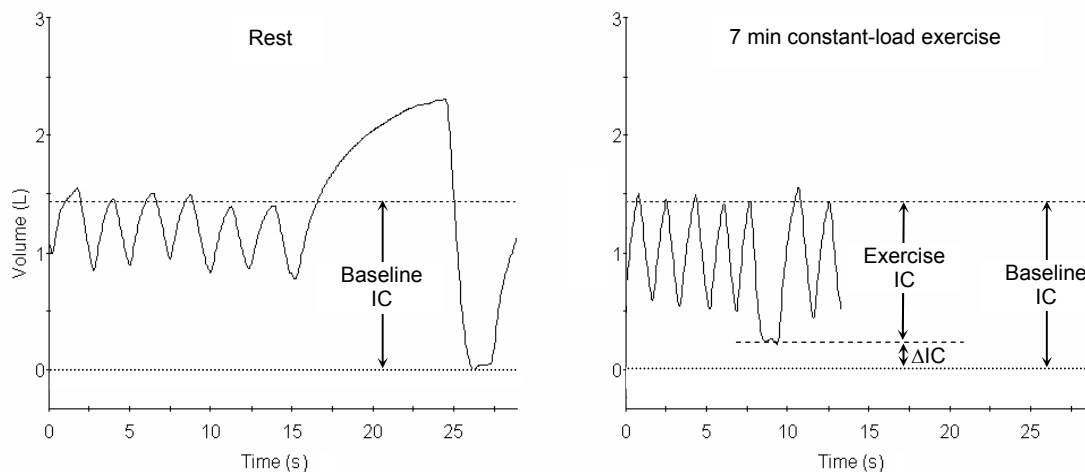


Figure 2.2. Inspiratory capacity (IC) measured at rest and during exercise in an individual with COPD. The change in IC (Δ IC) represents the difference between resting and exercise IC. Note: an upward deflection of the volume-time curve represents expiration.

Ratings of breathlessness

During the CE and IE tests, the subjects were asked to provide ratings of their perceived shortness of breath using a word-labelled visual analogue scale (LVAS) (Lansing et al., 2003). Following a clear explanation of the scale, the subjects were asked to rate their breathlessness at rest, following 7 min of exercise and at the end of exercise.

Statistical analysis

Data are presented as mean \pm standard error of the mean (SEM). The changes in the dependent variables within the CE and IE bouts and between exercise modes were assessed using a two-way analysis of variance (ANOVA) with repeated measures for time. Bonferroni *post-hoc* tests were used when significant main effects were identified. The differences between the two exercise modes in time to exhaustion, total work completed, EELV and subjects' rating of breathlessness were compared using paired samples *t*-tests. Relationships between the dependent variables were assessed using Pearson's correlation

coefficients. Statistical significance was accepted at $P < 0.05$. Data were analysed using SPSS v10.0 and SigmaPlot v8.0 (Statistical Packages for the Social Sciences Inc., Chicago, IL, USA).

RESULTS

The physical characteristics and peak exercise values obtained during incremental cycling, and pulmonary function test results are presented in Tables 2.2 and 2.3, respectively. Pulmonary function results demonstrated that the subjects had moderate COPD. Peak \dot{V}_{O_2} was reduced by about 40% relative to normal age-predicted values (Jones et al., 1985).

Table 2.2. Subject characteristics and peak exercise values obtained during incremental exercise.

Age (yr)	68 ± 2
Height (cm)	165 ± 4
Body mass (kg)	68.7 ± 4.4
\dot{V}_{O_2} peak (L·min ⁻¹)	1.03 ± 0.10
\dot{V}_{O_2} peak (mL·kg ⁻¹ ·min ⁻¹)	14.8 ± 0.7
Peak RER	1.00 ± 0.03
\dot{V}_E peak (L·min ⁻¹)	38.4 ± 4.8
Peak heart rate (beats·min ⁻¹)	126 ± 4
W _{peak} (W)	57 ± 8

Values presented are means ± SEM. \dot{V}_{O_2} peak: peak O₂ uptake; RER: respiratory exchange ratio; \dot{V}_E peak: peak expired ventilation; W_{peak}: peak power output.

Figure 2.3 displays the metabolic and cardiopulmonary responses measured during CE and IE. Significant main effects for the mode by time interaction were observed for \dot{V}_{O_2} ($P < 0.001$), \dot{V}_{CO_2} ($P < 0.001$), \dot{V}_E ($P < 0.001$) and heart rate

($P < 0.001$). For both modes of exercise, \dot{V}_{O_2} , \dot{V}_{CO_2} and \dot{V}_E increased significantly from unloaded cycling to the loaded exercise transition (measured 1 min after the power output was applied). These variables then remained unchanged throughout the duration of IE, but continued to increase up to 6 min of CE. During CE, the end-exercise values for \dot{V}_{O_2} , \dot{V}_{CO_2} and \dot{V}_E were not significantly different from the 6-min values. There was a significant increase in heart rate from unloaded cycling to the end of exercise in both CE and IE (Figure 2.3, panel D). However, the increase in heart rate between consecutive time points was only significant from 3 min of CE onwards and between 6 min and the end of exercise during IE.

Table 2.3. Pulmonary function test results.

FEV ₁ (L)	1.35 ± 0.19
FEV ₁ (% predicted)	52 ± 5
FVC (L)	2.86 ± 0.41
FVC (% predicted)	87 ± 8
FEV ₁ /FVC (%)	48 ± 2
TLC (L)	6.64 ± 0.66
TLC (% predicted)	126 ± 6
FRC (L)	4.40 ± 0.43
FRC (% predicted)	144 ± 7
DL _{CO} (mL·min ⁻¹ ·mmHg ⁻¹)	9.3 ± 0.8
DL _{CO} (% predicted)	46 ± 5

Values presented are means ± SEM. FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; FRC: functional residual capacity; DL_{CO}: lung diffusion capacity for carbon monoxide.

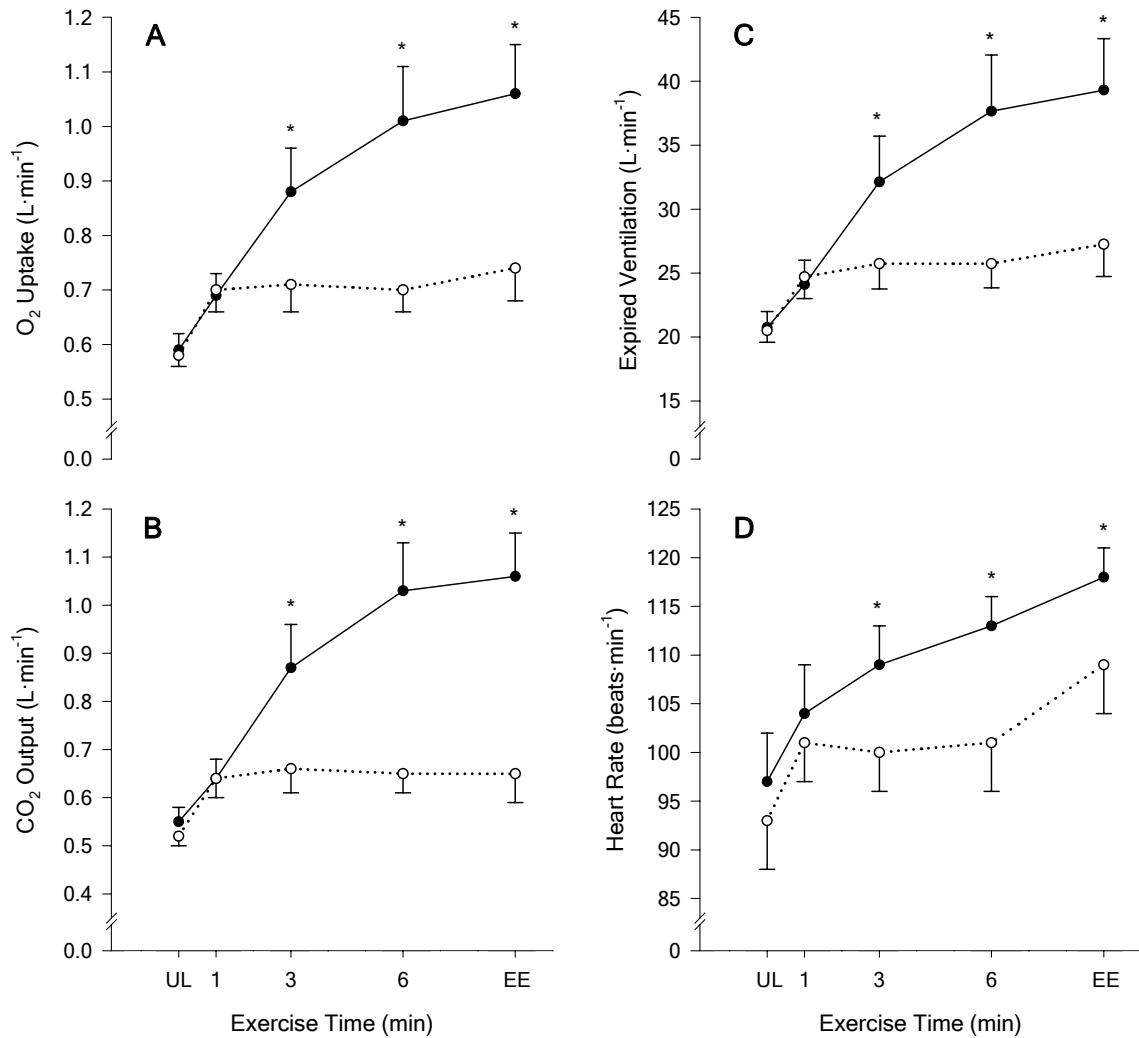


Figure 2.3. Oxygen (O_2) uptake (panel A), carbon dioxide (CO_2) output (panel B), expired ventilation (panel C) and heart rate (panel D) responses during continuous (●) and intermittent (○) exercise. Error bars denote SEM. The rest intervals were eliminated from the IE trend to equalise the time-line between exercise modes. UL: unloaded cycling; EE: end exercise.

* $P < 0.05$, continuous exercise different from intermittent exercise.

Continuous exercise resulted in significantly greater values for \dot{V}_{O_2} , \dot{V}_{CO_2} , \dot{V}_E and heart rate in comparison to IE, from 3 min of exercise onwards. At the end of exercise, mean differences between CE and IE were as follows: $\dot{V}_{O_2} = 0.25 \pm 0.04$ L·min⁻¹; $\dot{V}_{CO_2} = 0.34 \pm 0.05$ L·min⁻¹; $\dot{V}_E = 9.14 \pm 1.8$ L·min⁻¹; heart rate = 15

± 4 beats \cdot min $^{-1}$. The predicted \dot{V}_{O_2} using time constant values calculated from the individual CE tests (0.85 ± 0.09 L \cdot min $^{-1}$) were not significantly different from the values measured during IE (0.82 ± 0.07 L \cdot min $^{-1}$). However, experimentally “speeding” on-transient kinetics through the use of a time constant value derived from healthy older individuals resulted in predicted \dot{V}_{O_2} values (0.97 ± 0.10 L \cdot min $^{-1}$) that were significantly greater than the measured \dot{V}_{O_2} values (Table 2.4).

Table 2.4. Measured and predicted oxygen uptake values for intermittent exercise.

Subjects	Measured \dot{V}_{O_2} (L \cdot min $^{-1}$)	Predicted \dot{V}_{O_2}	Predicted \dot{V}_{O_2}
		(L \cdot min $^{-1}$)	(L \cdot min $^{-1}$)
		τ_P from Table 2.1	$\tau_P = 42$ s
1	0.76	0.72	0.81
2	0.78	0.79	0.87
3	0.88	0.89	1.01
4	0.77	0.75	0.85
5	1.05	1.29	1.37
6	0.97	1.00	1.25
7	0.50	0.54	0.60
Mean \pm SEM	0.82 ± 0.07	0.85 ± 0.09	$0.97 \pm 0.10^*$

\dot{V}_{O_2} : oxygen uptake; τ_P : phase II time constant. The measured \dot{V}_{O_2} values represent the mean end exercise-interval values obtained over the entire intermittent exercise test duration. The predicted \dot{V}_{O_2} values were calculated using a single-term (Equation 2.3) exponential model (see text for details). * $P < 0.05$, significantly different from measured \dot{V}_{O_2} value (repeated measures ANOVA).

A significant effect of the mode by time interaction was also observed for plasma lactate concentrations ($P < 0.001$). Plasma lactate concentration increased from rest through to the end of exercise during both IE and CE (Figure 2.4). While plasma lactate concentrations during CE were systematically greater than during IE, these differences were only significant at 6 min of exercise and at the end of exercise. The increase in plasma lactate concentrations from rest to the end of exercise was significantly greater during CE ($3.05 \pm 0.65 \text{ mmol}\cdot\text{L}^{-1}$) compared to IE ($1.81 \pm 0.43 \text{ mmol}\cdot\text{L}^{-1}$). The mean difference between exercise modes for plasma lactate concentration at end exercise was $1.66 \pm 0.37 \text{ mmol}\cdot\text{L}^{-1}$.

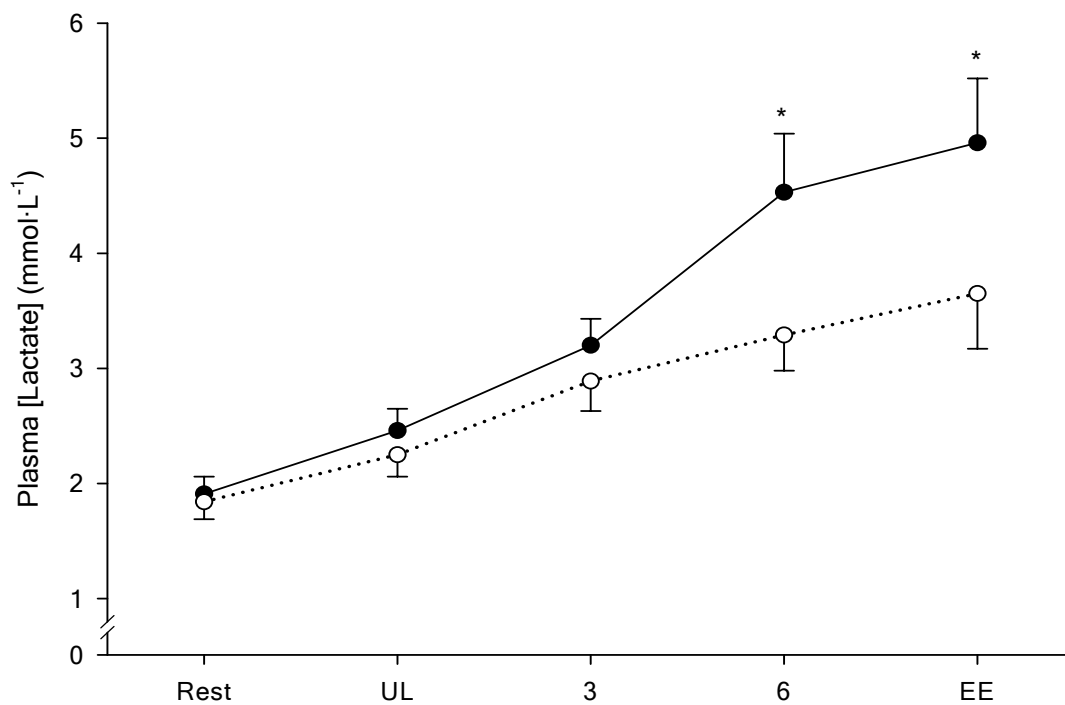


Figure 2.4. Plasma lactate response during continuous (●) and intermittent (○) exercise. Error bars denote SEM. UL: unloaded cycling; EE: end exercise. The rest intervals were eliminated from the IE trend to equalize the time-line between exercise modes. * $P < 0.05$, continuous exercise different from intermittent exercise.

The subjects were able to exercise longer and complete a significantly greater amount of work during IE (29.2 ± 0.8 min; 70.5 ± 10.2 kJ) compared to CE (11.1 ± 2.4 min; 30.5 ± 7.4 kJ). However, while 8 of the 10 subjects were able to perform 60 min of IE (which amounts to 30 min of exercise), no subject was able to complete 30 min of CE.

Figure 2.5 illustrates the change from rest to the end of exercise in EELV and breathlessness during IE and CE. The change in the degree of breathlessness from rest to the end of CE (5.60 ± 0.87) was significantly greater than that observed during IE (2.07 ± 0.54). Similarly, EELV (a measure of DH) increased to a greater extent during CE (0.52 ± 0.13 L) than during IE (0.23 ± 0.07 L). There

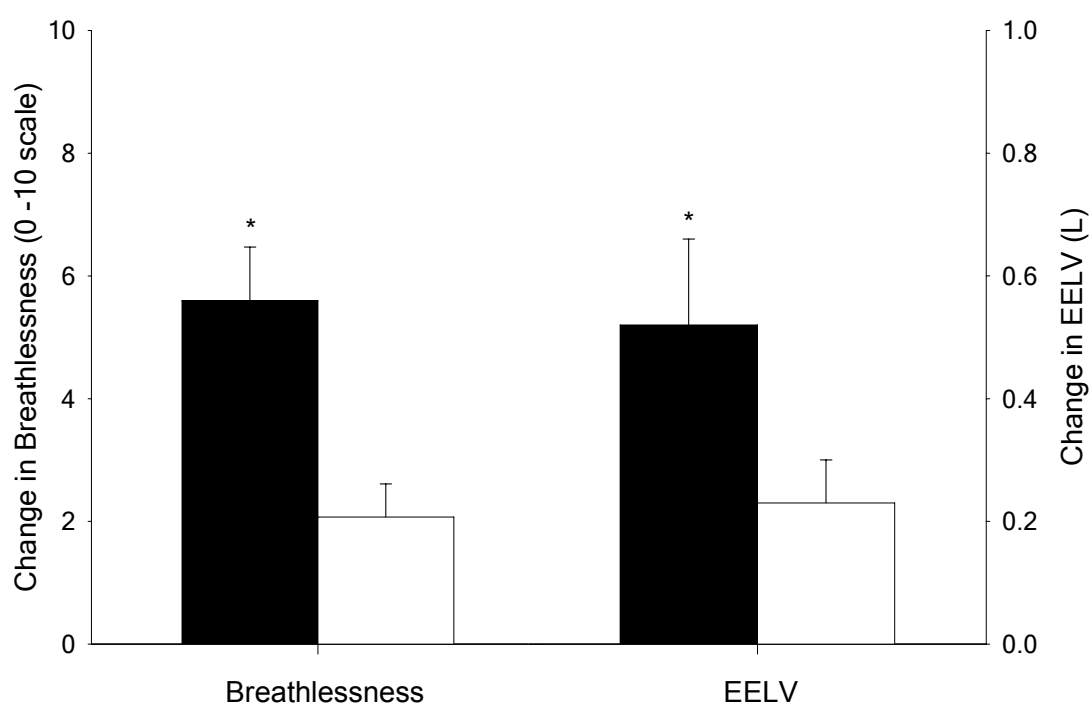


Figure 2.5. Change from rest to end-exercise in ratings of perceived breathlessness and end-expiratory lung volume (EELV) during continuous (filled bars) and intermittent exercise (open bars). Error bars denote SEM. * $P < 0.05$, continuous exercise different from intermittent exercise.

was a significant positive correlation between the degree of breathlessness measured at the end of exercise and the change in EELV for both CE ($r = 0.61$, $P < 0.05$) and IE ($P = 0.67$, $P < 0.05$).

DISCUSSION

In the present study, patients with COPD were able to complete a greater total amount of work during IE compared to CE. Since the majority of the subjects attained the 60 min time-limit during IE but none achieved the 30 min CE limit, there was potential for an even greater amount of work to be completed during IE. Intermittent exercise was associated with lower measured physiological responses, with \dot{V}_{O_2} , \dot{V}_{CO_2} , \dot{V}_E , heart rate and plasma lactate concentrations all systematically lower than in CE. Moreover, subjects demonstrated a lower level of DH during IE compared to CE, as assessed by the change in EELV, and this may in turn have contributed to their lower sensation of breathlessness. The results of the present study indicate that IE is better tolerated than CE in COPD patients because of improved ventilatory mechanics as well as reduced metabolic and cardiovascular perturbations.

As previously discussed, the amplitude of the \dot{V}_{O_2} response at a given exercise intensity during IE is determined primarily by the duration of the exercise period (Åstrand et al., 1960). The 1-min intervals used during IE in the present study would therefore result in lower \dot{V}_{O_2} as well as \dot{V}_{CO_2} , \dot{V}_E and heart rate values, given that these variables are tightly coupled to metabolism within the active muscle during exercise. When exponential models were applied to the \dot{V}_{O_2} data measured during the CE bouts, the predicted \dot{V}_{O_2} values at the end of 1 min of exercise were not significantly different from the \dot{V}_{O_2} values obtained during the

exercise intervals of the IE bouts (see Table 2.4). Moreover, the measured \dot{V}_{O_2} values were not significantly different between exercise modes during the first minute of exercise following the application of the predetermined power output (Figure 2.3). Figure 2.6 clearly illustrates the similar time course for the increase in \dot{V}_{O_2} during the first minute of exercise for both modes of exercise in a representative subject. The responses then diverge as the rest intervals are introduced into the IE bout. The peak exercise \dot{V}_{O_2} response for the rest of IE remains similar to the value measured at the end of the first exercise interval. Thus, the lower \dot{V}_{O_2} value observed during IE compared to CE appears to be due to the delayed kinetic response typical of a step change in activity level (for example, from rest to exercise).

One aspect of cardiorespiratory kinetics that may also impact upon the amplitude of the gas exchange responses reported is the “speed” with which these variables respond to a change in exercise intensity. The slowing of on-transient \dot{V}_{O_2} kinetics in COPD patients relative to healthy control subjects (Nery et al., 1982; Palange et al., 1995), may result in IE values below that expected for a given external power output for an age-matched healthy subject. When the \dot{V}_{O_2} amplitude was predicted using a time constant value derived from healthy older individuals (Sabapathy et al., 2004), the estimated value was significantly greater than that measured during IE. The dependence of the \dot{V}_{O_2} amplitude on the time constant value during the on-transient phase suggests that the lower \dot{V}_{O_2} values observed during IE compared to CE may also reflect a slower than normal on-transient response in patients with COPD than in healthy individuals.

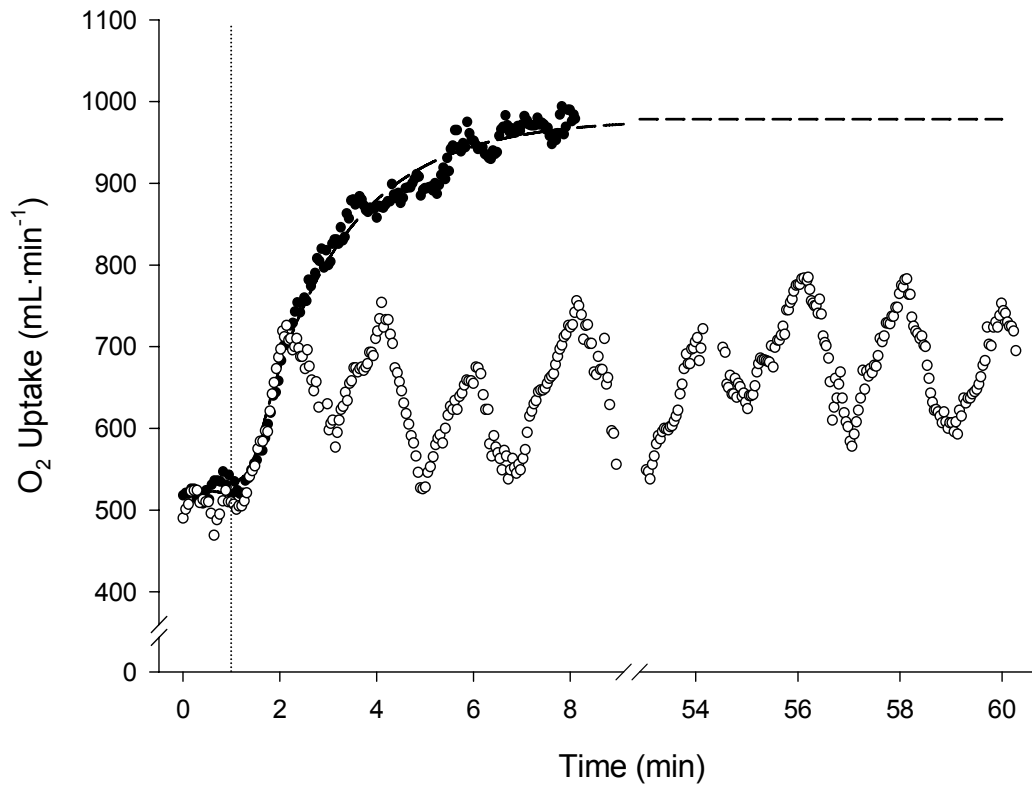


Figure 2.6. Oxygen uptake (\dot{V}_{O_2}) responses to a single bout of continuous (●) and intermittent (○) exercise in a representative subject. The data represent the middle five of seven breath average responses. The vertical dotted line indicates the application of the pre-determined power output. For clarity, only transitions early and late in the intermittent bout are depicted. A line of best fit (dashed line) was applied to the continuous exercise data, projecting to its asymptotic value and extrapolated through to the end of the intermittent bout. The data illustrates the similar time course for the increase in \dot{V}_{O_2} during the first minute of exercise. The responses then diverge as the rest intervals are introduced into the intermittent bout. The peak exercise \dot{V}_{O_2} response for the remainder of intermittent exercise remains similar to the value measured at the end of the first exercise interval.

The slower \dot{V}_{O_2} kinetics in individuals with COPD would result in a greater reliance on phosphocreatine stores and anaerobic glycolysis at the onset of exercise or during a transition from lower to higher exercise intensities in these individuals (Palange et al., 1995). Consequently, an earlier or relatively greater efflux of lactate into the blood may occur. Previous studies have reported an “excessive” lactic acidosis relative to \dot{V}_{O_2} in COPD patients (Casaburi et al., 1991; Maltais et al., 1996). During IE, it has been demonstrated that lactate production occurs primarily during the exercise period (Saltin and Essén, 1971), while the rest period is associated with net lactate removal (Essén, 1978). Thus, despite the possibility of a greater reliance on anaerobic metabolism to fuel the energetic demands for IE, the short exercise intervals interspersed with rest periods resulted in systematically lower plasma lactate values observed during IE. The greater plasma lactate response associated with CE compared to IE may also have contributed, in part, to the higher \dot{V}_E observed during CE. The buffering of hydrogen ions linked with lactic acid production ultimately results in the formation of ‘non-metabolic’ CO_2 (Wasserman et al., 1999). Both an increase in hydrogen ion concentration and excess non-metabolic CO_2 production serve to stimulate ventilation (Whipp, 1981).

In many individuals with COPD, the increasing ventilatory demand during exercise results in the progressive trapping of air due to incomplete lung emptying (O'Donnell, 2001). The accompanying increase in EELV is termed DH. This increase in EELV during exercise, compounded by an already elevated resting functional residual capacity (see Table 2.2), curtails the ability of the COPD patient to expand tidal volume in line with the greater ventilatory demand (Babb et al., 1991). An increase in \dot{V}_E must then be mediated primarily by an increase in breathing frequency, which reduces expiratory flow time and further

exacerbates the degree of DH. Dynamic hyperinflation has been associated with an increase in dyspnoea and may play an important role in the observed exercise intolerance in COPD patients (Babb et al., 1991; O'Donnell et al., 2001). In the present study, the degree of DH was significantly lower during IE than in CE. Moreover, EELV showed a positive correlation with perceived breathlessness. Given the dependence of DH on \dot{V}_E , it seems reasonable to suggest that the lower level of perceived breathlessness and DH observed during IE was primarily a function of the lower \dot{V}_E during this mode of exercise. Additionally, the rest intervals may have provided the subjects with the opportunity to “deflate” their lungs, allowing lung volume to return to, or approach, passive FRC before the start of the next exercise bout. This would reduce the degree of DH achieved in the subsequent exercise bout.

The findings of the present study suggest that further examination of training intensity and volume, as well as exercise mode, could improve exercise prescription practices in pulmonary rehabilitation programs. In particular, the use of IE training at intensities comparable to those used in CE protocols may result in similar levels of functional improvement. Recently, Morris et al. (2002) and Vogiatzis et al. (2002) compared CE and IE training in healthy older individuals and in patients with COPD, respectively. These studies demonstrated that when total work performed was equalised between the exercise modes, the benefits gained are independent of exercise mode as well as intensity. Furthermore, it is our opinion that IE could possibly benefit individuals ranging in disease severity. For those individuals with severe airflow limitation, breathlessness can be a major psychological deterrent to the pursuit of an active lifestyle (Kaplan et al., 1993). The decreased perception of breathlessness associated with IE may improve adherence to training programs as well as encourage individuals with lung

disease to reverse the debilitating effects of a sedentary lifestyle. The greater options associated with IE protocol design (exercise to rest ratios as well as a greater range of tolerated intensities) could benefit even those with mild disease. Even if lung mechanics were not a limiting factor, there is evidence that metabolic and morphological changes in the skeletal muscles of patients with COPD may result in poorer exercise tolerance (American Thoracic Society/European Respiratory Society, 1999). In the present study, the lower measured levels of plasma lactate during IE compared to CE suggest either a lower degree of metabolic perturbation during IE or, greater lactate clearance (during the rest intervals) with better maintenance of intramuscular as well as blood homeostasis. This would be of benefit to individuals whose exercise tolerance is limited by peripheral factors.

In summary, we demonstrated that individuals with moderate COPD were able to complete a greater amount of total work during IE compared to CE performed at 70% of W_{peak} . Measures of gas exchange, plasma lactate, DH and perceived breathlessness were significantly lower during IE than during CE. The findings of the present study suggest that further examination of training intensity and volume, as well as exercise mode, could improve exercise prescription practices in pulmonary rehabilitation programs.

REFERENCES

- Åstrand, I., Åstrand, P.-O., Christensen, E.H., Hedman, R. (1960). Intermittent muscular work. *Acta Physiol Scand.* 48: 448-453.
- Åstrand, I., Åstrand, P.-O., Christensen, E H, Hedman, R. (1960). Myoglobin as an oxygen-store in man. *Acta Physiol Scand.* 48: 454-460.
- American Thoracic Society/European Respiratory Society. (1999). Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 159: S1-S40.
- Babb, T.G., Viggiano, R., Hurley, B., Staats, B., Rodarte, J.R. (1991). Effect of mild-to-moderate airflow limitation on exercise capacity. *J Appl Physiol.* 70: 223-230.
- Barstow, T.J. (1994). Characterisation of \dot{V}_{O_2} kinetics during heavy exercise. *Med Sci Sports Exerc.* 26: 1327-1334.
- Cappoose, R., Schols, A.M.W.J., Baarends, E.M., Mostert, R., Akkermans, M.A., Janssen, P.P., Wouters, E.F.M. (1999). Interval versus continuous training in patients with severe COPD: a randomized clinical trial. *Eur Respir J.* 14: 258-263.
- Casaburi, R., Patessio, A., Ioli, F., Zanaboni, S., Donner, C.F., Wasserman, K. (1991). Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis.* 143: 9-18.
- Essén, B. (1978). Studies on the regulation of metabolism in skeletal muscle using intermittent exercise as an experimental model. *Acta Physiol Scand.* 454: S3-S32.

- Jones, N.L., Makrides, L., Hitchcock, C., Chypchar, T., McCartney, N. (1985). Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis.* 131: 700-708.
- Kaplan, R.M., Eakin, E.G., Ries, A.L. (1993). Psychosocial issues in the rehabilitation of patients with chronic obstructive pulmonary disease. In: *Principles and Practice of Pulmonary Rehabilitation*. Casaburi, R., Petty, T.L. (Eds.). W. B. Saunders Co., Philadelphia, pp. 351-365.
- Lansing, R.W., Moosavi, S.H., Banzett, R.B. (2003). Measurement of dyspnea: word labeled visual analog scale vs. verbal ordinal scale. *Respir Physiol Neurobiol.* 134 : 77-83.
- Maltais, F., LeBlanc, P., Jobin, J., Bérubé, C., Bruneau, J., Carrier, L., Breton, M.J., Falardeau, G., Belleau, R. (1997). Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 155: 555-561.
- Maltais, F., Simard, A.-A., Simard, C., Jobin, J., Desgagnés, P., LeBlanc, P. (1996). Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med.* 153: 288-293.
- Morris, N., Gass, G., Thompson, M., Bennett, G., Basic, D., Moreton, H. (2002). Rate and amplitude of adaptation to intermittent and continuous exercise in older men. *Med Sci Sports Exerc.* 34: 471-477.
- Morris, N., Gass, G., Thompson, M., Conforti, D. (2003). Physiological responses to intermittent and continuous exercise at the same relative intensity in older men. *Eur J Appl Physiol.* 90: 620-625.

- Nery, L.E., Wasserman, K., Andrews, J.D., Huntsman, D.J., Hansen, J.E., Whipp, B.J. (1982). Ventilatory and gas exchange kinetics during exercise in chronic airways obstruction. *J Appl Physiol.* 53: 1594-1602.
- O'Donnell, D.E. (2001). Ventilatory limitations in chronic obstructive pulmonary disease. *Med Sci Sports Exerc.* 33: S647-S655.
- O'Donnell, D.E., Revall, S.M., Webb, K.A. (2001). Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 164: 770-777.
- Palange, P., Galassetti, P., Mannix, E.T., Farber, M.O., Manfredi, F., Serra, P., Carlone, S. (1995). Oxygen effect on O₂ deficit and \dot{V}_{O_2} kinetics during exercise in obstructive pulmonary disease. *J Appl Physiol.* 78: 2228-2234.
- Pauwels, R.A., Buist, A.S., Calverley, P.M.A., Jenkins, C.R., Hurd, S.S. (2001). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. *Am J Respir Crit Care Med.* 163: 1256-1276.
- Sabapathy, S., Schneider, D.A., Comadira, G., Johnston, I., Morris, N.R. (2004). Oxygen uptake kinetics during severe exercise: a comparison between young and older men. *Respir Physiol Neurobiol.* 139: 203-213.
- Saltin, B., Essén, B. (1971). Muscle glycogen, lactate, ATP and CP during intermittent exercise. In: *Muscle Metabolism During Exercise*. Pernow, B., Saltin, B. (Eds.). Plenum Press, New York, pp. 419-424.
- Smodlaka, V.N., Adamovich, D.R. (1974). Reconditioning of emphysema patients. *NY State J Med.* 74: 951-955.

- Vogiatzis, I., Nanas, S., Roussos, C. (2002). Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J.* 20: 12-19.
- Wasserman, K., Hansen, J.E., Sue, D.Y., Casaburi, R., Whipp, B.J. (1999). *Principles of Exercise Testing and Interpretation*. Lippincott, Williams & Wilkins, Baltimore.
- Whipp, B.J. (1981). The control of exercise hyperpnea. In: *Regulation of Breathing*. Hornbein, T. (Ed.). Marcel Dekker, New York, pp. 1069-1139.
- Whipp, B.J., Casaburi, R. (1982). Characterizing O₂ uptake response kinetics during exercise. *Int J Sports Med.* 3: 97-99.

ABBREVIATED TERMS

A	Amplitude of the oxygen uptake response (subscripts B, C, P and S refer to baseline unloaded cycling, and the cardiodynamic, primary and slow components, respectively)
CE	Continuous exercise
CO ₂	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
DH	Dynamic hyperinflation
DL _{CO}	Lung diffusion capacity for carbon monoxide
ECG	Electrocardiograph
EE	End exercise
EELV	End expiratory lung volume
FEV ₁	Forced expiratory volume in 1 s
FRC	Functional residual capacity

FVC	Forced vital capacity
IC	Inspiratory capacity
IE	Intermittent exercise
LVAS	Word-labelled visual analogue scale
O ₂	Oxygen
SEM	Standard error of the mean
t	Time
TD	Time delay (subscripts C, P and S refer to the cardiodynamic, primary and slow components, respectively)
TLC	Total lung capacity
UL	Unloaded cycling
\dot{V}_{CO_2}	Carbon dioxide output
\dot{V}_E	Expired ventilation
\dot{V}_{O_2}	Oxygen uptake
W _{peak}	Peak power output
τ	Tau or time constant; time taken to reach 63% of the final amplitude in an exponential function (subscripts C, P and S refer to the cardiodynamic, primary and slow components, respectively)

[Blank Page]

**C
H
A
P
T
E
R

3**

Study 2

**Continuous and Intermittent Exercise Training in Chronic
Obstructive Pulmonary Disease Patients**

CONTENTS

Introduction
65

Methods
67

Results
76

Discussion
89

References
99

**Abbreviated
Terms**
105

[Blank Page]

INTRODUCTION

Endurance training as part of pulmonary rehabilitation has been reported to result in improved exercise capacity, exertional dyspnoea, quality of life and a reduced demand for medical services in patients with chronic obstructive pulmonary disease (COPD) (Wijkstra et al., 1994; Carrieri-Kohlman et al., 1996; Casaburi et al., 1997). The prescription of exercise training in patient populations is primarily derived from results obtained in healthy individuals (Wasserman et al., 1999). Thus, exercise programs for COPD patients typically include a mixture of training intensity (30-70% of peak oxygen uptake, \dot{V}_{O_2} peak, or peak power output, W_{peak}), duration (20-40 min), frequency (2-5 days per wk) and mode (continuous dynamic exercise such as cycling, running or walking; involving large muscle groups). It has also been argued that training intensity should be high in order to elicit physiological adaptations that will benefit COPD patients (Ambrosino and Strambi, 2004; Troosters et al., 2005). However, patients with COPD may not be able to sustain prolonged periods of high-intensity exercise (Maltais et al., 1997). The findings of Maltais et al. (1997) agree with the results obtained in Study One (Chapter 2), where patients with moderate COPD were only able to complete approximately 11 min of continuous exercise (CE) performed at 70% of peak power output. Consequently, intermittent exercise (IE) has been suggested as an alternative training mode that may be better tolerated in COPD patients (Coppoolse et al., 1999; Vogiatzis et al., 2002; Vogiatzis et al., 2005).

Intermittent exercise is characterised by repeated bouts of short-duration exercise (e.g., 60 s) separated by periods of lower-intensity exercise or rest, and may be more suited to COPD patients, whose daily activities typically require short bursts of exertion, interspersed with periods of recovery (Smoldlaka and

Adamovich, 1974). In healthy individuals, acute IE bouts are associated with lower values for heart rate, oxygen uptake (\dot{V}_{O_2}), carbon dioxide production (\dot{V}_{CO_2}), expired ventilation (\dot{V}_E) and blood lactate concentration as well as an increase in exercise tolerance when performed at the same absolute intensity as CE (Åstrand et al., 1960; Saltin et al., 1976; Morris et al., 2003). Similarly, the results of Study One (Chapter 2) demonstrated a lower degree of physiological perturbation, less lung hyperinflation and dyspnoea, as well as increased exercise tolerance during IE compared to CE bouts in patients with moderate COPD.

Endurance training studies comparing CE and IE in healthy individuals have produced conflicting results. Some studies have shown greater adaptations with CE than with IE (Henriksson and Reitman, 1976; Saltin et al., 1976), while other researches have reported opposite results (Gorostiaga et al., 1991). Studies have also demonstrated similar adaptations for both modes of training (Eddy et al., 1977; Cunningham et al., 1979). However, Morris et al. (2002) recently demonstrated that adaptations to endurance training appear to be independent of mode (IE v CE) when the total amount of work completed within each exercise mode is the same. Therefore, the conflicting results from previous studies may be due to the failure to compare IE and CE training conducted at the same intensity or not accounting for the total work completed. Similarly, studies comparing IE and CE training in COPD patients have also produced conflicting results because either the total work performed was not standardised between the modes, or the IE protocol was performed at a higher absolute intensity than the CE program (Coppoolse et al., 1999; Vogiatzis et al., 2002).

The present study compared the adaptations to 8 wk of IE and CE cycle ergometry training, performed at the same relative intensity and matched for total work completed, in patients with moderate COPD. It was hypothesised that in COPD patients, IE and CE training of matched intensity (commencing at 50% of peak power output) and total work will be associated with: 1) lower exercise heart rate, and perception of breathlessness and lower limb fatigue during IE training; 2) equivalent improvements in exercise capacity (\dot{V}_{O_2} peak), exercise tolerance (W_{peak}), and distance covered during a 6-min walk test (6MWD); 3) similar reductions in breathlessness, perceived leg fatigue and blood lactate concentration during constant-load submaximal exercise; 4) similar degree of speeding of \dot{V}_{O_2} on-transient (phase II) kinetics during constant-load exercise.

METHODS

Subjects and experimental design

This was a prospective, two-group study (CE v IE training) of 24 volunteers with COPD. Inclusion criteria for the study were 1) patients classified as having moderate COPD (Pauwels et al., 2001), 2) shortness of breath on exertion, and 3) no documented history of substantial co-morbidity. Additionally, subjects were stable upon entry into the study with no acute exacerbations of the disease in the 2 months prior to commencement of the training program. All testing was performed in the Physiology of Exercise Research Laboratory, Gold Coast campus, Griffith University, Australia.

Five participants did not complete the training program due to either exacerbation of the disease (2 patients), musculoskeletal injury unrelated to this study (2 patients) and social/family commitments (1 patient). Thus, the remaining 19 participants (10 males and 9 females) formed the study population. Although a

compliance rate of 80% was required for inclusion in the study, attendance rate averaged 90%, and no participant was excluded based on this criterion. The experimental protocol was approved by the Griffith University Human Research Ethics Committee and all participants provided written, informed consent (see Appendix A).

The subjects were familiarised with all testing procedures prior to commencement of the study. Pre-training testing began 2 wk before the start of the training program. During this period the subjects performed a symptom-limited incremental exercise test on a cycle ergometer. At least 48 h after the incremental test, the subjects also performed two identical constant-load submaximal exercise tests on a cycle ergometer, and 6-min walk tests (6MWT). Each constant-load test, and the 6MWT were performed at least 24 hr apart. Once all baseline testing procedures were performed, the subjects completed the St George's Hospital Respiratory Questionnaire (SGRQ). The subjects were stratified according to age, gender and pulmonary function, and randomly assigned to either CE or IE training. The subjects then undertook 8 wk of supervised CE or IE training. After completing the 8-wk program, the pre-training testing procedures were repeated.

Pre-training and post-training procedures

Pulmonary function assessment

Pulmonary function was measured via open circuit spirometry (MedGraphics CardiO₂, Cardiopulmonary Diagnostic Systems, St. Paul, MN, USA), using established techniques (American Thoracic Society, 1994). Lung diffusion capacity for carbon monoxide (DL_{CO}) was measured using the single-breath carbon monoxide test (Collins GS Modular PFT, Warren E. Collins, Inc, Braintree, MA, USA). Disease severity was classified in accordance with The Global

Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (Pauwels et al., 2001).

Incremental exercise test

The incremental exercise test used to measure peak \dot{V}_{O_2} was performed on a Lode (Excalibur Sport, Groningen, Netherlands) cycle ergometer. Subjects commenced unloaded cycling for 2 min and then the power output was increased by $4 \text{ W} \cdot 30 \text{ s}^{-1}$ for the male subjects and by $3 \text{ W} \cdot 30 \text{ s}^{-1}$ for the female subjects until volitional termination of the test. At the end of the test, subjects were asked to provide ratings of perceived breathlessness and leg fatigue using a word-labelled visual analogue scale (LVAS) (Lansing et al., 2003). During the incremental cycling test, subjects breathed through a mouthpiece and wore a nose-clip. Throughout exercise, \dot{V}_{O_2} , \dot{V}_{CO_2} and \dot{V}_E were measured breath-by-breath and averaged over 30-s intervals using a metabolic measuring system (MedGraphics Cardio₂ with BreezeSuite v3.01 software, Cardiopulmonary Diagnostic Systems, St. Paul, MN, USA). A 12-lead electrocardiograph (ECG) configuration was used to monitor cardiac rhythm and to determine heart rate (MedGraphics Cardio₂, Cardiopulmonary Diagnostic Systems, St. Paul, MN, USA). Peak exercise values for incremental cycling were calculated as the average of the two highest consecutive 30-s values obtained prior to termination of exercise. The gas exchange threshold (GET) was determined non-invasively using the simplified V-slope method described by Schneider et al. (1993) and the ventilatory equivalent method (Wasserman et al., 1999) (see Figure 3.1). Visual determination of the GET was performed by two investigators in a blinded manner. If threshold placement could not be agreed upon, the GET was determined as the average of both methods.

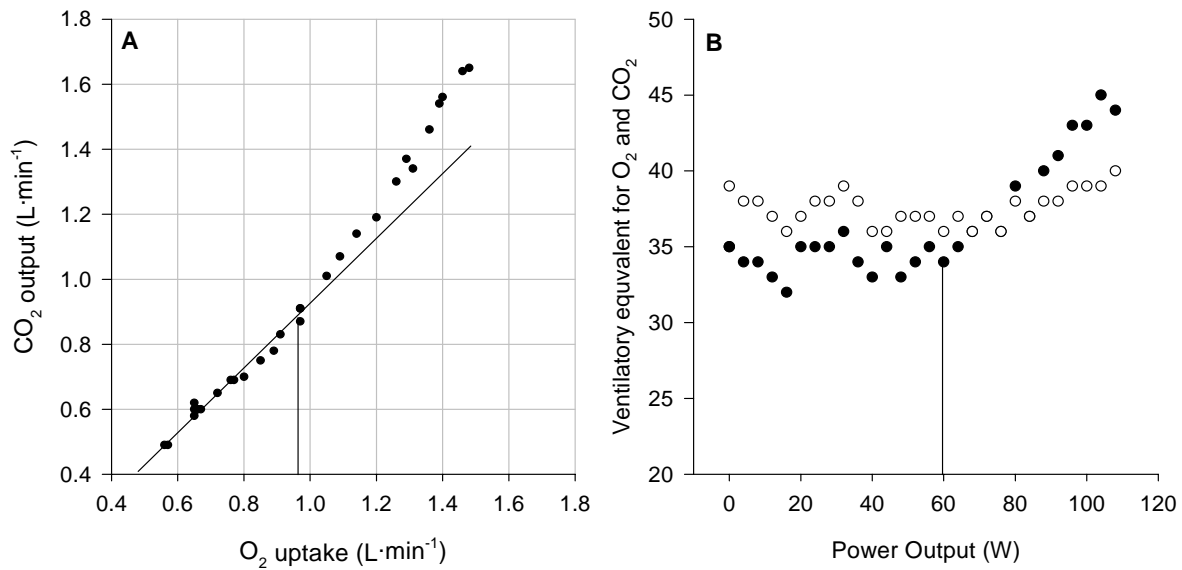


Figure 3.1. Detection of the gas exchange threshold (GET) in a subject using the simplified V-slope method (panel A) and the ventilatory equivalents for O₂ (●) and CO₂ (○) (panel B). The vertical lines indicate the GET.

Prior to, and at 1-min intervals during the incremental test, subjects were asked to perform a maximal inspiratory manoeuvre to total lung capacity in order to measure inspiratory capacity (IC). The IC manoeuvre was demonstrated to each subject during the familiarisation session as well as before the exercise test. The subjects were also required to practice the manoeuvre to ensure that satisfactory measurements could be obtained. At each measurement point, the subjects were prompted to begin the inspiratory manoeuvre and verbally encouraged by an investigator to ensure that a maximal effort was performed. During IC measurements, an investigator inspected the tidal breaths which were displayed on-line in real-time. In the event that an unsatisfactory IC manoeuvre was performed, the subject was asked to repeat the measurement. The difference in IC from rest to exercise (expressed as a percentage of resting IC) was used as a measure of dynamic lung hyperinflation (DH). Thus, a decrease in IC during exercise indicates an increase in DH.

Submaximal exercise test and \dot{V}_{O_2} kinetics

Each subject performed two identical 6-min constant-load submaximal exercise tests on a Lode (Excalibur Sport, Groningen, Netherlands) cycle ergometer. The constant-load tests were performed on separate days. The power output used during the 6-min submaximal exercise test was calculated as 40% of the difference between the power output attained at the GET and W_{peak} ($\Delta 40\%$). The same absolute power output was used during the pre- and post-training tests. The test protocol comprised 3 min of seated rest on the ergometer followed by 6 min of constant-load exercise at the subject's pre-determined $\Delta 40\%$ power output. Sixty seconds before exercise commenced, the pedals were manually cranked by an investigator until pedal/flywheel revolutions reached $80 \text{ rev}\cdot\text{min}^{-1}$. The subject's feet were then placed on the pedals, which were held stationary while the internal flywheel continued revolving. This procedure took approximately 15 s to complete, allowing the subjects another 45 s of seated rest. The 60 s interval also permitted the flywheel to slow to $60 \text{ rev}\cdot\text{min}^{-1}$, which was the cycling cadence used throughout the 6-min exercise test. Pilot testing ensured that this protocol was reliable. The subjects were then given a 5-s countdown to begin cycling with the pre-determined workload applied at the end of the countdown. The subjects then cycled for 6 min, maintaining pedal cadence at $60 \text{ rev}\cdot\text{min}^{-1}$. The reason for manually increasing flywheel speed prior to the onset of exercise was to avoid the initial inertia (from the flywheel) that each subject had to overcome when commencing cycling from a stationary start.

During the test, gas exchange was measured breath-by-breath as described for the incremental exercise test. Heart rate and rhythm were monitored via 3-lead ECG, with the ECG electrodes placed in a CM5 configuration (Lohmeier M607, Munich, Germany). Ratings of breathlessness and leg fatigue were measured at

rest and at the end of exercise, as described for the incremental exercise test. These variables, including the blood lactate measurements described below were averaged across the two exercise transitions performed before training and the two repeat bouts performed after training. Blood samples were collected at rest and at the end of exercise from a hyperaemic earlobe, and immediately analysed for blood lactate concentration (LactatePro, Arkray Inc., Japan).

The breath-by-breath \dot{V}_{O_2} data from each trial were inspected for aberrant breaths, with data points exceeding 3 standard deviations from the local mean edited. The \dot{V}_{O_2} data from each of the two trials were then interpolated to 1-s values, time aligned and averaged. Two non-linear regression models were used to describe the time course of the \dot{V}_{O_2} response:

$$\dot{V}_{O_2}(t) = A_B + A_P(1 - e^{-(t-TD_P)/\tau_P}) + A_S(1 - e^{-(t-TD_S)/\tau_S}) \quad \text{Equation 3.1}$$

$$\dot{V}_{O_2}(t) = A_B + A_P(1 - e^{-(t-TD_P)/\tau_P}) \quad \text{Equation 3.2}$$

where $\dot{V}_{O_2}(t)$ is the \dot{V}_{O_2} at time t ; A_B is the baseline \dot{V}_{O_2} measured during rest, while A_P and A_S represent the primary (phase II) and slow component amplitudes, respectively; TD_P and TD_S , τ_P and τ_S are the time delays and time constants of the primary and slow components, respectively. The last 90 s of rest and the first 20 s of data from exercise onset (phase I) were excluded from the fitting procedure. Equation 3.1 was applied first and if the amplitude of the slow component (A_S) was not significantly greater than 0, Equation 3.2 was used. The choice of model function used was also assessed using the sum of squared residuals. A statistically significant (F-test, $P < 0.05$) reduction in the sum of residual squared errors arising from adding parameters (i.e. using Equation 3.1 instead of Equation 3.2) suggests that the more complex model would provide a

better characterisation of the \dot{V}_{O_2} response. If Equation 3.1 was used, the measured slow component at the end of 6 min of constant-load exercise (A'_S) was calculated using the model equation:

$$A'_S = A_S(1 - e^{-(t_e - TD_S)/\tau_S}) \quad \text{Equation 3.3}$$

where t_e is 360 s (or 6 min) and represents the end of exercise. 95% confidence intervals (95% CI) for the time delay and time constant parameters of the model were calculated using non-linear least squares regression (Sabapathy et al., 2004; Koga et al., 2005):

$$95\% \text{ CI} = \text{SEE} \cdot t_{\text{dis}} \quad \text{Equation 3.4}$$

where SEE is the standard error of the parameter estimates and t_{dis} is the value from the t -distribution (two-tailed) with the degrees of freedom set at 360 (i.e. the 6-min duration of constant-load exercise amounting to 360 data points). In order to make comparisons of the relative change in \dot{V}_{O_2} between the two groups, the gain (G_{TOT}), or change in \dot{V}_{O_2} per unit increment in power output ($\text{mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$) was calculated (Bell et al, 1998).

Six-minute walk test

The 6MWT was conducted in accordance with the guidelines published by the American Thoracic Society (ATS, 2002). Briefly, the test was performed indoors along a straight, flat corridor. A 30-m walking course with distance markers placed at 3-m intervals and turnaround points marked by a cone at each end was laid along the corridor. The test was preceded by 10 min of seated rest. Prior to commencement of the test, baseline oxygen saturation and heart rate were measured using a pulse oximeter (Ohmeda 3800, The BOC Group, Louiseville, CO, USA) and telemetric heart rate monitor (Polar S810i, Polar Electro Oy,

Finland) while perceived breathlessness and leg fatigue were recorded using the LVAS. The subjects were asked to walk at a self-selected pace, with the object of the test being to walk as far as possible over a 6-min duration. During the test, the subjects were permitted to slow down or stop and rest as necessary. After the test, the baseline measurements were repeated and the subject's 6MWD was recorded. The test was then repeated after at least 30 min of rest. If the difference between the trials in 6MWD was greater than 10%, a third test was performed. The greatest 6MWD of the repeated trials was reported. The mean difference (\pm SEM) between trials in 6MWD for all the subjects was $4.4 \pm 1.2\%$ during the pre-training evaluation, and $2.6 \pm 1.4\%$ for the post-training tests.

Assessment of Quality of Life

Health related quality of life (HRQoL) was assessed using the SGRQ (see Appendix C). The SGRQ is a self-directed, disease-specific questionnaire with three component indices that are calculated using empirically derived weightings: symptom, activity and impact (Jones et al., 1992). A total score is also calculated from the component indices, providing a 'global' estimate of an individual's respiratory health. The scoring system uses a 0-100 range scale, with higher scores indicating poorer levels of health. The minimum clinically important difference (MCID) for the SRGQ has been established as a change in a component and/or total score of four units (Jones, 2005). Where the mean change is less than four units but the treatment effect is statistically significant and the 95% CI includes the MCID, then the change in score would be considered "not significantly inferior to a clinically significant effect" (Jones, 2005). The subjects were asked to complete the SGRQ before commencing the training program, and at the completion of training.

Training protocol

The subjects were stratified according to age, gender and pulmonary function, and then randomly allocated to either a CE or IE training group. This procedure ensured that the training groups were matched with respect to age, gender and lung function. Subjects in both the CE and IE groups trained for 8 wk on Monark cycle ergometers (Models 824E and 818E, Varberg, Sweden). The calibration for each cycle ergometer was checked and adjusted, if necessary, prior to every training session. For both CE and IE groups, training intensity at the onset of the program corresponded to 50% of W_{peak} achieved during the baseline incremental test. This training intensity was maintained for the first six sessions (2 wk). Thereafter, the training power output used was increased by approximately 5% of the initial intensity every week. The subjects in the CE group exercised for 30 min whereas the IE group performed cycles of 60 s exercise and 60 s rest for a total of 60 min (i.e. 30 min of accumulated exercise). Training sessions were conducted 3 times per week between 7 am and 12 noon. During the training sessions, cardiac rhythm was monitored continuously via 3-lead ECG (Lohmeier M607, Munich, Germany). Heart rate and ratings of breathlessness and leg fatigue were recorded at rest and every 5 min during exercise. Blood pressure and SpO_2 were also monitored at 5-min intervals. During IE, these measurements were obtained at the end of a 60-s exercise interval rather than during a rest interval.

Statistical analysis

Data are presented as mean \pm standard error of the mean (SEM). Between-group (IE v CE) comparisons of baseline characteristics were performed using independent samples *t*-tests. Two-way analysis of variance (ANOVA) with one between group factor (IE v CE) and one within group factor (pre- v post-training)

was used to assess statistical significance for the dependent variables. Variables measured during the 8-wk training period were assessed using two-way ANOVA with repeated measures for time. Bonferroni *post-hoc* tests were used when significant main effects were identified. The associations between training-related changes in the dependent variables were examined using parametric and non-parametric correlation statistics, as appropriate. Statistical significance was accepted at $P < 0.05$. Data were analysed using SPSS v10.0 and SigmaPlot v8.0 (Statistical Packages for the Social Sciences Inc., Chicago, IL, USA).

RESULTS

The physical characteristics of the subjects and pulmonary function test are presented in Table 3.1. The pulmonary function test results indicate that the subjects had a moderate degree of airflow obstruction (i.e., forced expiratory volume in 1 s, FEV₁ less than 80% predicted but greater than 30% predicted, with FEV₁/forced vital capacity, FVC, below 70%). The subjects in each group were well-matched with respect to age, physical characteristics and lung function as there were no significant differences in these variables between the CE and IE groups.

Table 3.2 provides the peak exercise and GET values determined during the incremental exercise test performed prior to exercise training. As with the physical characteristics and pulmonary function test results, there were no significant differences between training groups for any of the variables examined during the incremental test. Thus, the CE and IE groups were well-matched with respect to exercise capacity. Peak \dot{V}_{O_2} averaged $66 \pm 4\%$ of normal age predicted values for the combined study population (Jones et al., 1985). The GET occurred at a similar percentage of \dot{V}_{O_2} peak in the CE and IE groups. The

power output achieved at the GET represented $60 \pm 4\%$ of W_{peak} in the CE group and $57 \pm 6\%$ of W_{peak} in the IE group, with no significant differences between the groups.

Table 3.1. Subject characteristics and pulmonary function test results.

	Study population (N=19)	CE (N=10)	IE (N=9)
Gender (Male:Female)	10:9	6:4	4:5
Age (yr)	64 ± 1	65 ± 2	63 ± 1
Height (cm)	168 ± 2	170 ± 3	166 ± 4
Body Mass (kg)	77.2 ± 2.9	82.2 ± 2.2	71.7 ± 5.1
FEV ₁ (L)	1.46 ± 0.13	1.48 ± 0.18	1.44 ± 0.20
FEV ₁ (% predicted)	52 ± 4	53 ± 7	51 ± 4
FVC (L)	2.86 ± 0.25	2.88 ± 0.31	2.84 ± 0.41
FVC (% predicted)	79 ± 4	79 ± 6	78 ± 6
FEV ₁ /FVC (%)	52 ± 3	53 ± 6	51 ± 3
DL _{CO} (mL·min ⁻¹ ·mmHg ⁻¹)	12.9 ± 1.2	12.7 ± 1.4	13.3 ± 2.0
DL _{CO} (% predicted)	56 ± 5	54 ± 6	58 ± 7

Values presented are means \pm SEM. CE: continuous exercise; IE: intermittent exercise; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; DL_{CO}: lung diffusion capacity for carbon monoxide.

The initial training intensity of 50% W_{peak} for both CE and IE groups corresponded to 43 ± 5 W for the CE group and 39 ± 5 W for the IE group. Exercise intensity was then increased progressively from the third week of the training program, with the CE group achieving a mean training intensity of $60 \pm 0.4\%$ and $77 \pm 2\%$ of W_{peak} by 4 and 8 wk of training, respectively. In the IE group, training intensity was $60 \pm 0.3\%$ of W_{peak} at 4 wk and $79 \pm 2\%$ of W_{peak} at 8 wk of training. By wk 8, the mean power output sustained by those

performing CE was 64 ± 7 W, while those using IE were exercising at 62 ± 8 W. There were no significant differences in training intensity between the CE and IE groups throughout the training program. All the subjects were able to complete the required duration of exercise at every training session. Since the duration of exercise was the same and training intensity was not different between the two groups, the total amount of work performed was also not significantly different between the CE (750 ± 90 kJ) and IE (707 ± 92 kJ) groups.

Table 3.2. Pre-training peak exercise and gas exchange threshold values measured during incremental cycle ergometry.

	Study population	CE	IE
\dot{V}_{O_2} peak (L·min ⁻¹)	1.15 ± 0.08	1.23 ± 0.12	1.07 ± 0.11
\dot{V}_{O_2} peak (mL·kg ⁻¹ ·min ⁻¹)	15.1 ± 1.0	15.1 ± 1.5	15.1 ± 1.4
\dot{V}_{O_2} peak (% age predicted)	66 ± 4	70 ± 6	61 ± 4
\dot{V}_{CO_2} peak (L·min ⁻¹)	1.26 ± 0.11	1.34 ± 0.15	1.16 ± 0.15
Peak RER peak	1.07 ± 0.02	1.08 ± 0.02	1.05 ± 0.05
\dot{V}_E peak (L·min ⁻¹)	42.3 ± 3.7	44.9 ± 5.2	39.4 ± 3.7
Peak heart rate (beats·min ⁻¹)	128 ± 4	127 ± 5	128 ± 7
W _{peak} (W)	79 ± 7	84 ± 11	73 ± 11
Δ Breathlessness (0-10 scale)	6.1 ± 0.5	6.3 ± 0.7	5.8 ± 0.8
Δ Leg Fatigue (0-10 scale)	6.4 ± 0.5	5.8 ± 0.8	7.0 ± 0.6
GET (L·min ⁻¹)	0.85 ± 0.05	0.94 ± 0.09	0.76 ± 0.05
GET (% \dot{V}_{O_2} peak)	75 ± 3	74 ± 4	76 ± 5
GET (W)	43 ± 4	49 ± 6	37 ± 4

Values presented are means \pm SEM. CE: continuous exercise; IE: intermittent exercise; \dot{V}_{O_2} peak: peak oxygen uptake; \dot{V}_{CO_2} peak: peak carbon dioxide output; RER: respiratory exchange ratio; \dot{V}_E peak: peak expired ventilation; W_{peak}: peak power output; Δ : change from rest to peak exercise values; GET: gas exchange threshold.

Figure 3.2 illustrates the mean dyspnoea, leg fatigue and heart rate values achieved by the CE and IE groups for each week of exercise training. Two-way repeated measures ANOVA revealed significant effects for exercise mode (CE v

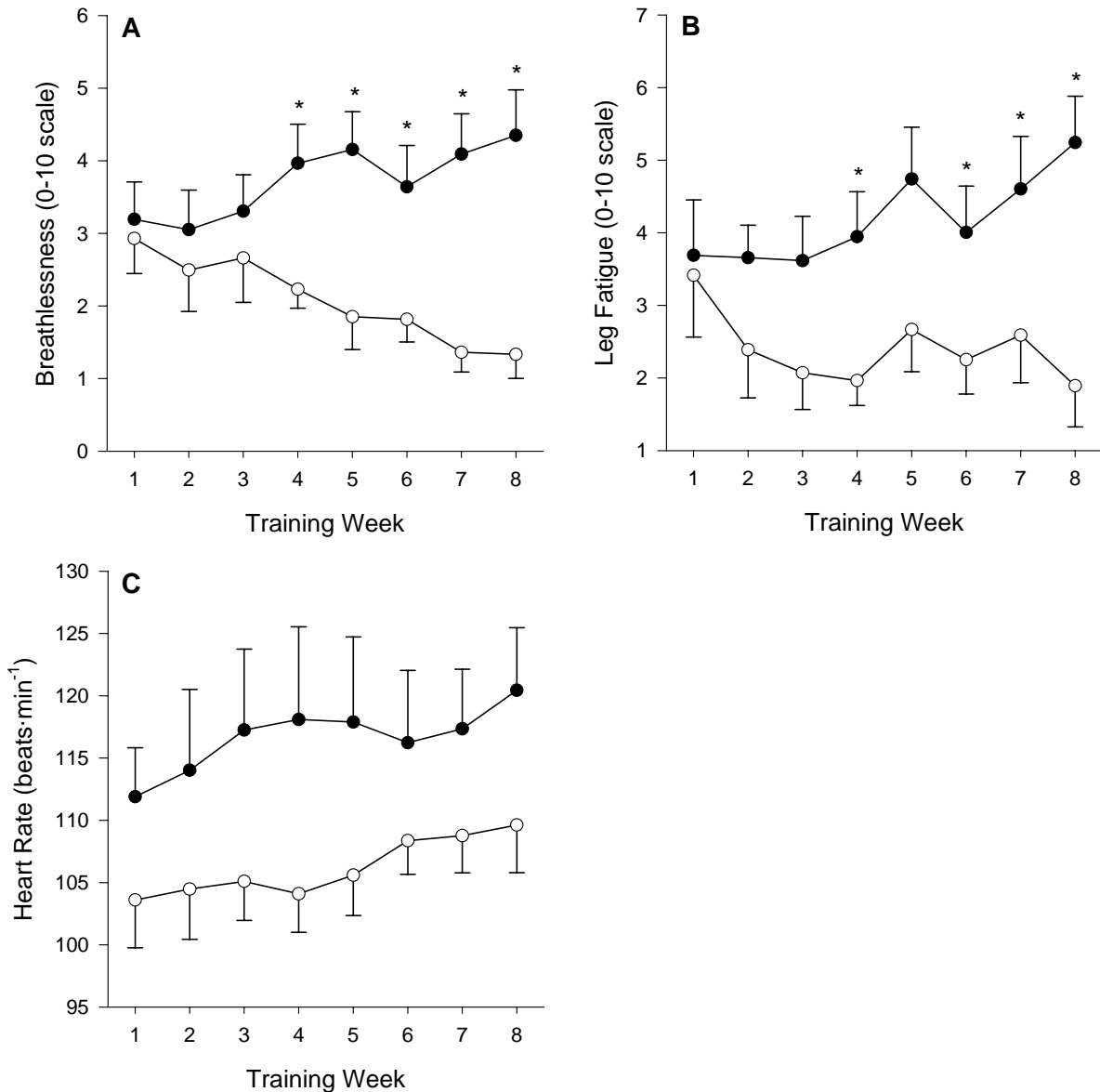


Figure 3.2. Mean (\pm SEM) values for breathlessness (panel A), leg fatigue (panel B) and heart rate (panel C) during 8 wk of continuous (●) and intermittent exercise (○) training. Training intensity was increased by 5% of initial intensity every week from the third week of training. The intermittent exercise values were measured at the end of an exercise interval. Each data point is the average of the last 10 min of training, and also represents the mean value for the three training sessions attended each week. * $P < 0.05$, continuous exercise different from intermittent exercise.

IE) but not time (training week) for ratings of perceived breathlessness and leg fatigue ($P < 0.05$) over 8 wk of training. Thus, breathlessness and leg fatigue were systematically greater during CE compared to IE training (Figure 3.2, panels A and B). There was a tendency for breathlessness and leg fatigue to decrease as the training sessions progressed during IE training and increase during CE training, but these trends did not reach statistical significance. Although heart rate tended to be higher during CE compared to IE training, and increased over the course of training in both groups, the differences between training modes and across time were not significant.

Results from the incremental exercise tests conducted before and after the 8-wk training program are presented in Table 3.3. Peak oxygen (O_2) uptake increased significantly by $12 \pm 5\%$ in the CE group and by $9 \pm 2\%$ in the IE group. While both training groups demonstrated significant improvements in aerobic power, no significant differences in \dot{V}_{O_2} peak existed between the two groups. Similarly, \dot{V}_{CO_2} peak values were significantly greater after training than before training in both groups. \dot{V}_E peak and peak exercise heart rate measured post-training were not significantly different from values measured before training within each group, and were also not different between the CE and IE groups. Both training groups achieved a significantly greater W_{peak} after exercise training. This improvement in exercise tolerance amounted to a $14 \pm 3\%$ increase in W_{peak} for the CE group and a $13 \pm 5\%$ increase for the IE group. The increases in W_{peak} during incremental cycling were not significantly different between groups. The perceived sensation of breathlessness was significantly lower at peak exercise after training in both groups, decreasing by $22 \pm 8\%$ in the CE group and by $12 \pm 5\%$ in the IE group. Again, the reduction in breathlessness scores with training was not significantly different between the two groups. Perceived leg fatigue was

unchanged with training in both groups and no significant differences existed between the two groups.

Table 3.3. Peak exercise values measured during incremental cycle ergometry pre- and post-training.

	CE		IE	
	Pre-training	Post-training	Pre-training	Post-training
\dot{V}_{O_2} peak (L·min ⁻¹)	1.23 ± 0.12	1.38 ± 0.13 [†]	1.07 ± 0.11	1.17 ± 0.13 [†]
\dot{V}_{CO_2} peak (L·min ⁻¹)	1.34 ± 0.15	1.54 ± 0.17 [†]	1.16 ± 0.15	1.29 ± 0.15*
\dot{V}_E peak (L·min ⁻¹)	44.9 ± 5.2	49.1 ± 4.9	39.4 ± 5.4	42.1 ± 6.1
Peak Heart Rate (beats·min ⁻¹)	127 ± 5	128 ± 6	128 ± 7	131 ± 8
W _{peak} (W)	84 ± 11	95 ± 11*	73 ± 11	82 ± 12 [†]
Δ Breathlessness (0-10 scale)	6.3 ± 0.7	5.2 ± 0.9 [†]	5.8 ± 0.8	5.3 ± 0.8 [†]
Δ Leg Fatigue (0-10 scale)	5.8 ± 0.8	5.4 ± 0.7	6.98 ± 0.6	5.85 ± 0.7
GET (L·min ⁻¹)	0.88 ± 0.05	0.92 ± 0.06	0.76 ± 0.05	0.82 ± 0.07
GET (% \dot{V}_{O_2} peak)	74 ± 4	69 ± 3 [†]	76 ± 5	73 ± 4
GET (W)	47.1 ± 5.4	53.0 ± 5.8 [†]	36.8 ± 3.7	46.1 ± 5.4 [†]

Values presented are means ± SEM. CE: continuous exercise; IE: intermittent exercise; \dot{V}_{O_2} peak: peak oxygen uptake; \dot{V}_{CO_2} peak: peak carbon dioxide output; \dot{V}_E peak: peak expired ventilation; W_{peak}: peak power output; Δ: change from rest to peak exercise values. * P<0.01, [†] P<0.05; significantly different from pre-training.

The \dot{V}_{O_2} measured at the GET was not altered by 8 wk of either CE or IE training. However, the GET occurred at a significantly lower percentage of post-training \dot{V}_{O_2} peak, but only in the subjects performing CE training. The GET occurred at a significantly greater power output post-training compared to pre-training in both groups.

Figure 3.3 illustrates the change in IC (normalised to resting IC) during incremental exercise for the CE group (panel A) and IE group (panel B) before and after training. During both incremental tests (pre- and post-training), IC decreased significantly from baseline values with increasing exercise intensity in the CE and IE groups. The decrease in IC with increasing exercise intensity was best described as a linear trend ($P < 0.001$). R^2 values for the linear curve-fit in the

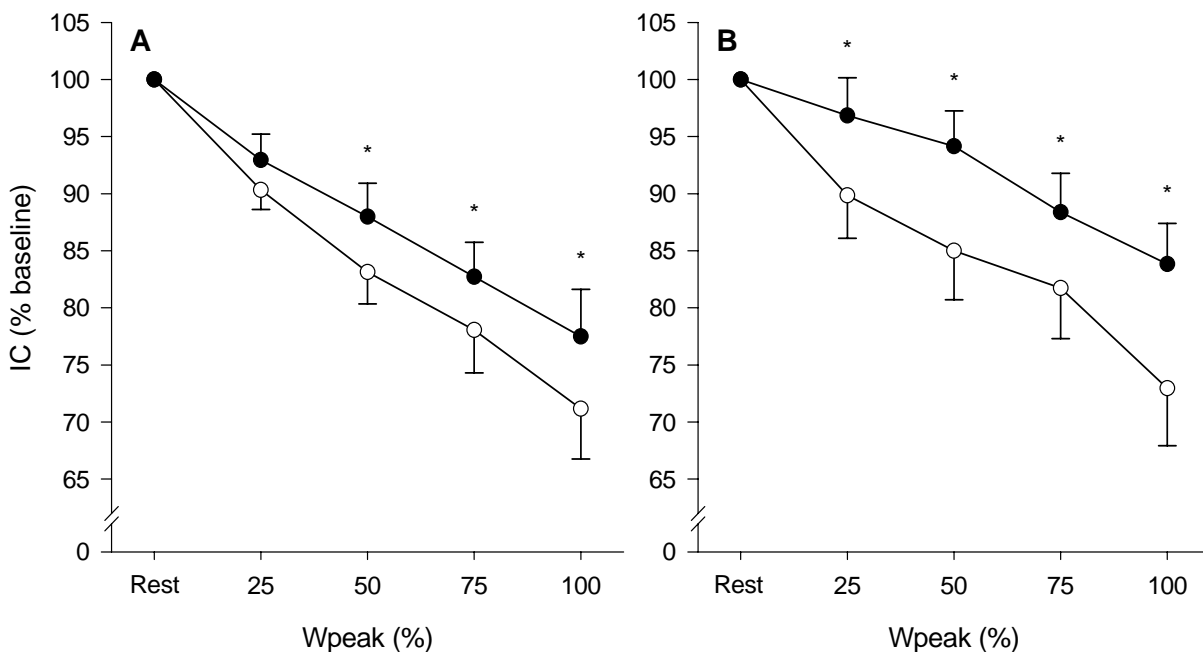


Figure 3.3. Changes in inspiratory capacity (IC) during incremental exercise pre- (○) and post-training (●) in the continuous exercise (panel A) and intermittent exercise (panel B) groups. Data points represent mean \pm SEM. IC is expressed as a percentage of baseline (resting) IC and plotted as a function of percent peak power output (Wpeak). * $P < 0.05$, significantly different from pre-training values.

CE group were 0.96 ± 0.01 (pre-training) and 0.87 ± 0.05 (post-training), while in the IE group, R^2 values averaged 0.83 ± 0.07 (pre-training) and 0.75 ± 0.08 (post-training). There was no significant effect of exercise-training mode on IC measured at any time point during incremental exercise either before or after exercise training. In the CE group, IC at peak exercise was $71 \pm 4\%$ of resting IC during the pre-training incremental test and $78 \pm 4\%$ during the post-training test ($P < 0.001$). This represents a 0.76 ± 0.13 L (pre-training) and 0.58 ± 0.10 L (post-training) decrease in IC. In the IE group, IC at peak exercise was $73 \pm 5\%$ and $84 \pm 4\%$ of resting IC during the pre-training and post-training tests, respectively ($P < 0.01$). These changes represent a pre-training decrease of 0.58 ± 0.11 L and a post-training decrease of 0.30 ± 0.05 L. The results indicate a reduction in DH occurred during incremental exercise in both groups after exercise training.

The $\Delta 40\%$ power output used during the constant-load exercise tests were not significantly different between training groups, averaging 62 ± 7 W (75.0 ± 2.5 %W_{peak}) for the subjects performing CE training and 51 ± 6 W (72.6 ± 3.8 %W_{peak}) for those performing IE training. Signal-to-noise ratios for the breath-by-breath \dot{V}_{O_2} responses were sufficiently high to enable adequate characterisation of the kinetics parameters in all the subjects. The coefficient of determination (R^2) for the model fits averaged 0.99, while the coefficient of correlation between the residuals and model fits averaged less than 10^{-3} . This suggests a good fit of the model to the measured \dot{V}_{O_2} values and that the deviation of the measured values from the mean were independent of time and randomly distributed about the regression line. Interestingly, only two subjects demonstrated a significant slow component amplitude during the pre-training tests ($A'_s = 76$ mL·min⁻¹ and 154 mL·min⁻¹). The \dot{V}_{O_2} responses for all the other subjects were more appropriately fit using Equation 3.2, when the model

selection criteria described in the Methods were used (see Figure 3.4). Thus, mean values are only reported for the primary component (phase II) of the \dot{V}_{O_2} response (Table 3.4).

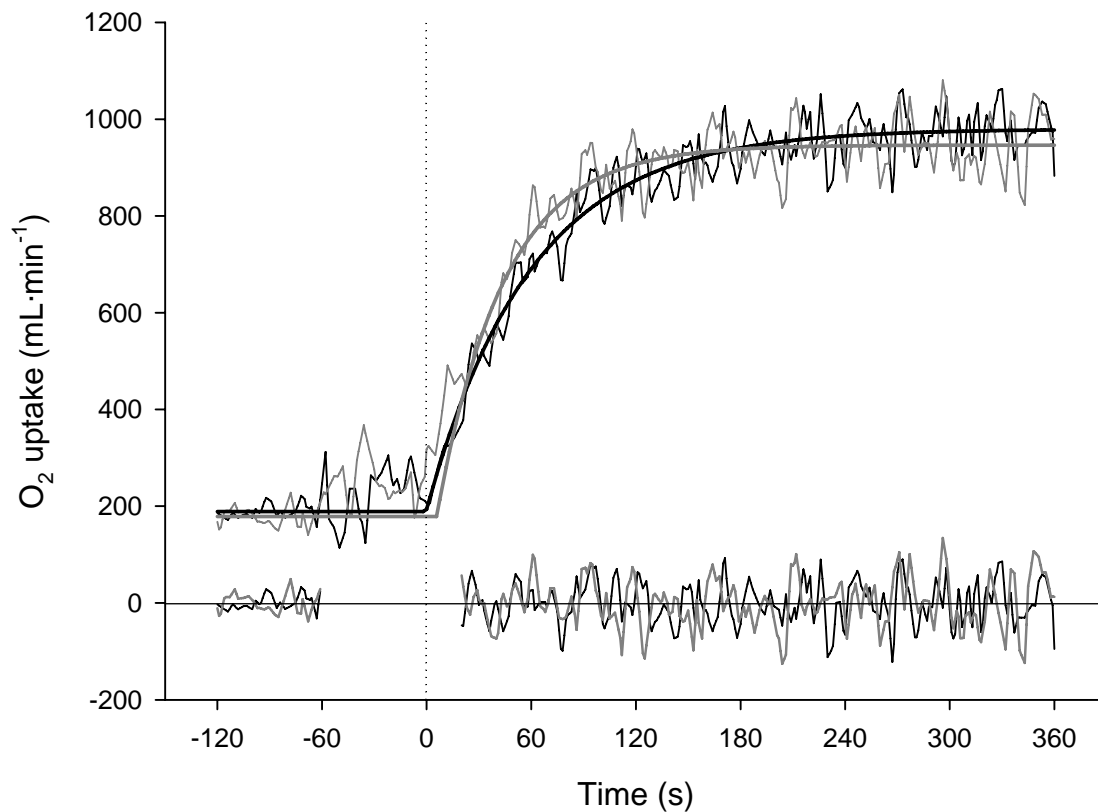


Figure 3.4. Breath-by-breath O_2 uptake responses, model fits and residuals in a representative subject during 6 min of constant-load submaximal exercise performed before (black lines) and after (grey lines) 8-wk of exercise training. The vertical dotted line indicates the onset of constant-load exercise, and is preceded by a period of seated rest. Only 2 min of seated rest prior to exercise are depicted in the graph.

Eight weeks of CE or IE training did not significantly affect baseline (A_B), phase II (A_P) or the total \dot{V}_{O_2} (A_{TOT}) amplitude and gain (G_{TOT}) components. However, there was a significant speeding of phase II kinetics in both groups with exercise training. The mean decrease in the phase II time constant pre- to post-training was nearly identical for the CE (10 ± 3 s or $15 \pm 5\%$) and IE groups (11 ± 3 s or $15 \pm 6\%$). Moreover, the heart rate, \dot{V}_{CO_2} and \dot{V}_E responses to the submaximal

exercise bouts (averaged over the last 30 s of constant-load exercise and across the two pre- and post-training transitions) were significantly reduced after training in the CE and IE groups (Table 3.5). The reductions in heart rate (CE: $9 \pm 3\%$; IE: $6 \pm 1\%$), \dot{V}_{CO_2} (CE: $5 \pm 2\%$; IE: $5 \pm 1\%$) and \dot{V}_E (CE: $10 \pm 3\%$; IE: $8 \pm 2\%$), and increase in O_2 pulse (CE: $9 \pm 3\%$; IE: $7 \pm 2\%$), were similar in both groups. There was a tendency for breathlessness and leg fatigue values to be lower during submaximal exercise performed after compared to before training, but these changes were not significant. Blood lactate concentrations were significantly reduced during the post-training constant-load tests compared to the pre-training tests (CE: $28 \pm 3\%$; IE: $17 \pm 7\%$), but the difference between the groups was not statistically significant (see Table 3.5).

Table 3.4. Oxygen uptake kinetic responses to 6 min of submaximal constant-load exercise pre- and post-training.

	CE		IE	
	Pre-training	Post-training	Pre-training	Post-training
A_B (mL·min ⁻¹)	369 ± 19	363 ± 19	304 ± 23	308 ± 22
A_P (mL·min ⁻¹)	743 ± 72	738 ± 75	664 ± 62	668 ± 70
A_{TOT} (mL·min ⁻¹)	1112 ± 85	1101 ± 89	968 ± 73	976 ± 76
TD_P (s)	7 ± 2 (4 ± 0.3)	7 ± 2 (4 ± 0.5)	7 ± 3 (4 ± 0.3)	7 ± 4 (3 ± 0.3)
τ_P (s)	57 ± 2 (7 ± 1)	47 ± 2 [†] (7 ± 1)	64 ± 5 (6 ± 1)	54 ± 5* (5 ± 1)
G_{TOT} (mL·min ⁻¹ ·W ⁻¹)	12.5 ± 0.7	12.3 ± 0.6	13.7 ± 1.0	13.6 ± 1.0

Values presented are means ± SEM with 95% confidence intervals in parentheses. CE: Continuous exercise; IE: Intermittent exercise; A_B : baseline oxygen uptake (\dot{V}_{O_2}) amplitude while seated on the ergometer; A_P : phase II amplitude; A_{TOT} : overall \dot{V}_{O_2} amplitude. τ_P : phase II time constant; TD_P : phase II onset time; G_{TOT} : overall gain. * $P < 0.01$, [†] $P < 0.05$; significantly different from pre-training.

Table 3.5. Cardiorespiratory, metabolic and subjective ratings of exertion in response to 6 min of submaximal constant-load exercise pre- and post-training.

	CE		IE	
	Pre-training	Post-training	Pre-training	Post-training
Heart Rate (beats·min ⁻¹)	122 ± 6	111 ± 5 [†]	123 ± 4	115 ± 4*
O ₂ pulse (mL·beat ⁻¹)	9.2 ± 0.8	10.0 ± 0.8 [†]	8.0 ± 0.7	8.7 ± 0.7 [†]
\dot{V}_{CO_2} (L·min ⁻¹)	1.22 ± 0.11	1.16 ± 0.11 [†]	1.03 ± 0.08	0.97 ± 0.07 [†]
\dot{V}_E (L·min ⁻¹)	41.4 ± 4.1	36.9 ± 3.5*	34.4 ± 3.1	31.6 ± 2.9*
Δ Lactate (mmol·L ⁻¹)	2.9 ± 0.4	2.2 ± 0.4*	2.5 ± 0.3	1.9 ± 0.2*
Δ Breathlessness (0-10 scale)	4.5 ± 0.5	3.6 ± 0.5	5.0 ± 0.7	4.1 ± 1.0
Δ Leg Fatigue (0-10 scale)	3.4 ± 0.7	3.0 ± 0.7	5.1 ± 0.8	3.9 ± 0.9

Values presented are means ± SEM. \dot{V}_{CO_2} : carbon dioxide output; \dot{V}_E : expired ventilation; IC: inspiratory capacity; Δ : difference between peak and resting values. * P<0.01, [†] P<0.05; significantly different from pre-training.

The results of the 6MWT are provided in Table 3.6. Pre-training 6MWD values were not significantly different between the CE and IE training groups. Eight weeks of exercise training resulted in an increase in walking distance of 53 ± 10 m in the CE group and 38 ± 13 m in the IE group. These improvements in 6MWD with exercise training were statistically significant in both groups (CE: P<0.01; IE: P<0.05) and represent a 12 ± 3% and 9 ± 3% increase from pre-training values in the CE and IE groups, respectively. The magnitude of improvement was not significantly different between the two groups, and post-training 6MWD values were not different between the training groups. Ratings of breathlessness, leg

fatigue and heart rate measured at rest were not different between the groups or between pre- and post-training tests. There were no significant training effects for ratings of breathlessness or lower limb fatigue measured at the end of the 6MWT. The subjects in the CE group achieved a significantly greater heart rate at the end of the 6MWT after 8 wk of training. Although the mean end-exercise heart rate was also greater during the post-training compared to pre-training 6MWT in the IE group, this difference was not significant.

Table 3.6. Six-Minute Walk Test results.

	CE		IE	
	Pre-training	Post-training	Pre-training	Post-training
6MWD (m)	453 ± 30	510 ± 31*	450 ± 35	489 ± 37 [†]
Heart Rate (beats·min ⁻¹)	114 ± 5	121 ± 5*	114 ± 4	119 ± 6
Δ Breathlessness (0-10 scale)	4.3 ± 0.6	3.6 ± 0.8	5.0 ± 0.9	4.3 ± 1.0
Δ Leg Fatigue (0-10 scale)	1.7 ± 0.5	3.1 ± 0.7	2.5 ± 0.6	2.2 ± 0.4

Values presented are means ± SEM. CE: continuous exercise training; IE: intermittent exercise training; 6MWD: six-min walk distance. * P<0.01, [†] P<0.05; significantly different from pre-training.

While none of the changes in SGRQ scores attained the MCID threshold, the 95% CI for all components of the questionnaire included the MCID (Figure 3.5, panel A). However, the changes in component scores with exercise training were not significant in either the CE or IE training groups.

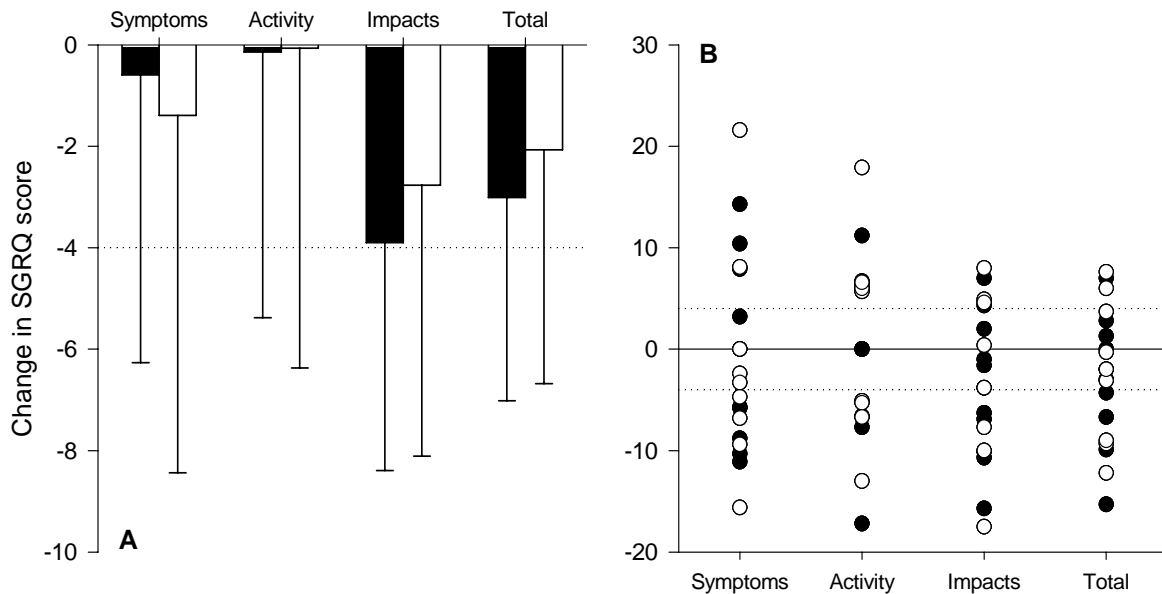


Figure 3.5. Mean change in the St. George's Hospital Respiratory Questionnaire (SGRQ) component scores after 8 wk of continuous (filled bars) and intermittent (open bars) exercise training (panel A). Panel B is a point-plot of each subject's score change for those performing continuous (●) and intermittent (○) exercise training. The errors bars represent 95% confidence intervals for the mean. The horizontal dotted lines indicate the minimal clinically important difference (i.e. a change in score of 4).

Significant correlations were observed between the percentage increase in \dot{V}_{O_2} peak and W_{peak} ($r = 0.95$, $P < 0.01$), and \dot{V}_{O_2} peak and 6MWD ($r = 0.71$, $P < 0.01$) following exercise training, when the IE and CE groups were combined ($N = 19$). The percentage increase in 6MWD also correlated significantly with the increase observed in W_{peak} ($r = 0.79$, $P < 0.01$; $N = 19$). The percent change in IC correlated negatively with perceived sensation of breathlessness during the incremental exercise test ($r = -0.54$, $P < 0.05$; $N = 19$). Thus, subjects with a greater improvement in IC (or a greater reduction in DH) at peak exercise, tended to demonstrate a larger reduction in breathlessness. Significant correlations were observed between the total work performed during exercise training and the

percent increase in \dot{V}_{O_2} peak ($r = 0.91$, $P < 0.01$), W_{peak} ($r = 0.95$, $P < 0.01$) and 6MWD ($r = 0.78$, $P < 0.01$). The percent decrease in \dot{V}_E measured at the end of constant-load exercise correlated significantly with the decrease observed in \dot{V}_{CO_2} ($r = 0.48$, $P < 0.05$).

DISCUSSION

The use of IE as a training intervention in patients with COPD has received some attention recently (Cappoose et al., 1999; Vogiatzis et al., 2002; Vogiatzis et al., 2005). In agreement with results obtained in healthy individuals (Eddy et al., 1977; Poole and Gaesser, 1985; Morris et al., 2002), the findings of these studies suggests that when total work performed within each exercise mode is the same, IE and CE training result in similar physiological and functional improvements in COPD patients (Vogiatzis et al., 2002; Vogiatzis et al., 2005). However, in training studies using COPD patients, IE was prescribed at a higher intensity than CE (Cappoose et al., 1999; Vogiatzis et al., 2002; Vogiatzis et al., 2005). In contrast, the present study adopted an approach similar to that used by Morris et al. (2002), where training was prescribed at a similar relative intensity (50% of W_{peak}) and total work performed was the same for both modes of training. Since mean W_{peak} values were not significantly different between the CE and IE groups and training intensity was increased by similar increments over the 8-wk period, absolute training intensity and the total work performed were not significantly different between the groups. The benefit of this approach from an experimental point of view is that the basic components that need to be considered when designing an exercise program (i.e., intensity, duration, frequency and mode) are held constant, except for training mode. Therefore, if training differences exist, they are most likely due to training mode. To illustrate this point, the similar functional and physiological adaptations between CE and IE

training reported by Vogiatzis et al. (2002) may not only be attributed to the same total work performed between the two groups, but also to the higher relative intensity used by those performing IE. By standardising exercise intensity, duration and frequency (thus, ensuring total work performed is the same), and varying only the exercise mode (CE v IE), the present study was able to determine the influence of training mode on the adaptations to endurance training in patients with COPD.

In the present study, subjects who undertook IE training experienced lower levels of perceived intensity of breathlessness and limb fatigue than the group who performed CE training during the 8-wk program. However, exercise capacity (\dot{V}_{O_2} peak) and exercise tolerance (W_{peak} and 6MWD) improved to a similar extent with training, irrespective of the exercise mode used. During constant-load exercise, the faster phase II on-transient kinetic response with training was independent of exercise mode, while training-induced reductions in submaximal exercise heart rate, \dot{V}_{CO_2} , \dot{V}_E and blood lactate were also similar between the IE and CE groups. Continuous and IE training also resulted in an equivalent reduction in the degree of DH during incremental exercise. Thus, when total work performed and relative intensity was the same between the two groups, 8 wk of CE and IE training resulted in similar functional improvements and physiological adaptations in patients with moderate COPD.

The significant correlations (and high coefficient values, $r > 0.70$ in all cases) between the percent changes in \dot{V}_{O_2} peak, W_{peak} and 6MWD for the combined study population suggests that the incremental exercise test and 6MWT assess similar physiological parameters - measures of exercise capacity or tolerance. Moreover, the magnitude of improvement in these measures was sensitive to the

volume of training (total work) performed. The 6MWT tends to assess a “submaximal” level of functional capacity since patients select their own level of walking speed and are permitted to stop and rest during the test (American Thoracic Society, 2002). However, it is suggested that the subjects in the present study approached “maximal effort” during the 6MWT since peak exercise heart rate values were not significantly different from those measured during incremental exercise for the pre- and post-training tests or between CE and IE groups. Although exercise training was conducted using cycle ergometry, it was worthwhile measuring 6MWD, since walking tends to be a more common and familiar form of activity than cycling (Singh, 1992). The improvement in 6MWD, and the significant correlation obtained between the peak incremental and 6MWT results, demonstrates that the training adaptations and improvements observed are not specific to the mode of exercise used during the training program. Rather, the training adaptations demonstrated from cycling in the present study were transferable to walking.

The similar increase in \dot{V}_{O_2} peak (CE: 12%; IE: 9%) and W_{peak} (CE: 14%; IE: 13%) that was observed in both training groups in the present study has not been found in previous studies comparing CE and IE in COPD patients. Coppoolse et al. (1999) found a significant increase in \dot{V}_{O_2} peak, with no change in W_{peak} , in subjects performing CE training, whereas those performing IE training improved W_{peak} with no significant change in \dot{V}_{O_2} peak. Two studies performed by Vogiatzis et al. (2002; 2005) reported significant increases in W_{peak} but no change in \dot{V}_{O_2} peak in both CE and IE trained groups. The results from these earlier studies suggest that mechanical efficiency may have improved with exercise training (Vogiatzis et al., 2002). The similar relative improvements in

W_{peak} and $\dot{V}_{\text{O}_2 \text{ peak}}$ as well as the nearly identical G_{TOT} values obtained during constant-load exercise pre- and post-training in the present study suggest that mechanical efficiency was not altered by 8 wk of CE or IE training.

An important finding in the present study is that exercise capacity was increased, with both groups achieving a significantly greater \dot{V}_{E} peak but lower sensation of breathlessness post-training compared to pre-training. Exertional breathlessness or dyspnoea is a major symptom limiting exercise performance in patients with COPD (O'Donnell and Webb, 1993). Thus, the COPD patients in the present study may have been able to exercise longer and attain a greater W_{peak} because the degree of breathlessness was lower following training. While the causes of dyspnoea are thought to be multi-factorial, DH has been shown to be an important mechanism contributing to dyspnoea in patients with COPD (O'Donnell and Webb, 1993). In the present study, a reduction in DH may account for the lower breathlessness scores reported during incremental exercise since the changes in IC and breathlessness with training were significantly correlated. A decrease in inspiratory and expiratory muscle recruitment and improved neuro-ventilatory coupling associated with a reduction in DH may have contributed to the reduced sensation of breathlessness observed at maximal exercise (Dodd et al., 1984; Belman et al., 1996).

In accordance with the Fick principle, the improvement in $\dot{V}_{\text{O}_2 \text{ peak}}$ with exercise training is mediated either by an increase in peak cardiac output or enhanced O_2 extraction by the exercising muscle. Morris et al. (2002) demonstrated that endurance-training induced increases in $\dot{V}_{\text{O}_2 \text{ peak}}$ in healthy older men were due primarily to an increase in peak cardiac output. In the present study, the increase

in \dot{V}_{O_2} peak with training while peak heart rate was unchanged in both the CE and IE groups, suggests that any increase in peak cardiac output would have been mediated primarily by raising stroke volume. Inflation of the lung during inspiration has been suggested to negatively impact cardiac output by reducing cardiac compliance and venous return (Wallis et al., 1983). Thus, the systematic reduction in DH observed during the post- compared to pre-training incremental test in the present study could have resulted in improved ventricular filling and increased stroke volume. However, it is uncertain if DH per se influences cardiac output since voluntarily induced lung hyperinflation in healthy adults does not appear to impact upon cardiac output (Stark-Leyva et al., 2004). Alternatively, a reduction in DH implies that the work of breathing may be reduced during incremental exercise. Since a respiratory muscle “steal” of blood flow has been suggested to occur in COPD patients during high-intensity exercise, a reduction in the work (and O_2 cost) of breathing could increase blood flow and O_2 supply to the exercising limb muscles, thereby increasing W_{peak} and \dot{V}_{O_2} peak (Richardson et al., 1999).

Training-induced alterations in muscle morphology and biochemistry could also account for the improvement in exercise capacity and tolerance by enhancing O_2 extraction by the working muscles. Recently, Vogiatzis et al. (2005) demonstrated that 10 wk of high-intensity interval (mean intensity: 124% W_{peak}) training induced significant increases in type I and IIa cross-sectional areas and capillary-to-fibre ratio while citrate synthase activity was also increased (from 14.2 ± 1.3 to 20.5 ± 4.2 $\text{mmol}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$), albeit non-significantly, in patients with COPD (FEV_1 : 40 ± 4 %predicted). Moreover, the magnitude of these changes was not significantly different from patients performing a similar volume of CE training (mean intensity: 75% W_{peak}). Sala and colleagues (1999) demonstrated that 8

wk of moderate- to high-intensity exercise training increased \dot{V}_{O_2} peak, W_{peak} and O_2 extraction ratio across an exercising limb while phosphocreatine recovery kinetics were faster in patients with moderate COPD (FEV_1 : 43 ± 9 % predicted) compared to healthy controls. These studies indicate that when total work is normalised between training groups, IE and CE elicit similar adaptations in muscle morphology, and that exercise training can enhance muscle O_2 extraction and muscle bioenergetics, leading to an improvement in \dot{V}_{O_2} peak and W_{peak} . In the present study, the faster phase II time constants after training in both CE and IE groups during constant-load exercise are also indicative of an improved coupling between oxidative metabolism (O_2 delivery and utilisation) and external work.

The speeding of τ_P (and the magnitude of speeding) with endurance training demonstrated in the present study is consistent with that observed by other investigators (Otsuka et al., 1997; Puente-Maetsu et al., 2000). The \dot{V}_{O_2} on-transient kinetic response has been shown to be more sensitive to exercise-training stimuli than the peak physiological variables determined during incremental exercise in healthy young and older individuals (Phillips et al., 1995; Fukuoka et al., 2002). Faster phase II time constants have been detected as early as 4 days after training commenced, long before changes in \dot{V}_{O_2} peak were observed (Phillips et al., 1995). Thus, the nearly identical degree of improvement in τ_P (~15% in both CE and IE groups) provides strong evidence that the physiological adaptations resulting from the IE and CE protocol used in the present study were similar, at least with respect to the determinants of τ_P .

As discussed earlier, the dynamic adjustment of \dot{V}_{O_2} in response to a step change in energy requirement can also be related to the Fick equation. Thus, the rate-limiting factors that determine the shape of the phase II response must reside in the mechanisms controlling O_2 delivery to the muscle (cardiac output and/or blood flow) or O_2 utilisation by the muscle (O_2 diffusion from capillary to mitochondria and/or oxidative phosphorylation) (Grassi et al., 1996; Hughson et al., 2001). Otsuka et al. (1997) and Puente-Maestu et al. (2000) reported faster heart rate kinetics with endurance training in patients with COPD and suggested that this finding indicates a more rapid adjustment of cardiac output (and therefore convective O_2 delivery to the muscle) at exercise onset. However, Sala et al. (1999) demonstrated that O_2 delivery to the muscle (the product of leg blood flow and arterial O_2 content) was unchanged, while O_2 extraction across the exercising muscle (arterio-venous O_2 difference) was significantly increased during incremental exercise performed after 8 wk of endurance training in COPD patients. Moreover, this improvement in O_2 extraction by the muscle appeared to be accentuated during submaximal exercise intensities, when compared to the responses in healthy control subjects. This finding suggests that factors intrinsic to the muscle (such as increased oxidative enzyme activity and muscle capillarisation discussed earlier) may have contributed to the observed speeding of the phase II \dot{V}_{O_2} response with CE and IE training in the present study.

The lower blood lactate responses post- compared to pre-training indicates either a reduced reliance on glycolytic metabolism or improved lactate degradation (i.e. the rate of lactate clearance/uptake exceeds its rate of appearance) (Maltais et al., 1996). The speeding of the phase II \dot{V}_{O_2} response results in a smaller O_2 deficit at the onset of exercise with less reliance on anaerobic energy sources such as (PCr), lactate and muscle O_2 stores (Özyener et al., 2001). Thus, the

faster on-transient kinetics could have attenuated the reliance on anaerobic metabolism, resulting in the lower blood lactate response to constant-load exercise after training. Additionally, training-induced biochemical changes in the muscle favouring oxidative processes such as increased tricarboxylic acid cycle and β -oxidation enzymes could also decrease anaerobic energy production (Maltais et al., 1996; Puente-Maetsu et al., 2003). Finally, the increase in the power output at which the GET occurred indicates that the constant-load exercise tests conducted post-training were performed at a lower relative intensity (particular with respect to the GET) than those performed before training. This may have contributed to the lower post-training lactate values observed in the present study.

The lower relative intensity of the constant-load exercise bouts conducted after training may also explain the reduction in submaximal heart rate and \dot{V}_E observed in both groups. Since mechanical efficiency appeared to be unaltered with either CE or IE training, improved distribution of blood flow and O_2 extraction by the exercising muscle could reduce the ventilatory demands during submaximal constant-load exercise. The significant correlation between the change in \dot{V}_E and \dot{V}_{CO_2} with exercise training suggests that the reduction in \dot{V}_E at the same submaximal power output can be attributed in part to a reduction in \dot{V}_{CO_2} , secondary to a decrease in blood lactate concentration. Bicarbonate buffering of hydrogen ions associated with lactate production results in the formation of non-metabolic carbon dioxide (CO_2) and drives \dot{V}_E such that arterial partial pressure for CO_2 is maintained relatively constant (Wasserman et al., 1973). Additionally, an attenuated metabolic acidosis because of the lower blood lactate concentration could result in a relatively smaller ventilatory chemoreflex

drive, reducing \dot{V}_E during the post-training submaximal exercise test (Casaburi et al., 1987). The lower heart rate and unchanged \dot{V}_{O_2} response would cause the O_2 pulse to increase. The O_2 pulse represents the product of stroke volume and O_2 extraction by the muscle. Thus an increased stroke volume or an improved ability of the skeletal muscle to extract O_2 could be responsible for the post-training reduction in submaximal exercise heart rate.

All component scores and the total score of the SGRQ tended to decrease in both training groups, with the Impact component approaching the MCID of 4 points (CE: -3.9 ± 2.3 ; IE: -2.8 ± 2.7). However, the changes from pre- to post-training were not statistically significant. Jones et al. (2005) suggested that when a change in component or total score is less than the MCID but the 95% CI includes the MCID, then this change can be considered clinically meaningful. While this was the case for all the components of the SGRQ in the present study (Figure 3.5), the lack of a statistical difference in pre- compared to post-training scores indicates that there was no trend for improved HRQoL after 8 wk of training. Inspection of the point plots illustrating the change in score for each individual shows that HRQoL did improve by a clinically significant margin in some subjects, while in others there appeared to be a worsening of quality of life (Figure 3.5, panel B). It is unclear why the physiological and functional adaptations demonstrated by these subjects did not translate to a consistently improved perception of HRQoL. Vogiatzis et al. (2002) demonstrated that 12 wk of intermittent exercise training resulted in significant improvements in quality of life scores, whereas Arnardóttir et al. (2006) reported that 8-wk of endurance training did not enhance HRQoL in COPD patients. Thus, the 8-wk duration of the training program used in the present study may not have been sufficiently long to produce changes in quality of life. Alternatively, the relatively small sample size

suggests that the present study may not have been adequately powered to detect changes in HRQoL.

In conclusion, the present study is the first to demonstrate that when exercise intensity, duration and frequency are the same, the cardiorespiratory and metabolic adaptations to 8 wk of exercise training in patients with moderate COPD are independent of the exercise mode used (CE or IE). Intermittent exercise training was better tolerated than CE training, with ratings of breathlessness and leg fatigue significantly lower during IE training. Peak \dot{V}_{O_2} and power output increased during incremental exercise and patients were able to walk a greater distance during a 6MWT following exercise training. Dynamic hyperinflation was systematically and significantly reduced with training during the incremental cycling test. The magnitude of these improvements were not significantly different between the CE and IE groups. During submaximal constant-load exercise, \dot{V}_{O_2} kinetics were faster after training than before training, with the magnitude of speeding nearly identical for the two groups. Additionally, submaximal exercise heart rate, \dot{V}_E , \dot{V}_{CO_2} and blood lactate concentrations were all significantly reduced with training. Thus, IE training is as effective as CE training in improving functional status in patients with moderate COPD. The decreased perception of breathlessness and leg fatigue associated with IE could improve adherence to training programs in COPD patients. Furthermore, with its variable combinations of exercise to rest ratio, duration, and tolerated intensities, IE is a flexible training mode that may be preferred to CE, particularly for patients who are unable to sustain prolonged periods of continuous activity.

REFERENCES

- Ambrosino, N. and S. Strambi (2004). New strategies to improve exercise tolerance in chronic obstructive pulmonary disease. *Eur Respir J.* 24: 313-363.
- Arnardóttir, R. H., S. Sörensen, I. Ringqvist and K. Larsson (2006). Two different training programmes for patients with COPD: A randomised study with 1-year follow-up. *Respir Med.* 100: 130-139.
- Åstrand, I., P.-O. Åstrand, E. H. Christensen and R. Hedman (1960). Intermittent muscular work. *Acta Physiol Scand.* 48: 448-453.
- American Thoracic Society (1994). Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med.* 152: 1107-1136.
- American Thoracic Society (2002). ATS Statement: Guidelines for the Six Minute Walk Test. *Am J Respir Crit Care Med.* 166: 111-117.
- Bell C, Paterson DH, Babcock MA, and Cunningham DA (1998). Characteristics of the \dot{V}_{O_2} slow component during heavy exercise in humans aged 30 to 80 years. *Adv Exp Med Biol.* 450: 219-222.
- Belman, M. J., W. C. Botnick and J. W. Shin (1996). Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 153: 967-975.
- Cappoose, R., A. M. W. J. Schols, E. M. Baarends, R. Mostert, M. A. Akkermans, P. P. Janssen and E. F. M. Wouters (1999). Interval versus continuous training in patients with severe COPD: a randomized clinical trial. *Eur Respir J.* 14: 258-263.

- Carrieri-Kohlman, V., J. M. Gormley, M. K. Douglas, S. M. Paul and M. S. Stulberg (1996). Exercise training decreases dyspnea and the distress and anxiety associated with it. *Chest*. 110: 1526-1535.
- Casaburi, R., T. W. Storer, K. Wasserman (1987). Mediation of reduced ventilatory response to exercise after endurance training. *J Appl Physiol*. 63: 1533-1538.
- Casaburi, R., J. Pórszász, M. R. Burns, E. R. Carithers, R. S. Y. Chang and C. B. Cooper (1997). Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 155: 1541-1551.
- Coppoolse, R., A. M. W. J. Schols, E. M. Baarends, R. Mostert, M. A. Akkermans, P. P. Janssen and E. F. M. Wouters (1999). Interval versus continuous training in patients with severe COPD: a randomized clinical trial. *Eur Respir J*. 14: 258-263.
- Cunningham, D. A., D. McCrimmon and L. F. Vlach (1979). Cardiovascular responses to interval and continuous training in women. *Eur J Appl Physiol*. 41: 187-197.
- Dodd, D. S., T. Brancatisano and L. A. Engel (1984). Chest wall mechanics during exercise in patients with severe chronic air-flow obstruction. *Am Rev Respir Dis*. 129: 33-38.
- Eddy, D. O., K. L. Sparks and D. A. Adelizi (1977). The effects of continuous and interval training in women and men. *Eur J Appl Physiol*. 37: 83-92.
- Fukuoka, Y., B. Grassi, M. Conti, D. Guiducci, M. Sutti, C. Marconi and P. Cerretelli (2002). Early effects of exercise training on \dot{V}_{O_2} on- and off-kinetics in 50-year-old subjects. *Pflügers Arch*. 443: 690-697.

- Gorostiaga, E. M., C. M. Walter, C. Foster and R. C. Hickson (1991). Uniqueness of interval and continuous training at the same maintained exercise intensity. *Eur J Appl Physiol.* 63: 101-107.
- Grassi, B., D. C. Poole, R. S. Richardson, D. R. Knight, B. K. Erickson and P. D. Wagner (1996). Muscle O₂ uptake kinetics in humans: implications for metabolic control. *J Appl Physiol.* 80: 988-998.
- Henriksson, J. and J. S. Reitman (1976). Quantitative measures of enzyme activities in type I and type II muscle fibres of man after endurance training. *Acta Physiol Scand.* 97: 392-397.
- Hughson, R. L., M. E. Tschakovsky and M. E. Houston (2001). Regulation of oxygen consumption at the onset of exercise. *Exerc Sports Sci Rev.* 29: 129-133.
- Jones, N. L., L. Makrides, C. Hitchcock, T. Chypchar and N. McCartney (1985). Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis.* 131: 700-708.
- Jones, P. W. (2005). St. George's Respiratory Questionnaire: MCID. *J COPD.* 2: 75-79.
- Jones, P. W., F. H. Quirk and C. M. Baveystock (1992). A self-complete measure for chronic airflow limitation: The St. George's Respiratory Questionnaire. *Am Rev Respir Dis.* 145: 1321-1327.
- Koga, S., T. Shijori and N. Kondo (2005). Measuring \dot{V}_{O_2} kinetics: The practicalities. In *Oxygen Uptake Kinetics in Sport, Exercise and Medicine*. A. M. Jones and D. C. Poole (Eds.). London, Routledge: 39-61.

- Lansing, R. W., S. H. Moosavi and R. B. Banzett (2003). Measurement of dyspnea: word labeled visual analog scale vs. verbal ordinal scale. *Respir Physiol Neurobiol.* 134: 77-83.
- Maltais, F., P. LeBlanc, J. Jobin, C. Bérubé, J. Bruneau, L. Carrier, M. J. Breton, G. Falardeau and R. Belleau (1997). Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 155: 555-561.
- Maltais, F., P. LeBlanc, C. Simard, J. Jobin, C. Bérubé, J. Bruneau, L. Carrier and R. Belleau (1996). Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit. Care Med.* 154: 442-447.
- Morris, N., G. Gass, M. Thompson, G. Bennett, D. Basic and H. Moreton (2002). Rate and amplitude of adaptation to intermittent and continuous exercise in older men. *Med Sci Sports Exerc.* 34: 471-477.
- Morris, N., G. Gass, M. Thompson and D. Conforti (2003). Physiological responses to intermittent and continuous exercise at the same relative intensity in older men. *Eur J Appl Physiol.* 90: 620-625.
- O'Donnell, D. E. and K. A. Webb (1993). Exertional breathlessness in patients with chronic airflow limitation: the role of lung hyperinflation. *Am Rev Respir Dis.* 148: 1351-1357.
- Otsuka, T., N. Kurihara, T. Fuji, S. Fujimoto and J. Yoshikawa (1997). Effect of exercise training and detraining on gas exchange kinetics in patients with chronic obstructive pulmonary disease. *Clin Physiol.* 17: 287-297.
- Özyener, F., H. B. Rossiter, S. A. Ward and B. J. Whipp (2001). Influence of exercise intensity on the on- and off-transient kinetics of pulmonary oxygen uptake in humans. *J Physiol.* 533: 891-902.

- Pauwels, R. A., A. S. Buist, P. M. A. Calverley, C. R. Jenkins and S. S. Hurd (2001). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. *Am J Respir Crit Care Med.* 163: 1256-1276.
- Phillips, S. M., H. J. Green, M. J. MacDonald and R. L. Hughson (1995). Progressive effect of endurance training on \dot{V}_{O_2} kinetics at the onset of submaximal exercise. *J Appl Physiol.* 79: 1914-1920.
- Poole, D. C. and G. A. Gaesser (1985). Responses of ventilatory and lactate thresholds to continuous and interval training. *J Appl Physiol.* 58: 1115-1121.
- Puente-Maetsu, L., M. L. Sanz, P. Sanz, J. M. Ruiz de Ona, J. L. Rodriguez-Hermosa and B. J. Whipp (2000). Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. *Eur Respir J.* 15: 1026-1032.
- Puente-Maetsu, L., T. Tena, C. Trascasa, J. Pérez-Parra, R. Godoy, M. J. García and W. M. Stringer (2003). Training improves muscle oxidative capacity and oxygenation recovery kinetics in patients with chronic obstructive pulmonary disease. *Eur J Appl Physiol.* 88: 580-587.
- Richardson, R. S., J. Sheldon, D. C. Poole, S. R. Hopkins, A. L. Ries and P. D. Wagner (1999). Evidence of skeletal muscle metabolic reserve during whole body exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 159(3): 881-5.
- Sabapathy, S., D. A. Schneider, G. Comadira, I. Johnston and N. R. Morris (2004). Oxygen uptake kinetics during severe exercise: a comparison between young and older men. *Respir Physiol Neurobiol.* 139: 203-213.

- Sala, E., J. Roca, R. M. Marrades, J. Alonso, J. M. Gonzalez-De-Suso, A. Moreno, J. A. Barbera, J. Nadal, L. de-Jover, R. Rodriguez-Roisin and P. D. Wagner (1999). Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 159(6): 1726-34.
- Saltin, B., B. Essén and P. K. Pederson (1976). Intermittent exercise: its physiology and some practical applications. In *Medicine and Sport*. E. Jokl (Ed.). Basel, Karger: 23-51.
- Schneider, D. A., S. E. Phillips and S. Stoffolano (1993). The simplified V-slope method of detecting the gas exchange threshold. *Med Sci Sports Exerc.* 25: 1180-1184.
- Singh, S. (1992). The use of field walking tests for assessment of functional capacity in patients with chronic airways obstruction. *Physiotherapy.* 78: 102-104.
- Smodlaka, V. N. and D. R. Adamovich (1974). Reconditioning of emphysema patients. *NY State J Med.* 74: 951-955.
- Stark-Leyva, K. N., K. C. Beck and B. D. Johnson (2004). Influence of expiratory loading and hyperinflation on cardiac output during exercise. *J Appl Physiol.* 96: 1920-1927.
- Troosters, T., R. Casaburi, R. Gosselink and D. Decramer (2005). Pulmonary rehabilitation in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 172: 19-38.
- Vogiatzis, I., S. Nanas and C. Roussos (2002). Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J.* 20: 12-19.

- Vogiatzis, I., G. Terzis, S. Nanas, G. Stratakos, D. C. M. Simoes, O. Georgiadou, S. Zakynthinos and C. Roussos (2005). Skeletal muscle adaptations to interval training in patients with advanced COPD. *Chest*. 128: 3838-3845.
- Wallis, T. W., J. L. Robotham, R. Compean and M. K. Kindred (1983). Mechanical heart-lung interaction with positive end-expiratory pressure. *J Appl Physiol*. 54: 1039-1047.
- Wasserman, K., J. E. Hansen, D. Y. Sue, R. Casaburi and B. J. Whipp (1999). *Principles of exercise testing and interpretation*. Baltimore: Lippincott, Williams & Wilkins.
- Wasserman, K., B. J. Whipp, S. N. Koyl and W. L. Beaver (1973). Anaerobic threshold and respiratory gas exchange during exercise. *J Appl Physiol*. 35: 236-243.
- Wijkstra, P. J., R. Van Altena, J. Kraan, V. Otten, D. S. Postma and G. H. Koeter (1994). Quality of life in patients with chronic obstructive pulmonary disease improves after rehabilitation at home. *Eur Respir J*. 7: 269-273.

ABBREVIATED TERMS

A	Amplitude of the oxygen uptake response (subscripts B, P and S refer to baseline (resting), and the primary and slow components, respectively)
ANOVA	Analysis of variance
CE	Continuous exercise
CO ₂	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
DH	Dynamic hyperinflation

DL _{CO}	Lung diffusion capacity for carbon monoxide
ECG	Electrocardiograph
FEV ₁	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GET	Gas exchange threshold
GOLD	Global Initiative for Chronic Obstructive Lung Disease
G	Gain, indicating the oxygen cost per minute per unit increment in power output (subscript TOT refers to the overall or total response)
HRQoL	Health-related quality of life
IC	Inspiratory capacity
IE	Intermittent exercise
LVAS	Word-labeled visual analogue scale
MCID	Minimal clinically important difference
O ₂	Oxygen
RER	Respiratory exchange ratio
r	Coefficient of correlation
R ²	Coefficient of determination
SEE	Standard error of the estimate
SEM	Standard error of the mean
SGRQ	St. George's Hospital Respiratory Questionnaire
t	Time
TD	Time delay (subscripts P and S refer to the primary and slow components, respectively)

t_{dis}	The value from the t -distribution (two-tailed) for a given degrees of freedom value
\dot{V}_{CO_2}	Carbon dioxide output
\dot{V}_{E}	Expired ventilation
\dot{V}_{O_2}	Oxygen uptake
W_{peak}	Peak power output
6MWD	6-min walk distance
6MWT	6-min walk test
95% CI	95% confidence interval
Δ	Delta; change
τ	Tau or time constant; time taken to reach 63% of the final amplitude in an exponential function (subscripts P and S refer to the primary and slow components, respectively)

[Blank Page]

**C
H
A
P
T
E
R
4**

Study 3

Lower Limb Vasodilatory Capacity in Patients with Moderate Chronic Obstructive Pulmonary Disease

CONTENTS

Introduction
111

Methods
113

Results
120

Discussion
125

References
131

**Abbreviated
Terms**
136

[Blank Page]

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major and increasing cause of disability in our aging population. Progressive damage to lung tissue is associated with increased shortness of breath on exertion leading to a “vicious cycle” of inactivity and worsening shortness of breath. While impaired lung mechanics is clearly the primary cause of disability in COPD patients, symptoms of leg fatigue are just as likely as breathlessness to cause these individuals to stop exercising (Killian et al., 1992). Exercise intolerance has been associated with changes in the peripheral muscle of patients with COPD. Prolonged physical inactivity and pathological dysfunction in the skeletal muscle of COPD patients are thought to decrease muscle mass and capillary density, alter muscle fibre-type distribution, lower the activity of oxidative enzymes, and increase glycolytic enzyme activity (see Casaburi et al., 1999, for a review). Although these morphological and biochemical changes contribute to exercise intolerance in patients with COPD, several studies indicate that muscle metabolism (and oxygen, O₂, utilisation) per se may not be the primary factor limiting exercise capacity (Richardson et al., 1999; Maltais et al., 2001). Therefore, it is also possible that exercise capacity in COPD patients is limited by factors mediating muscle blood flow and O₂ delivery to the active muscle.

The impact of COPD on blood flow and O₂ delivery to the exercising muscle is not well understood. While there is some evidence to suggest that leg blood flow may not be limited at rest and during submaximal exercise in COPD patients (Maltais et al., 1998), Simon et al. (2001) have reported a plateau in lower limb blood flow during incremental exercise in some individuals with severe COPD. The inability to increase leg blood flow and O₂ delivery in line with a rising metabolic rate may contribute to muscle fatigue and adversely affect exercise tolerance. One factor that could limit limb blood flow during exercise is a loss of

vasodilatory capacity (as measured by peak blood flow or conductance following reactive hyperaemia). Casiglia et al. (1998) reported that peak hyperaemic calf blood flow (CBF) was not significantly different in patients with moderate-to-severe COPD when compared to control subjects. However, peak CBF in this study tended to be twice as high in the COPD patients than in the control subjects. Peak CBF in the control group was, in turn, approximately three times lower than previously published values (Kroese, 1977a). Thus, while COPD patients with even mild-to-moderate levels of disease show a loss of exercise capacity, it is unclear what the impact of COPD (and associated physical inactivity) is on skeletal muscle vasodilatory capacity.

In healthy older individuals, maximal or peak CBF and peak conductance are significantly correlated with peak \dot{V}_{O_2} peak, leading some researchers to suggest that the ability to regulate blood flow may be a limiting factor to exercise capacity in these individuals (Snell et al., 1987; Martin et al., 1991). Vasodilatory capacity has also been shown to increase with endurance training in young and older individuals (Martin et al., 1990; Martin et al., 1991). These studies demonstrate that an increase in physical activity could improve limb vasodilatory capacity. Based on the evidence presented, it may be that a reduction in \dot{V}_{O_2} peak, secondary to a decline in physical activity, is accompanied by a loss in the maximal ability of the peripheral vasculature to increase muscle blood flow in patients with COPD.

To date, no study has examined the relationship between exercise capacity and lower limb CBF and conductance in patients with moderate COPD. The aim of this study was to compare exercise capacity and peak CBF responses in patients with moderate COPD. It was hypothesised that patients with moderate COPD

would have a lower \dot{V}_{O_2} peak, peak CBF and peak calf conductance when compared to age-matched healthy subjects.

METHODS

Subjects and experimental design

Eighteen male subjects aged between 60 and 80 yr volunteered to participate in this study: 9 individuals with moderate COPD and 9 healthy age-matched control subjects (control group). Inclusion criteria for the COPD patients were 1) moderate expiratory flow limitation as evidenced by a forced expiratory volume in 1 s (FEV₁) between 80% and 30% of predicted values (Pauwels et al., 2001), 2) shortness of breath on exertion, and 3) no documented history of substantial co-morbidity. Diagnosis of COPD was based on a medical history questionnaire and pulmonary function test results. The control subjects were healthy non-smokers with no current or past history of cardiopulmonary disorders. Subjects were excluded from the study if they were taking vasoactive medications that may have impacted blood flow.

All testing was performed in the Physiology of Exercise Research Laboratory, Gold Coast campus, Griffith University, Australia. Subjects visited the laboratory on three separate occasions. During the first visit, subjects underwent preliminary health screening and were familiarised with the methods to be used in the study. On the second visit, an incremental exercise test was performed on a cycle ergometer. The third and final visit involved the measurement of CBF, calf volume and percentage body fat. The study was approved by the Griffith University Human Research Ethics Committee and all subjects provided written informed consent prior to their participation.

Experimental procedures

Pulmonary function assessment and anthropometry

Pulmonary function was measured and assessed using standard techniques (American Thoracic Society, 1994). Forced vital capacity (FVC), FEV₁, residual volume (RV), and diffusion capacity for carbon monoxide (DL_{CO}) were measured using a Collins GS Modular Pulmonary Function Testing system (Braintree, MA, USA). Maximal voluntary ventilation (MVV) was estimated as FEV₁ × 35 (Mohan-Kumar and Gimenez, 1984). Disease severity was classified in accordance with The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (Pauwels et al., 2001).

To estimate percentage body fat, skinfold thickness was measured using a Harpenden skinfold calliper (Baty International, West Sussex, UK) at four sites on the upper body: biceps, triceps, subscapular and suprailiac (Durnin and Wormsley, 1969). An estimate of leg adiposity was obtained by measuring skinfold thickness of the anterior thigh and medial calf of the right leg (i.e., the leg in which blood flow and calf volume were determined). Calf volume was estimated using a geometric disc-model method previously described by Kaulesar Sukul et al. (1993). Briefly, calf circumference was measured with a non-elastic measuring tape, at 3 cm intervals (i.e. discs of height h) along the length of the calf. Calf volume (V) was calculated using the following formula:

$$V = \sum_{i=1}^n \frac{C_i^2}{4\pi} h = \sum_{i=1}^n \pi r_i^2 h = \sum_{i=1}^n \pi r_i^2 \quad \text{Equation 4.1}$$

where C_i is the circumference of the disc at interval i with a radius r_i .

Incremental exercise test

The incremental exercise test used to measure \dot{V}_{O_2} peak was performed on a Lode cycle ergometer (Excalibur Sport, Groningen, Netherlands). Subjects commenced unloaded cycling for 3 min and then the power output was increased by $8 \text{ W}\cdot\text{min}^{-1}$ for the COPD group and by $15 \text{ W}\cdot\text{min}^{-1}$ for the healthy control group. Subjects were encouraged to maintain a pedal cadence of $60\text{-}70 \text{ rev}\cdot\text{min}^{-1}$ until volitional termination of the test.

Throughout the incremental cycling test, O_2 uptake (\dot{V}_{O_2}) and expired ventilation (\dot{V}_E) were measured breath-by-breath and averaged over 30-s intervals using a metabolic measuring system (MedGraphics CPX/D, St. Paul, MN, USA). A 12-lead electrocardiograph was used to monitor cardiac rhythm and to determine heart rate. Peak exercise values for incremental cycling were calculated as the average of the two highest consecutive 30-s values obtained prior to termination of exercise. A medical practitioner supervised each incremental exercise test.

Calf blood flow and conductance

Calf blood flow was measured using venous occlusion plethysmography (Whitney, 1953). All blood flow tests were conducted at the same time in the morning in a quiet room with a constant ambient temperature between 23° and 24° C . Subjects fasted for 3 h before the test and did not consume any caffeine or alcohol during the morning of the test. Additionally, all subjects refrained from strenuous exercise for 24 h prior to the test.

Prior to the blood flow measurements, the subject was instructed to lie supine on a bed for 30 min. The right leg was elevated to the level of the heart by supporting the lower part of the leg (18 cm above and parallel to the bed) using a

foam block under the knee and a strap supporting the foot. A 22 cm contoured thigh cuff was placed around the lower part of the thigh, just above the knee, and connected to a Rapid Cuff Inflator (Hokanson E20, Bellevue, WA, USA). The foot was isolated from the circulation by a 5 cm cuff positioned around the ankle and inflated to 240 mmHg. A mercury-in-rubber strain gauge was placed around the calf at the point of greatest girth. The strain gauge was interfaced to a computer via a Biopac Data Acquisition System (AcqKnowledge software, Biopac Systems Inc., CA, USA). The signal from the strain gauge was sampled at 100 Hz and filtered using a Hanning 3 Hz low-pass filter. Figure 4.1 shows a schematic representation of the experimental set-up used to measure calf blood flow in this study.

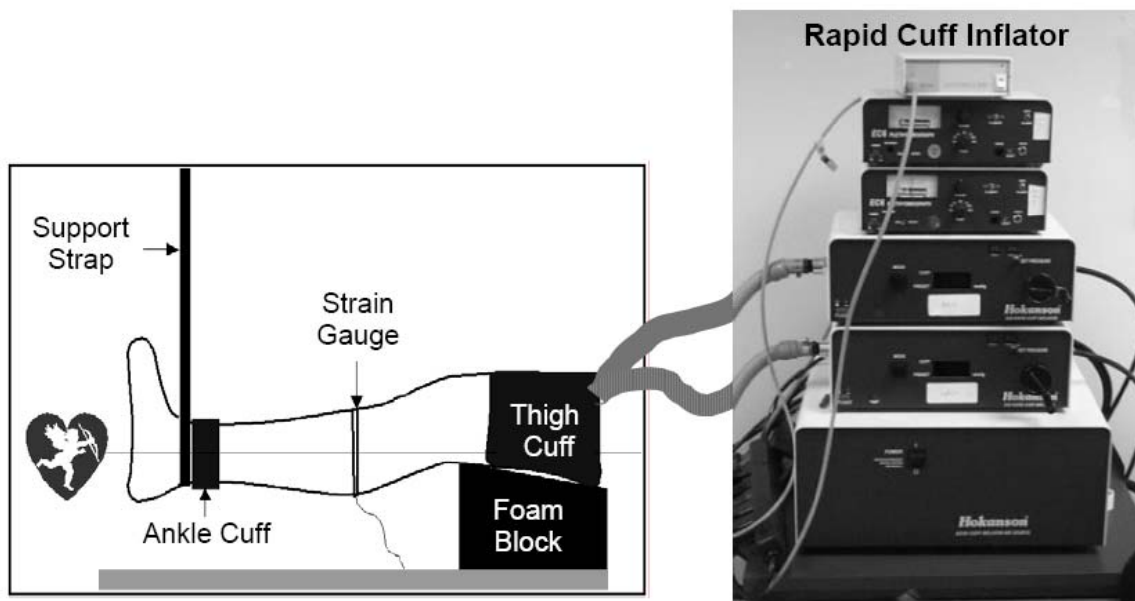


Figure 4.1. Schematic illustration of the experimental set-up used to measure hyperaemic calf blood flow.

Baseline CBF was recorded in two trials of 3 min duration. During each trial, the thigh cuff was intermittently inflated to 60 mmHg (thereby permitting arterial inflow of blood but occluding venous outflow), in a duty cycle of 30 s (15 s on and 15 s off). Calf blood flow was then determined by measuring the increase in calf

circumference (i.e., the initial slope of the signal recorded from the strain gauge) immediately after the cuff was inflated (Siggaard-Anderson, 1970). In order to avoid movement artefact, the first second of the signal immediately after the cuff

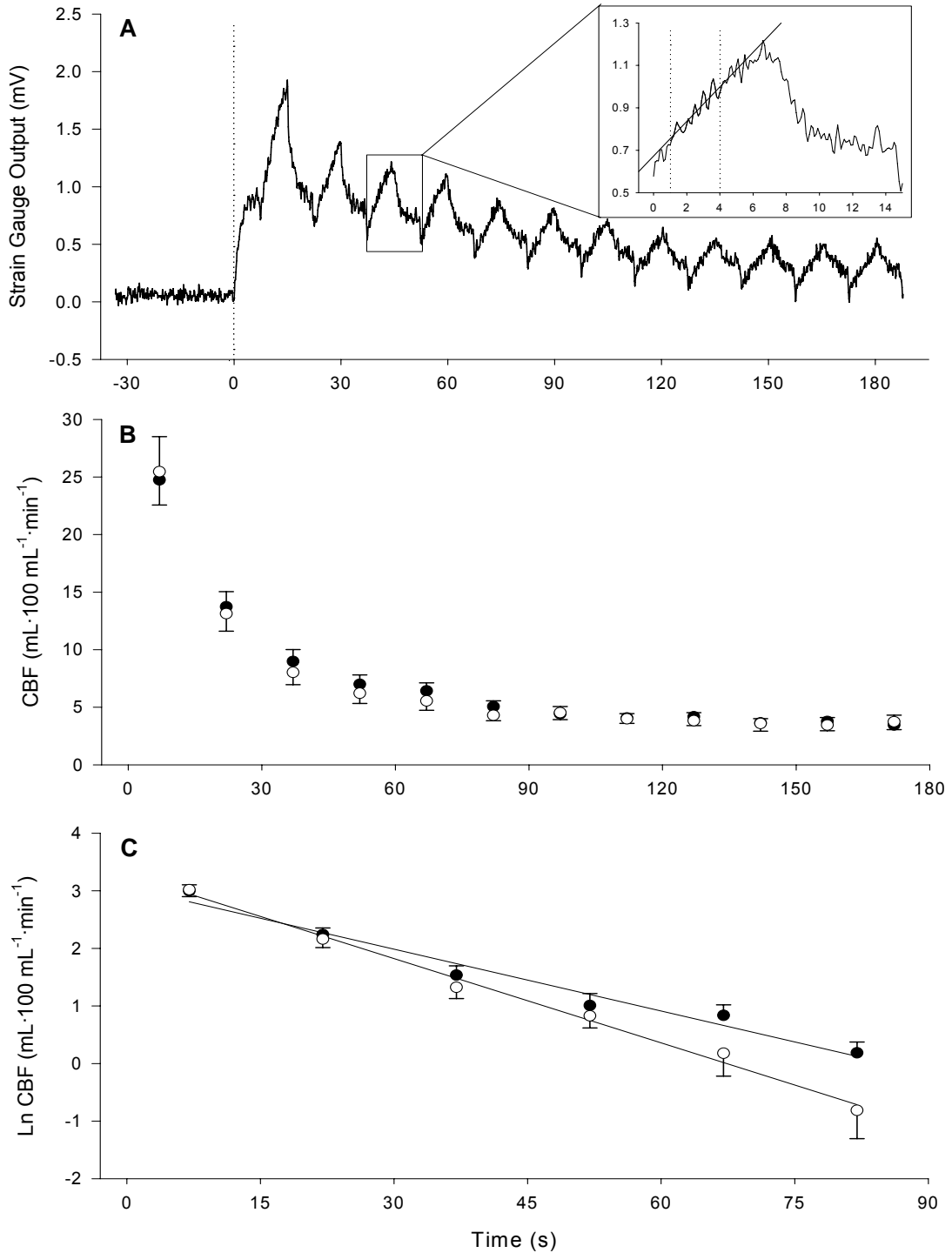


Figure 4.2 (See overleaf for figure legend)

Figure 4.2. Panel A: A plethysmograph tracing in a representative subject illustrating the hyperaemic blood flow response following 5 min of arterial occlusion. The vertical dotted line (time = 0 s) indicates the point when the cuff was released after 5 min of ischaemia, with the first blood flow measurement performed 7 s after cuff release. The figure inset shows the slope of the initial increase in calf volume during a single venous occlusion cycle, from which calf blood flow is calculated. Panel B: The time course change in calf blood flow (CBF) immediately after arterial occlusion in healthy control subjects (○) and patients with chronic obstructive pulmonary disease (●). Panel C: The log-transformation of the blood flow versus time values presented in Panel B. The slopes of the lines-of-best fit represent the rates of decay in CBF. Only the first 90 s of data (i.e. the period when CBF was decreasing in both groups) was included in this analysis. The data in Panels B and C represent mean values \pm SEM.

was inflated was excluded from the analysis. The initial slope was then determined from the following 3 s of data (see Figure 4.2, Panel A). The mean value of at least six serial blood flow measurements was determined as baseline CBF per trial in millilitres per 100 millilitres calf volume per minute ($\text{mL}\cdot 100 \text{ mL}^{-1}\cdot \text{min}^{-1}$).

Peak CBF was determined following two successive 5-min periods of arterial occlusion, which were induced by inflating the thigh cuff to a pressure of 220 mmHg (Chiba et al., 1997). A resting period of 15 minutes was permitted between the two successive ischaemic periods to ensure blood flow had returned to baseline (Siggaard-Anderson, 1970; Proctor et al., 2005). Immediately after the 5-min period of arterial occlusion, twelve serial blood flow measurements were recorded over a period of 3 min by intermittently inflating the thigh cuff to a pressure of 80 mmHg (Marchiori et al., 1994). To monitor reactive hyperaemic blood flow over time, a duty cycle of 15 s was used (8 s on, 7 s off), as previously

described (Chiba et al., 1997). The first blood flow measurement commenced 7 s after the end of the arterial occlusion period, and peak CBF was accepted as the highest flow obtained during the successive measurements. All peak CBF measurements are also presented as a multiple of baseline CBF. The day-to-day test-retest reliability (intra-class correlation coefficient) for measuring resting and peak CBF was 0.95 and 0.96, respectively (n=10 subjects). From each subject's blood flow versus time curve (Figure 4.2, Panel B), the rate of decay in CBF (the slopes of the logarithmic function of blood flow versus time, illustrated in Figure 4.2, Panel C) was determined (Fry, 1993). Excess blood flow was determined by calculating the area under the blood flow versus time curve minus baseline CBF for the duration of the 3-min post-ischaemic measurement period.

During the measurement of baseline and post-ischaemic CBF, heart rate, and systolic and diastolic blood pressure were recorded using a Finapres (Ohmeda 2300 Finapres, Engelwood, CO, USA). The calculated mean arterial pressure (MAP) signal from the Finapres was recorded simultaneously with the strain gauge signal from the plethysmograph using the data acquisition software. Baseline and peak calf conductance were calculated from CBF and MAP:

$$\text{Calf conductance} = \frac{\text{CBF (mL} \cdot 100 \text{ mL}^{-1} \cdot \text{min}^{-1})}{\text{MAP (mmHg)}} \text{ mL} \cdot 100 \text{ mL}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$$

Equation 4.2

Statistical analysis

All results are presented as group means \pm standard error of the mean (SEM). Differences between groups in the dependent variables were determined using independent-sample t-tests. The time-course change in hyperaemic CBF was assessed using a two-way repeated measures analysis of variance with Bonferroni *post-hoc* adjustments. Pearson's product-moment correlation

coefficients were calculated to assess the relationships between blood flow measurements and \dot{V}_{O_2} peak. Statistical significance was accepted at $P < 0.05$.

Data were analysed using SPSS v10.0 (Statistical Packages for the Social Sciences Inc., Chicago, IL, USA).

RESULTS

The physical characteristics of the subjects are presented in Table 4.1. The groups were well matched with respect to their physical characteristics. There were no significant differences between the groups in age, height, weight, blood pressure, calf volume, percentage body fat or sum of the leg skinfolds.

Table 4.1. Physical characteristics of the subjects.

	Control Group	COPD Group
Age (yr)	71.7 ± 1.0	70.1 ± 2.0
Height (cm)	172.7 ± 1.5	170.4 ± 1.7
Body mass (kg)	80.9 ± 2.9	77.8 ± 2.8
Resting SBP (mmHg)	127.8 ± 4.6	128.0 ± 3.2
Resting DBP (mmHg)	75.6 ± 1.9	77.4 ± 2.1
Body fat (%)	21.4 ± 0.9	22.5 ± 1.4
Sum of leg skinfolds (mm)	22.4 ± 2.7	24.4 ± 2.9
Calf volume (L)	2.25 ± 0.11	2.18 ± 0.09

Values presented are group means ± SEM. COPD: chronic obstructive pulmonary disease; SBP: systolic blood pressure (supine), DBP: diastolic blood pressure (supine).

Pulmonary function test results for the two groups are presented in Table 4.2. The patients with COPD had significantly lower FVC, FEV₁, FEV₁/FVC, MVV, and DL_{CO} values when compared to the control group. Residual volume was significantly greater in the COPD group. All lung function values for the control

subjects were within the range of predicted values for healthy individuals of that age group (Knudson et al., 1983).

Table 4.2. Pulmonary function test results.

	Control Group	COPD Group
FEV ₁ (L)	3.05 ± 0.18	1.48 ± 0.10*
FEV ₁ (% predicted)	106 ± 6	52 ± 3*
FVC (L)	4.08 ± 0.21	3.45 ± 0.20 [†]
FVC (% predicted)	111 ± 4	96 ± 4 [†]
FEV ₁ / FVC (%)	75 ± 2	43 ± 2*
MVV (L·min ⁻¹)	106.7 ± 6.4	52.0 ± 3.3*
RV (L)	3.33 ± 0.17	4.06 ± 0.23 [†]
RV (% predicted)	135 ± 7	172 ± 9 [†]
DL _{CO} (mL·min ⁻¹ ·mmHg ⁻¹)	21.0 ± 1.1	12.4 ± 1.9*
DL _{CO} (% predicted)	87 ± 5	51 ± 8*

Values presented are group means ± SEM. COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in 1 sec; FVC: forced vital capacity; MVV: maximal voluntary ventilation; RV: residual volume; DL_{CO}: diffusion capacity for carbon monoxide. * P<0.001, [†] P<0.05: COPD group significantly different from Control group.

The results of the incremental exercise test are provided in Table 4.3. Peak O₂ uptake was significantly lower in the COPD group. The average peak power output (W_{peak}) achieved in the COPD group was only 42.8% of W_{peak} attained by the control group. Peak exercise heart rate was also significantly lower in the COPD group. The control subjects reached 101% of their age-predicted maximum heart rate, whereas the patients with COPD only reached 80% of their predicted maximum. Peak exercise ventilation (\dot{V}_E peak), RER and power output values were all significantly lower in the COPD group. However, when \dot{V}_E peak

was expressed as a percentage of MVV, no significant difference was found between the two groups. The COPD group reached 84% of their estimated MVV, while the control group reached 86%. During the incremental cycling test, all subjects in the control group stopped exercise because of leg fatigue. In the COPD group, four subjects stopped exercise due to leg fatigue, two because of shortness of breath, and three from a combination of leg fatigue and breathlessness.

Table 4.3. Peak exercise values obtained during incremental cycling.

	Control Group	COPD Group
\dot{V}_{O_2} peak (L·min ⁻¹)	2.04 ± 0.12	1.19 ± 0.08*
\dot{V}_{O_2} peak (mL·kg ⁻¹ ·min ⁻¹)	25.2 ± 0.86	15.8 ± 1.2*
Peak heart rate (beats·min ⁻¹)	147 ± 5	118 ± 7 [†]
Peak heart rate (% age predicted)	101 ± 3	80 ± 4 [†]
\dot{V}_E peak (L·min ⁻¹)	90.7 ± 6.2	42.8 ± 3.7*
Peak RER value	1.28 ± 0.02	1.06 ± 0.04*
W _{peak} (W)	166 ± 9	71 ± 7*

Values presented are group means ± SEM. COPD: chronic obstructive pulmonary disease; \dot{V}_{O_2} peak: peak oxygen uptake; \dot{V}_E peak: peak exercise ventilation; RER: respiratory exchange ratio; W_{peak}: peak power output. [†] P<0.0001, * P<0.01: COPD group significantly different from Control group.

There were no significant differences between the two groups in resting or peak CBF (Figure 4.3, Panel A). The resting (COPD: 3.8 ± 0.3 mL·100 mL⁻¹·min⁻¹; Control: 3.7 ± 0.5 mL·100 mL⁻¹·min⁻¹) and peak (COPD: 24.7 ± 2.2 mL·100 mL⁻¹·min⁻¹; Control: 25.5 ± 3.0 mL·100 mL⁻¹·min⁻¹) CBF results in the present study were comparable to those reported in other studies that used similar methods of determining CBF in older individuals (Kroese, 1977a, 1977b). Baseline and peak

calf conductance were also not significantly different between the COPD patients and healthy control subjects (Figure 4.3, Panel B). There were no significant differences between the groups in peak CBF expressed as a function of resting CBF (peak CBF/baseline CBF) (COPD: 6.8 ± 0.6 , Control: 7.3 ± 0.8). Similarly, the comparison of peak conductance as a function of resting conductance (peak conductance/baseline conductance) was not significantly different between the groups (COPD: 6.8 ± 0.6 , Control: 7.6 ± 0.8).

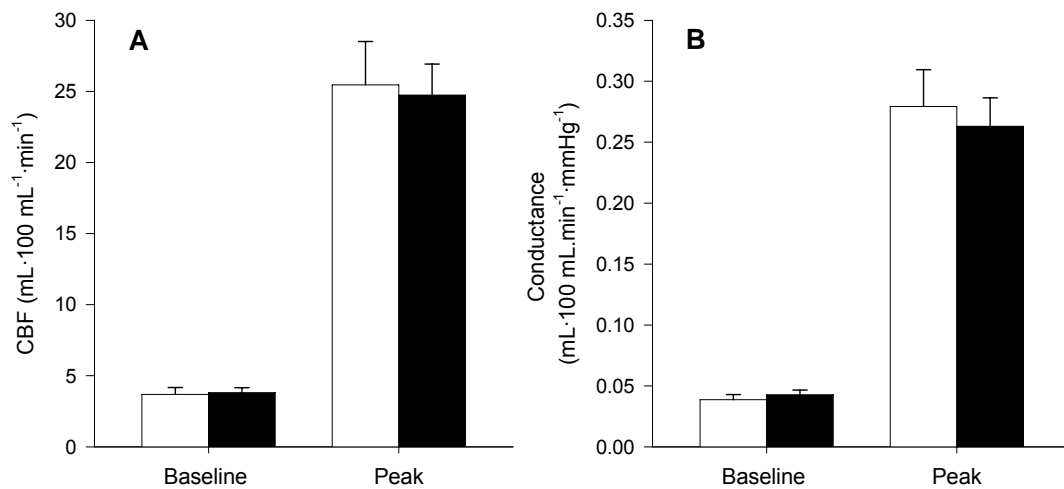


Figure 4.3. Baseline and peak calf blood flow (CBF) (Panel A) and conductance (Panel B) responses in healthy control subjects (open bars) and patients with chronic obstructive pulmonary disease (filled bars). The data represent mean values \pm SEM.

Figure 4.2 (Panel B) illustrates the time-course changes in CBF in both groups. CBF attained its peak value at the first measurement point, 7 s after cuff release, and then decreased significantly in both groups during the first 90 s of the 3-min measurement period. Thereafter, CBF returned to baseline values, with no further decrease observed in either group. Although there were no significant differences in CBF between the groups at any measurement period, the rate of decay in CBF was significantly slower in the COPD group (-0.036 ± 0.002 mL·100 mL⁻¹·min⁻¹·s⁻¹) than in the control group (-0.048 ± 0.005 mL·100 mL⁻¹·min⁻¹·s⁻¹) (Figure 4.2,

Panel C). However, excess flow above baseline measured during the hyperaemic period was not significantly different between the groups (COPD: 8.3 ± 0.7 mL·100 mL⁻¹, Control: 7.5 ± 1.0 mL·100 mL⁻¹).

In the control group, \dot{V}_{O_2} peak (L·min⁻¹) was significantly correlated with both peak CBF (Figure 4.4, Panel C) and peak conductance (Figure 4.4, Panel D),

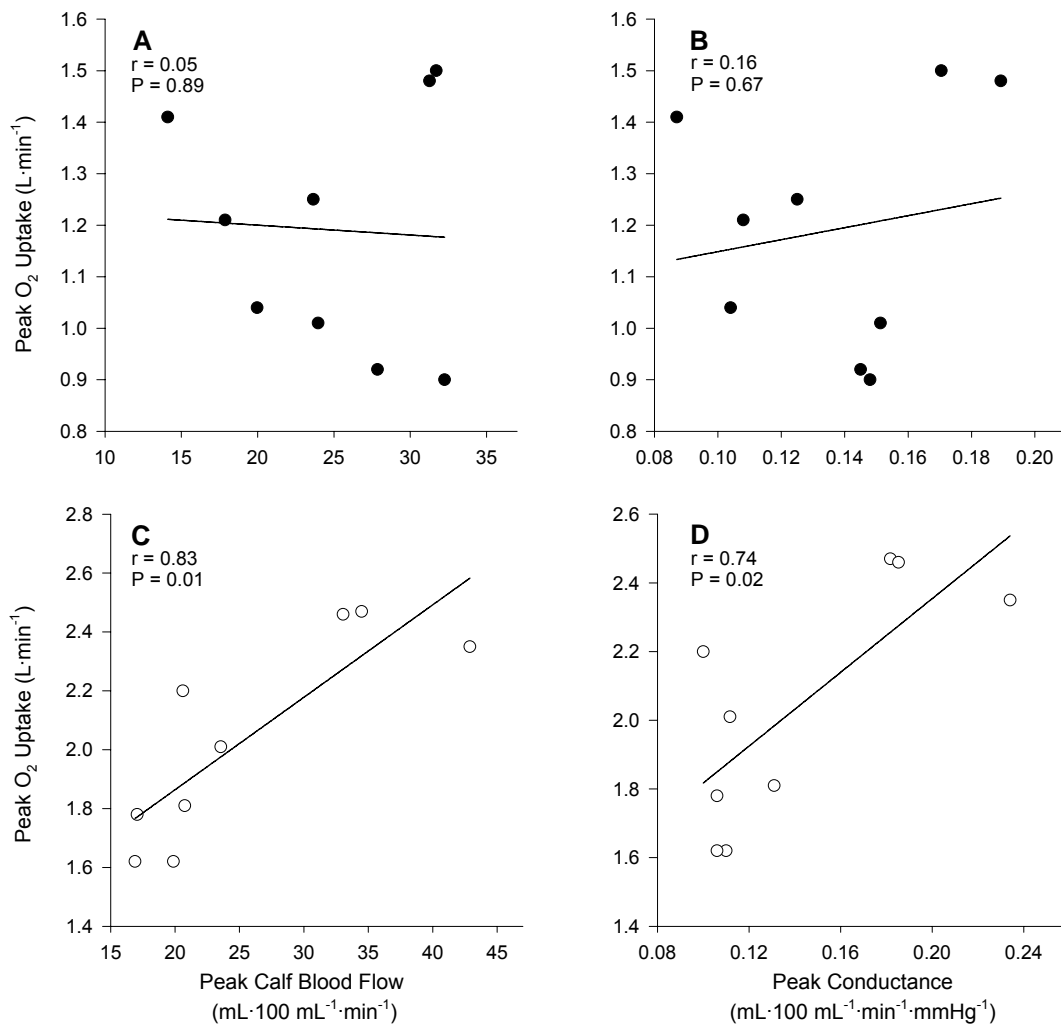


Figure 4.4. The relationship between peak oxygen (O₂) uptake and peak calf blood flow, and peak O₂ uptake and peak conductance in patients with chronic obstructive pulmonary disease (Panels A and B) and in healthy control subjects (Panels C and D).

whereas there was no significant relationship between \dot{V}_{O_2} peak and peak CBF or peak conductance observed in the COPD group (Figure 4.4, Panels A and B, respectively). Peak CBF was not significantly correlated with \dot{V}_E peak or peak heart rate in either group.

DISCUSSION

This is the first study to examine the relationship between peak CBF responses and \dot{V}_{O_2} peak in patients with moderate COPD. Although COPD patients had a much lower \dot{V}_{O_2} peak than age-matched healthy controls, there was no difference between the groups in resting or peak CBF and conductance. Moreover, the significant positive correlation between either peak CBF or peak conductance and \dot{V}_{O_2} peak observed in the healthy older subjects was not seen in the COPD group.

Peak O_2 uptake and W_{peak} during incremental cycling were markedly lower in the COPD group compared to healthy controls. Seven of the subjects in the COPD group stopped exercise because of leg fatigue or a combination of leg fatigue and breathlessness, whereas only two subjects stopped because of shortness of breath alone. Moreover, both groups reached a similar \dot{V}_E peak as a percentage of MVV (84% for the COPD group versus 86% for the control group) during incremental cycling. Since peak exercise heart rate was significantly lower in COPD patients (80% of age-predicted maximum) than in healthy control subjects (101% of age-predicted maximum), it is concluded that the patients in the present study did not experience a central cardiovascular limitation to exercise. Rather, lower limb muscle fatigue and dyspnoea were the primary reasons for stopping exercise.

The only other study to examine CBF responses in COPD patients with strain-gauge plethysmography reported that subjects with mild-to-severe COPD had significantly greater resting CBF, but similar peak CBF when compared to control subjects (Casiglia et al., 1998). When the COPD group was further differentiated into those with mild obstruction ($FEV_1 = 79 \pm 6$ % predicted) and those with more severe obstruction ($FEV_1 = 49 \pm 18$ % predicted), it was revealed that only those with severe disease had significantly higher resting CBF when compared to healthy control subjects. While the authors concluded that patients with COPD tended to be chronically vasodilated when compared to healthy controls, their results suggest that this statement applies only to those subjects with more severe obstruction. The resting CBF results of the present study disagree with those of Casiglia et al. (1998) – in a group of COPD patients with a comparable degree of expiratory flow limitation ($FEV_1 = 52 \pm 8$ % predicted) as the subjects examined in their study, resting CBF was not significantly different to healthy control subjects.

In the present study, it was hypothesised that peak CBF would be lower in the COPD group than in the control group. However, the results suggest that the ability to maximally vasodilate the calf muscle vasculature was not mitigated in individuals with moderate COPD. The hyperaemia that follows ischaemia (induced by arterial occlusion) is thought to arise from a combination of myogenic relaxation of blood vessels, and the accumulation of locally-released vasoactive metabolites (e.g., prostaglandins, nitric oxide, K^+ and H^+) during the ischaemic period (Shepherd, 1983). Evidence suggests that a reduction of myogenic tone and hypoxia induced vasodilator-prostaglandin synthesis contribute primarily to the peak flow response (Carlsson et al., 1987; Engelke et al., 1996; Win and Marshall, 2005). Additionally, prostaglandins, nitric oxide, and possibly other

vasoactive metabolites such as adenosine mediate the remainder of the hyperaemia response (Carlsson et al., 1987; Tagawa et al., 1994), as blood flow progressively returns to baseline. Since resting and peak CBF were not different between COPD patients and healthy control subjects, our results suggest that the factors mediating the hyperaemic response observed in the present study are not affected by moderate lung disease.

Another factor that has been shown to impact upon the reactive hyperaemic response is muscle mass. Wascher et al. (1998) demonstrated that gender differences in forearm peak reactive hyperaemic flow and excess flow could be accounted for primarily by differences in lean muscle mass between male and female subjects. Therefore, changes in vasodilatory capacity may only occur in more severe COPD, when cachexia is evident. In the present study, percent body fat, calf volume, and skinfold thickness of the calf muscle were not significantly different between COPD and healthy control groups. This suggests that lean muscle mass of the calf was not different between the two groups and could, in part, explain the similar blood flow results obtained in the present study.

The observation that peak CBF and conductance were significantly correlated with \dot{V}_{O_2} peak in healthy control subjects, but not COPD patients, suggests that factors other than vasodilatory capacity limit exercise capacity in patients with COPD. However, this finding does not negate the possibility that impaired blood flow or O_2 delivery contribute to skeletal muscle fatigue and exercise cessation in COPD patients. Abnormal ventilatory mechanics and dynamic lung hyperinflation in COPD patients could increase the O_2 cost of breathing during exercise, resulting in the redirection of blood flow from the active limb muscles to the respiratory muscles. The O_2 cost of breathing is known to be greater for a given

ventilatory demand in COPD patients compared to healthy controls (Evison and Cherniack, 1968). Moreover, a plateau in lower limb blood flow has been reported in some patients with severe COPD during incremental exercise (Simon et al., 2001). This finding suggests a respiratory “steal” of blood that may otherwise have been directed to the exercising muscles, and has also been observed in healthy athletes during intense exercise (Harms et al., 1997). A reduction in muscle perfusion relative to metabolic demand may also occur due to a blunted cardiac output response to exercise, which has been reported in some COPD patients during incremental cycling (Bogaard et al., 1998). Finally, a reduced arterial O₂ content (hypoxemia) as a result of diffusion impairment or ventilation to perfusion inequalities in patients with COPD may adversely affect O₂ diffusion across the capillary-muscle interface during periods of high metabolic demand. Studies have shown that O₂ supplementation in COPD patients with varying degrees of hypoxemia enhances O₂ delivery and muscle blood flow, and increases \dot{V}_{O_2} and W_{peak} (Richardson et al., 1999; Maltais et al., 2001).

While we found no difference between the groups in peak CBF, the rate of decline in CBF (i.e., duration of hyperaemic flow) following ischaemia was significantly slower in COPD patients than in control subjects (Figure 4.1, Panel C). The magnitude of the hyperaemic response (total excess flow) is dependent upon peak flow when the period of ischaemia is 5 min or less; when ischaemia is imposed for longer periods, total excess flow is primarily affected by a longer duration of hyperaemia, or a slower rate of decay in blood flow is observed (Patterson and Whelan, 1955; Carlsson et al., 1987; Wascher et al., 1998). Thus, it is not clear what the slower rate of decay in peak CBF in COPD patients reflects, considering that the duration of ischaemia in the present study was 5 min and excess flow values were similar for both groups.

One could hypothesise that the slower fall in CBF (and calf conductance) reflects a slower 'wash out' of metabolites following the period of ischaemia or a greater accumulation of vasoactive metabolites during the ischaemic period. Engelke et al. (Engelke et al., 1996) hypothesised that the decay in blood flow following ischaemia could be determined by the interaction between vasodilating and vasoconstricting prostaglandins. In COPD patients, urinary levels of prostaglandin-like compounds such as isoprostane F_{2α}-III, a marker of oxidative stress, are greater than in healthy control subjects (Pratico et al., 1998). These compounds could interact with locally-produced prostaglandins during as well as post-ischaemia to affect the rate of blood flow decay. The selective loss of slow-twitch oxidative fibres (Whittom et al., 1998) and decreased activity of oxidative enzymes (Maltais et al., 1996) in the skeletal muscles of COPD patients could also result in a greater and/or more prolonged efflux of vasoactive metabolites (K⁺ and H⁺) into the circulation during the ischaemic period. Alternatively, the difference in the rate of decay between the two groups may not be physiologically important despite attaining statistical significance since similar excess flow values were obtained for both groups.

In summary, it was hypothesised that a reduced vasodilatory capacity would contribute to the diminished exercise capacity observed in COPD patients. Contrary to this hypothesis, the present study demonstrated that there were no differences in either baseline or peak CBF between patients with COPD and a group of age-matched, healthy controls. Moreover, peak CBF and conductance were significantly correlated with \dot{V}_{O_2} peak in the control subjects but not in the COPD patients. The results of the present study show that vasodilatory capacity is not related to a loss of exercise capacity in patients with moderate COPD. Future studies should examine the effect of manipulating the duration of

ischaemia on total excess flow and the rate of blood flow decay, as well as the impact of disease severity and exercise training on reactive and functional hyperaemia in COPD patients.

REFERENCES

- American Thoracic Society. (1994). Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med.* 152: 1107-1136.
- Bogaard, H.J., Dekker, B.M., Arntzen, B.W.G.J., Woltjer, H.H., van Keimpema, A.R.J., Postmus, P.E., de Vries, P.M.J.M. (1998). The haemodynamic response to exercise in chronic obstructive pulmonary disease: assessment by impedance cardiography. *Eur Respir J.* 12: 374-379.
- Carlsson, I., Sollevi, A., Wennmalm, A. (1987). The role of myogenic relaxation, adenosine and prostaglandins in human forearm reactive hyperaemia. *J Physiol (Lond).* 389: 147-161.
- Casaburi, R., Gosselink, R., Decramer, D., Dekhuijzen, R. (1999). Skeletal muscle dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 159: S1 - S40.
- Casiglia, E., Pavan, L., Marcato, L., Leopardi, M., Pizziol, A., Salvador, P., Zuin, R., Pessina, A.C. (1998). Subjects with obstructive pulmonary disease tend to be chronically vasodilated. *Clin Sci (Lond).* 95: 287-294.
- Chiba, M., Nakamura, M., Kanaya, Y., Kobayashi, N., Ueshima, K., Kawazoe, K., Hiramori, K. (1997). Improvement in lower limb vasodilatory reserve and exercise capacity in patients with chronic heart failure due to valvular heart disease. *Eur Heart J.* 18: 1931-1936.
- Durnin, J.V., Wormsley, J. (1969). The relationship between skinfold thickness and body fat in adults of middle age. *J Physiol (Lond).* 200: 105P - 106P.
- Engelke, K.A., Halliwill, J.R., Proctor, D.N., Dietz, N.M., Joyner, M.J. (1996). Contribution of nitric oxide and prostaglandins to reactive hyperemia in the human forearm. *J Appl Physiol.* 81: 1807-1814.

- Evison, H., Cherniack, R.M. (1968). Ventilatory cost of exercise in chronic obstructive pulmonary disease. *J Appl Physiol.* 25: 21-27.
- Fry, C. (1993). A numerical method for the calculation of the time constant of exponential functions (letter to the editor). *Cardiovasc Res.* 27: 1552-1553.
- Harms, C.A., Babcock, M.A., McClaran, S.R., Pegelow, D.F., Nিকেle, G.A., Nelson, W.B., Dempsey, J.A. (1997). Respiratory muscle work compromises leg blood flow during maximal exercise. *J Appl Physiol.* 82: 1573-1583.
- Kaulesar Sukul, D.M., den Hoed, P.T., Johannes, E.J., van Dolder, R., Benda, E. (1993). Direct and indirect methods for the quantification of leg volume: comparison between water displacement volumetry, the disk model method and the frustum sign model method, using the correlation coefficient and the limits of agreement. *J Biomed Eng.* 15: 477-480.
- Killian, K.J., LeBlanc, P., Martin, D.H., Summers, E., Jones, N.L., Campbell, E.J.M. (1992). Exercise capacity and ventilatory, circulatory and symptom limitation inpatients with chronic airflow limitation. *Am Rev Respir Dis.* 146: 935 - 940.
- Knudson, R., Lebowitz, M., Holberg, C., Burrows, B. (1983). Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis.* 127: 725-734.
- Kroese, A.J. (1977a). The influence of age on reactive hyperaemia in the human calf: a study with strain gauge plethysmography. *Scand J Clin Lab Invest.* 37: 105-109.

- Kroese, A.J. (1977b). Reactive hyperaemia in the calf of trained and untrained subjects: a study with strain gauge plethysmography. *Scand J Clin Lab Invest.* 37: 111-115.
- Maltais, F., Jobin, J., Sullivan, M.J., Bernard, S., Whittom, F., Killian, K.J., Desmeules, M., Belanger, M., LeBlanc, P. (1998). Metabolic and hemodynamic responses of lower limb during exercise in patients with COPD. *J Appl Physiol.* 84: 1573-1580.
- Maltais, F., Simard, A.-A., Simard, C., Jobin, J., Desgagnés, P., LeBlanc, P. (1996). Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med.* 153 : 288-293.
- Maltais, F., Simon, M., Jobin, J., Desmeules, M., Sullivan, M.J., Belanger, M., Leblanc, P. (2001). Effects of oxygen on lower limb blood flow and O₂ uptake during exercise in COPD. *Med Sci Sports Exerc.* 33: 916-922.
- Marchiori, G.E., Briggs, R., Arnold, J.M. (1994). Forearm vascular responsiveness to prolonged venous occlusion in normal subjects. *Clin Invest Med.* 17: 77-87.
- Martin, W.H., Kohrt, W.M., Malley, M.T., Korte, E., Stoltz, S. (1990). Exercise training enhances leg vasodilatory capacity of 65-yr-old men and women. *J Appl Physiol.* 69: 1804-1809.
- Martin, W.H., Ogawa, T., Kohrt, W.M., Malley, M.T., Korte, E., Kieffer, P.S., Schechtman, K.B. (1991). Effects of aging, gender, and physical training on peripheral vascular function. *Circulation.* 84: 654-664.
- Mohan-Kumar, T., Gimenez, M. (1984). Maximal ventilation at rest and exercise in patients with chronic pulmonary disease. *Respiration.* 46: 291-302.

- Patterson, G.C., Whelan, R.F. (1955). Reactive hyperaemia in the human forearm. *Clin Sci (Lond)*. 14: 197-211.
- Pauwels, R.A., Buist, A.S., Calverley, P.M.A., Jenkins, C.R., Hurd, S.S. (2001). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. *Am J Respir Crit Care Med*. 163: 1256-1276.
- Pratico, D., Basili, S., Vieri, M., Cordova, C., Violi, F., Fitzgerald, G.A. (1998). Chronic obstructive pulmonary disease is associated with an increase in urinary levels of isoprostane F_{2α}-III, an index of oxidative stress. *Am J Respir Crit Care Med*. 158: 1709-1714.
- Proctor, D.N., Le, K.E., Ridout, S.J. (2005). Age and regional specificity of peak limb vascular conductance in men. *J Appl Physiol*. 98: 193-202.
- Richardson, R.S., Sheldon, J., Poole, D.C., Hopkins, S.R., Ries, A.L., Wagner, P.D. (1999). Evidence of skeletal muscle metabolic reserve during whole body exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 159: 881-885.
- Shepherd, J.T. (1983). Circulation to skeletal muscle. In: *Handbook of physiology. The cardiovascular system. Peripheral circulation and organ blood flow*. Shepherd, J.T., Abboud, F.M. (Eds.). American Physiological Society, Bethesda, MD, pp. 319-370.
- Siggaard-Anderson, J. (1970). Venous occlusion plethysmography on the calf. Evaluation of diagnosis and results of vascular surgery. *Dan Med Bull*. 17 (Suppl I) : 1-68.

- Simon, M., LeBlanc, P., Jobin, J., Desmeules, M., Sullivan, M.J., Maltais, F. (2001). Limitation of lower limb \dot{V}_{O_2} during cycling exercise in COPD patients. *J Appl Physiol.* 90: 1013-1019.
- Snell, P.G., Martin, W.H., Buckley, J.C., Blomqvist, C.G. (1987). Maximal vascular leg conductance in trained and untrained men. *J Appl Physiol.* 62: 606-610.
- Tagawa, T., Imaizumi, T., Endo, T., Shiramoto, M., Harasawa, Y., Takeshita, A. (1994). Role of nitric oxide in reactive hyperemia in human forearm vessels. *Circulation.* 90: 2285-2290.
- Wascher, T.C., Bammer, R., Stollberger, R., Bahadori, B., Wallner, S., Toplak, H. (1998). Forearm composition contributes to differences in reactive hyperaemia between healthy men and women. *Eur J Clin Invest.* 28: 243-248.
- Whitney, R.J. (1953). The measurement of volume changes in human limbs. *J Appl Physiol.* 121: 1-27.
- Whittom, F., Jobin, J., Simard, P.-M., LeBlanc, P., Simard, C., Bernard, S., Belleau, R., Maltais, F. (1998). Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc.* 30: 1467-1474.
- Win, S., Marshall, J.M. (2005). Contribution of prostaglandins to the dilation that follows isometric forearm contraction in human subjects: effects of aspirin and hyperoxia. *J Appl Physiol.* 99: 45-52.

ABBREVIATED TERMS

CBF	Calf blood flow
COPD	Chronic obstructive pulmonary disease
DBP	Diastolic blood pressure
DL _{CO}	Lung diffusion capacity for carbon monoxide
FEV ₁	Forced expiratory volume in 1 s
FVC	Forced vital capacity
H ⁺	Hydrogen ion
K ⁺	Potassium ion
MAP	Mean arterial pressure
MVV	Maximal voluntary ventilation
O ₂	Oxygen
RV	Residual volume
SBP	Systolic blood pressure
SEM	Standard error of the mean
\dot{V}_E	Expired ventilation
\dot{V}_{O_2}	Oxygen uptake
W _{peak}	Peak power output

**C
H
A
P
T
E
R
5**

Study 4

Oxygen Uptake Kinetics during 'Heavy' Exercise in Chronic Obstructive Pulmonary Disease Patients

CONTENTS

Preface
139

Introduction
140

Methods
142

Results
147

Discussion
153

References
164

**Abbreviated
Terms**
171

[Blank Page]

Preface

This chapter comprises a retrospective comparison of data reported in Chapter 2 and results obtained from a previously published paper by the author (Sabapathy et al., 2004). The study focused exclusively on the dynamic changes in oxygen uptake (kinetics) observed at the onset of high-intensity constant-load exercise. In view of certain methodological limitations, it is appropriate to view the data presented in this chapter as a pilot study. The results of this study will either support (or refute) a more formal characterisation of the oxygen uptake kinetic responses to high-intensity exercise in COPD patients. Despite its limitations, the data presented is novel, in that no published studies have reported the kinetic responses to high-intensity exercise in COPD patients.

INTRODCUTION

The study of oxygen uptake (\dot{V}_{O_2}) kinetics refers to the use of a method of exploring the physiological mechanisms that contribute to the dynamic responses observed in \dot{V}_{O_2} , particularly during exercise transients (for example, from low to higher intensity constant-load exercise or vice versa). A mathematical modelling approach has been applied to identify a number of physiologically distinct phases associated with the kinetics of \dot{V}_{O_2} at the onset of constant-load (square wave) exercise (Whipp and Wasserman, 1972; Morton, 1986). Currently, the \dot{V}_{O_2} response to square wave exercise transitions is characterised by three transient components or phases.

At the onset of exercise, there is an immediate and rapid increase in \dot{V}_{O_2} , lasting between 15 and 30 s. Termed phase I (or the cardiodynamic component), this rapid early rise in \dot{V}_{O_2} represents the circulatory transit delay between exercising muscles and the lungs, during which time pulmonary blood flow increases as a result of an immediate increase in cardiac output with little or no change in the arterio-venous oxygen (O_2) difference (Whipp et al., 1982). Following the phase I response, the phase II rise in \dot{V}_{O_2} (also known as the fast or primary component) is best characterised as an exponential function that attains a steady-state value (phase III) within 2-3 min (Whipp et al., 1982). The phase I to II transition reflects the arrival to the lung of blood with greater O_2 extraction from the exercising muscles. The phase III steady-state in \dot{V}_{O_2} is observed for exercise intensities below an individual's blood lactate threshold (BLT). If the work intensity is above the BLT, then \dot{V}_{O_2} may not reach an asymptote, and a slowly developing

component of increasing \dot{V}_{O_2} (termed the \dot{V}_{O_2} slow component) is observed (Whipp, 1994; Gaesser and Poole, 1996).

The phase II kinetic profile is thought to be due to a complex interaction between the factors governing O_2 delivery to the muscle and its subsequent utilisation by the exercising muscle (Grassi et al., 1996; Hughson et al., 2001). Thus, the speed of the response (i.e. the time constant, τ , calculated as the time taken to attain 63% of the asymptotic amplitude) reflects the dynamics of O_2 transport from air to mitochondria as well as the 'inertial' characteristics of the oxidative pathways in the muscle. Functionally, a slower phase II kinetic response implies a greater O_2 deficit with greater reliance on anaerobic metabolism (intramuscular phosphocreatine, O_2 stores and lactate utilisation) at the onset of exercise. Physiologically distinct from the phase II on-transient component, the \dot{V}_{O_2} slow component that occurs during heavy-intensity exercise is known to arise primarily from the working muscle (Poole et al., 1991). Evidence suggests that the additional recruitment of muscle fibres is a major cause of the slow component (Krustrup et al., 2004). From a functional viewpoint, the rising \dot{V}_{O_2} during the slow component phase has the potential of driving \dot{V}_{O_2} to maximum values despite the work intensity being classified as submaximal. Thus, the \dot{V}_{O_2} slow component has been implicated in the fatigue process by potentially limiting the capacity for prolonged activity at work intensities above the BLT.

The potential for \dot{V}_{O_2} kinetics to provide mechanistic insights into physiological function has resulted in its use to assess pathologic dysfunction in a number of disease conditions such as chronic heart failure (Sietsema et al., 1994), coronary artery disease (Adachi et al., 2000), peripheral vascular disease (Sietsema,

1992), and cystic fibrosis (Hebestreit et al., 2005). Oxygen uptake kinetics in patients with chronic obstructive pulmonary disease (COPD) have also been examined (Nery et al., 1982; Palange et al., 1995; Otsuka et al., 1997; Puente-Maestu et al., 2000; Puente-Maestu et al., 2001; Somfay et al., 2002). Studies in COPD patients have all demonstrated a slowing of on-transient \dot{V}_{O_2} kinetics, as evidenced by a relatively longer phase II τ (range: 56 – 116 s) when compared to healthy controls (Nery et al., 1982; Palange et al., 1995; Somfay et al., 2002). In these studies, the constant-load exercise bouts were all limited to the moderate-intensity domain (below the BLT).

There is currently no information addressing \dot{V}_{O_2} kinetics in COPD patients for exercise intensities performed above the BLT, where a slow component of \dot{V}_{O_2} is usually evident. Indeed, it is not known if patients with COPD are able to exercise at intensities high enough to induce a slow component. If a slow component is observed in COPD patients, then this gradual rise in \dot{V}_{O_2} may be an important determinant of exercise tolerance, particularly when coupled with an already reduced \dot{V}_{O_2} peak and peak power output. Therefore, the aim of this study was to compare \dot{V}_{O_2} kinetics in COPD patients with healthy age-matched control subjects during 7-min bouts of heavy-intensity constant-load exercise.

METHODS

Subjects and experimental design

This was a retrospective study comparing the \dot{V}_{O_2} kinetics during heavy-intensity constant-load cycling in patients with COPD and healthy age-matched control subjects. Seven healthy untrained older men and 7 patients with moderate COPD

(4 men and 3 women) volunteered to participate and constituted the study population. Subjects visited the laboratory on at least two different occasions, with each visit separated by a minimum of 24 h. Cardiorespiratory fitness of the participants was assessed during an incremental test to volitional fatigue on a cycle ergometer. During subsequent visits, subjects performed between one and three 7-min constant-load cycling tests at an intensity equivalent to 70% of the peak power output attained during the incremental exercise test (W_{peak}). Oxygen uptake kinetics during the constant-load bouts were then characterised using non-linear regression techniques. This study was approved by the Griffith University Human Research Ethics Committee and all subjects provided written, informed consent.

Experimental procedures

Pulmonary function assessment

Pulmonary function was measured and assessed using standard techniques (American Thoracic Society, 1994). Spirometry (forced expiratory volume in 1 s, FEV₁; and forced vital capacity, FVC) and inspiratory capacity (IC) during exercise were measured using a closed-circuit pulmonary function testing system (Collins GS Modular PFT, Warren E. Collins, Inc, Braintree, MA, USA).

Incremental exercise test

The incremental exercise test was performed on a Lode electronically braked cycle ergometer (Excalibur Sport, Groningen, Netherlands), and included 3 min of unloaded cycling followed by step-wise increments in power output until volitional termination of the test. In the healthy older group, power output was increased by 8 W·30 s⁻¹, while power output was increased by 4 W·30 s⁻¹ for the male subjects and by 3 W·30 s⁻¹ for the female subjects in the COPD group. During the

incremental cycling test, gas exchange variables were measured breath-by-breath and averaged over 30-s intervals using a metabolic measuring system (MedGraphics Cardio₂, Cardiopulmonary Diagnostic Systems, St. Paul, MN, USA). A 12-lead electrocardiograph (ECG) configuration was used to monitor cardiac rhythm and to determine heart rate (MedGraphics Cardio₂, Cardiopulmonary Diagnostic Systems, St. Paul, MN, USA). Peak exercise values for incremental cycling were calculated as the average of the two highest consecutive 30-s values obtained prior to termination of exercise. The gas exchange threshold (GET) was determined non-invasively using the simplified V-slope method described by Schneider et al. (1993) and the ventilatory equivalent method (Wasserman et al., 1999).

Constant-load exercise test and \dot{V}_{O_2} kinetics

The power output used for the constant-load tests was calculated as 70% of W_{peak} . Subjects were asked to begin pedalling and to maintain a constant cadence of between 60-70 rev·min⁻¹ throughout the test. After 3 min of unloaded cycling, the workload was applied instantaneously without prior warning given to the subjects. The subjects then continued to exercise for a further 7 min at the pre-determined power output. During the test, \dot{V}_{O_2} was measured breath-by-breath, and heart rate and rhythm were monitored using an electrocardiograph (Lohmeier M 607, Munich, Germany) with the ECG electrodes placed in a CM5 configuration. In the patients with COPD, IC was measured at rest (while seated on the cycle ergometer), and at 7 min of constant-load exercise (Collins GS Modular PFT, Warren E. Collins, Inc, Braintree, MA, USA). At each measurement point, the subjects were prompted and encouraged to inspire maximally to total lung capacity. Inspiratory capacity was quantified as the change in volume from end-expiration during a normal tidal breath and end-inspiration during the

maximal inspiratory manoeuvre. The change in IC from rest to exercise (ΔIC) was used as a measure of dynamic lung hyperinflation (DH). A greater decrease in IC (increasingly negative ΔIC) would indicate a larger magnitude of DH.

Participants in the COPD group performed between two and three repetitions of the constant-load test while the healthy older individuals only performed a single transition. Thus, preliminary data processing procedures differed between the experimental groups. To maximise signal-to-noise ratios and improve confidence in parameter estimation, the breath-by-breath \dot{V}_{O_2} data in those individuals who performed only a single constant-load transition (i.e. subjects in the healthy older group) were smoothed by applying a middle five-of-seven breath averaging procedure. With this technique, the two greatest outlying breaths within a seven-breath bin were edited and the remaining breaths averaged. The bin was then advanced by one-breath intervals and the procedure repeated, providing a smoothed data set that contained the same number of data points as the original breath-by-breath set. Finally, the data points were interpolated to provide second-by-second values. In the COPD group, smoothing was performed by inspecting the breath-by-breath \dot{V}_{O_2} values from each transition for outlying breaths, with data points greater than 3 standard deviations from the local (5-breath) mean edited. The \dot{V}_{O_2} values were subsequently interpolated to 1-s values and the repeat transitions averaged to provide a single data set.

A three component exponential model was used to describe the time course of the \dot{V}_{O_2} response during constant-load exercise for each subject. The curve-fitting procedure used an iterative non-linear algorithm to minimise the residual

sum of squares, satisfying the criterion for convergence. The model is a three-exponential term equation of the form:

$$\dot{V}_{O_2}(t) = A_B + A_C(1 - e^{-(t-TD_C)/\tau_C}) + A_P(1 - e^{-(t-TD_P)/\tau_P}) + A_S(1 - e^{-(t-TD_S)/\tau_S})$$

Equation 5.1

where $\dot{V}_{O_2}(t)$ is the \dot{V}_{O_2} at time t ; A_B is the baseline \dot{V}_{O_2} during unloaded cycling, while A_C , A_P and A_S represent the cardiodynamic (phase I), primary (phase II) and slow component amplitudes, respectively; TD_C , TD_P and TD_S , and τ_C , τ_P and τ_S are the time delays and time constants of phase I and the primary and slow components, respectively. Since A_S represents an asymptotic amplitude and could therefore constitute an extrapolated value, the measured slow component at the end of 7 min of constant-load exercise (A'_S) was calculated using the model equation:

$$A'_S = A_S(1 - e^{-(t_e - TD_S)/\tau_S})$$

Equation 5.2

where t_e is 420 s (or 7 min) and represents the end of exercise. If the amplitude of the slow component (A_S) was not significantly different from 0, the model was reduced to three compartments with exponential terms describing phase I and phase II:

$$\dot{V}_{O_2}(t) = A_B + A_C(1 - e^{-(t-TD_C)/\tau_C}) + A_S(1 - e^{-(t-TD_S)/\tau_S})$$

Equation 5.3

The choice of model function used was also assessed using the sum of squared residuals. A statistically significant (F-test, $P < 0.05$) reduction in the sum of residual squared errors arising from adding parameters (i.e. using equation 5.1 instead of equation 5.3) suggests that the more complex model would provide a better characterisation of the \dot{V}_{O_2} response. Confidence intervals (95% CI) for the time delay and time constant parameters of the model were calculated using non-linear least squares regression (Sabapathy et al., 2004; Koga et al., 2005):

$$95\% \text{ CI} = \text{SEE} \cdot t_{\text{dis}}$$

Equation 5.4

where SEE is the standard error of the parameter estimates and t_{dis} is the value from the t -distribution (two-tailed) with the degrees of freedom set at 420 (i.e. the 7-min duration of constant-load exercise amounting to 420 data points).

In order to make comparisons of the relative change in \dot{V}_{O_2} between the two groups, the gain (G), or change in \dot{V}_{O_2} per unit increment in power output was calculated (Bell et al., 1998).

Statistical analysis

All results are presented as group means \pm standard error of the mean (SEM). Differences between the healthy subjects and patients with COPD in peak exercise values and the kinetic parameters determined for the constant-load tests were examined using independent sample t -tests. Accuracy of the curve fitting procedure was assessed by calculating the coefficient of determination (R^2) and coefficient of correlation (r) between the model fit and residuals. Associations between the dependent variables were examined using Pearson's correlation coefficient. Statistical significance was accepted at $P < 0.05$. Data were analysed using SPSS v10.0 and SigmaPlot v8.0 (Statistical Packages for the Social Sciences Inc., Chicago, IL, USA).

RESULTS

The physical characteristics of the subjects and pulmonary function test results are presented in Table 5.1. The two groups were matched with respect to age, height and body mass. The healthy older subjects' lung function results were within the normal range for their age, while the patient group presented with

moderately severe COPD (FEV₁ between 30% and 80% of predicted values and the FEV₁/FVC ratio below 70%).

Table 5.1. Subject characteristics and pulmonary function test results in healthy older subjects and patients with COPD.

	Healthy	COPD
Gender (Male:Female)	7:0	4:3
Age (yr)	70 ± 1	68 ± 2
Height (cm)	173 ± 1	165 ± 6
Body Mass (kg)	82.0 ± 5.3	72.7 ± 5.1
FEV ₁ (L)	2.93 ± 0.13	1.44 ± 0.22*
FEV ₁ (% predicted)	98 ± 4	55 ± 6*
FVC (L)	3.88 ± 0.23	2.98 ± 0.44 [†]
FVC (% predicted)	99 ± 5	89 ± 8
FEV ₁ /FVC (%)	77 ± 2	49 ± 3*

Values presented are means ± SEM. COPD: chronic obstructive pulmonary disease. FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity. * P<0.01, [†] P<0.05; significantly different from healthy group. * P<0.01, [†] P<0.05; significantly different from healthy group.

Peak \dot{V}_{O_2} and W_{peak} were significantly lower in the COPD patients compared to the healthy subjects (Table 5.2). The healthy subjects also attained a significantly greater peak heart rate and respiratory exchange ratio (RER) at the end of the incremental exercise test than the COPD patients. The mean \dot{V}_{O_2} and power output values obtained at the GET were significantly higher in the healthy (1.24 ± 0.06 L·min⁻¹ at 81 ± 6 W) compared to the COPD (0.81 ± 0.08 L·min⁻¹ at 36 ± 6 W) group. However, the GET occurred at a significantly greater percentage of

\dot{V}_{O_2} peak and Wpeak in the COPD ($75 \pm 3\%$ \dot{V}_{O_2} peak; $55 \pm 3\%$ Wpeak) compared to healthy subjects ($56 \pm 1.1\%$ \dot{V}_{O_2} peak; $43 \pm 2\%$ Wpeak). The mean constant-load exercise intensity was 131 ± 9 W and 46 ± 7 W in the healthy older subjects and COPD patients, respectively ($P < 0.05$).

Table 5.2. Peak incremental exercise values in healthy older subjects and patients with COPD.

	Healthy	COPD
\dot{V}_{O_2} peak (L·min ⁻¹)	2.21 ± 0.12	$1.11 \pm 0.13^*$
\dot{V}_{O_2} peak (mL·kg ⁻¹ ·min ⁻¹)	26.5 ± 1.2	$15.1 \pm 1.0^*$
\dot{V}_{O_2} peak (% predicted)	112 ± 6	$74 \pm 5^*$
Peak RER value	1.24 ± 0.03	$1.02 \pm 0.04^*$
Peak heart rate (beats·min ⁻¹)	157 ± 6	$126 \pm 5^*$
Wpeak (W)	185 ± 11	$65 \pm 9^*$

Values presented are means \pm SEM. COPD: chronic obstructive pulmonary disease; \dot{V}_{O_2} peak: peak oxygen uptake; RER: respiratory exchange ratio; Wpeak: peak power output. * $P < 0.01$, significantly different from healthy group.

Figure 5.1 illustrates the \dot{V}_{O_2} responses and model fits for a representative older subject and COPD patient. The mean values for the coefficient of determination (R^2) of the model fit were $99.0 \pm 0.2\%$ in the healthy older group and $98.7 \pm 0.4\%$ in the COPD patients, while the coefficient of correlation (r) averaged $<10^{-4}$ in both groups. These results suggest a good fit of the model to the measured \dot{V}_{O_2} values and that the deviations of the measured responses from the mean were independent of time and randomly distributed around the regression line.

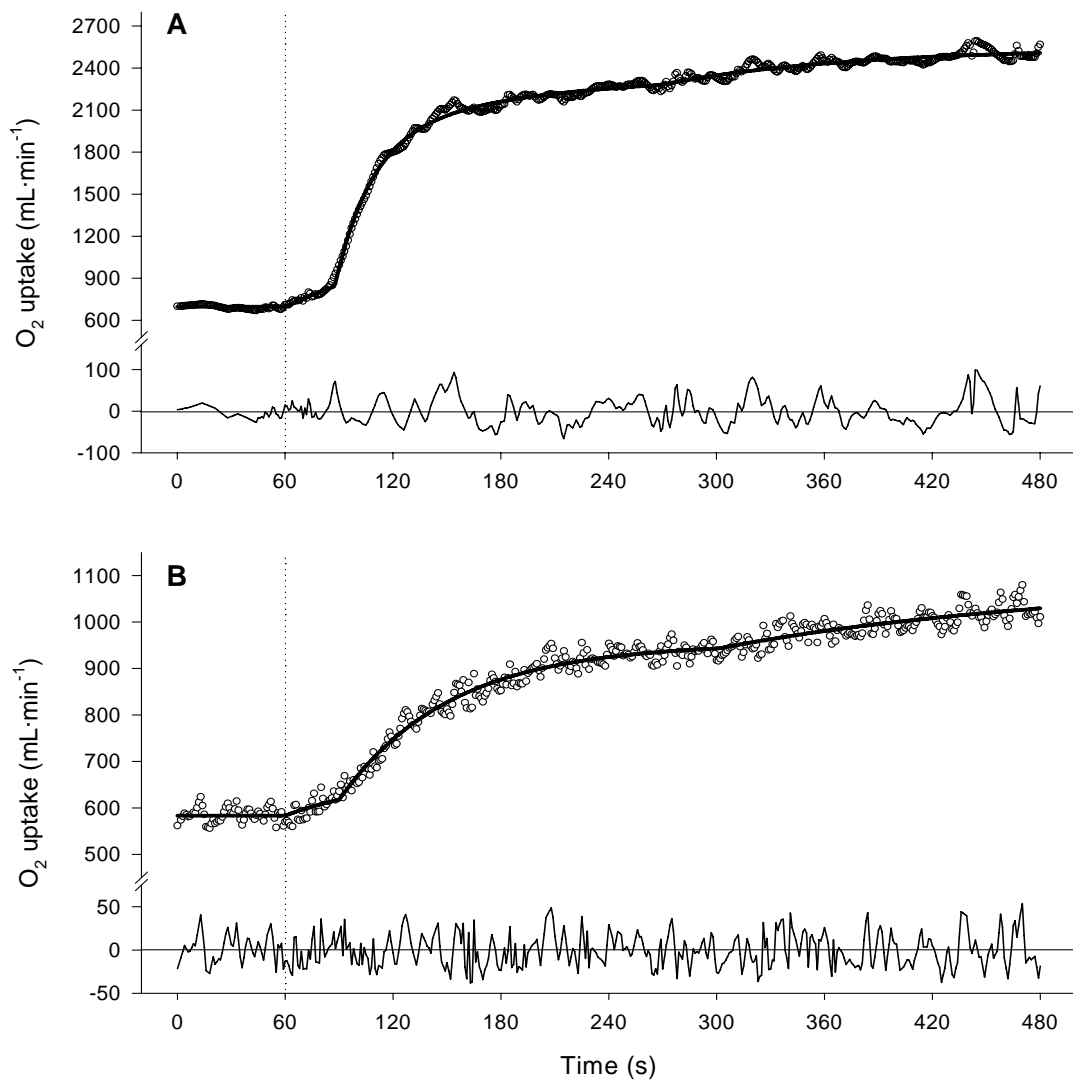


Figure 5.1. Oxygen (O₂) uptake responses to constant-load exercise in a representative healthy older subject (panel A) and COPD patient (panel B). Data points represent second-by-second values for the transition from unloaded cycling to 70% of peak power output. The solid lines indicate the model fit, with the residuals shown at the bottom of each panel. The vertical dotted lines indicate the onset of the pre-determined power output.

The group mean \dot{V}_{O_2} kinetic parameters for the constant-load exercise bouts are provided in Table 5.3. The mean \dot{V}_{O_2} values at the end of 7 min of constant-load cycling (A_{TOT}) were significantly greater in the healthy older subjects compared to

Table 5.3. Oxygen uptake responses to constant-load cycling in healthy older subjects and patients with COPD.

	Healthy	COPD
A_B (mL·min ⁻¹)	684 ± 17	610 ± 37
A_C (mL·min ⁻¹)	53 ± 18	78 ± 21
A_P (mL·min ⁻¹)	1049 ± 86	391 ± 66*
A'_S (mL·min ⁻¹)	213 ± 35	49 ± 11*
A_{TOT} (mL·min ⁻¹)	1962 ± 103	1114 ± 125*
TD_P (s)	20 ± 4	21 ± 3
TD_S (s)	182 ± 18	197 ± 17
τ_P (s)	44 ± 4	82 ± 8*
G_P (mL·min ⁻¹ ·W ⁻¹)	9.0 ± 0.4	12.8 ± 1.1*
G_{TOT} (mL·min ⁻¹ ·W ⁻¹)	11.1 ± 0.1	13.7 ± 0.8 [†]

Values presented are means ± SEM. COPD: chronic obstructive pulmonary disease; A: amplitude of baseline unloaded cycling (A_B), phase I (A_C), the primary (A_P) and slow (A_S) components, and the overall response (A_{TOT}); TD: time delay indicating the onset of the primary (TD_P) and slow (TD_S) components; τ_P : time constant of the primary component; G: gain, representing the O₂ cost per watt increment in power output for the primary component (G_P) and overall response (G_{TOT}). * P<0.01, † P<0.05; significantly different from healthy group.

COPD patients. Baseline \dot{V}_{O_2} measured during unloaded cycling (A_B) and the amplitude of phase I (A_C) were not significantly different between the healthy older subjects and COPD patients, while the amplitude of the primary (A_P) and slow (A'_S) components were significantly greater in the former. At the onset of the

slow component, \dot{V}_{O_2} had already attained $79 \pm 1\%$ of \dot{V}_{O_2} peak in the healthy controls and $97 \pm 3\%$ in the COPD group ($P < 0.01$). The end-exercise \dot{V}_{O_2} values were $90 \pm 2\%$ and $102 \pm 6\%$ of \dot{V}_{O_2} peak in the healthy and COPD groups ($P < 0.05$), respectively. The slow component comprised a significantly greater proportion of A_{TOT} in the healthy control group ($18 \pm 2\%$) than in the COPD group ($10 \pm 2\%$). The time delay parameters representing the onset of the primary (TD_P) and slow (TD_S) components were similar between the two groups. 95% CI for TD_P and TD_S were 8 ± 1 s and 33 ± 13 s in the COPD group, and 3 ± 0.4 s and 21 ± 2 s in the healthy older subjects, respectively. Phase II on-transient kinetics (τ_P) were significantly slowed in the COPD patients (95% CI: 13 ± 6 s) by approximately 50% when compared to their healthy age-matched counterparts (95%CI: 7 ± 1 s). Moreover, the gains for the primary component and the overall response were significantly higher in patients with COPD than in healthy subjects.

Inspiratory capacity decreased by 0.61 ± 0.12 L from rest to the end of constant-load exercise in the patients with COPD. Moreover, in the five patients who developed a \dot{V}_{O_2} slow component, A'_S was significantly correlated with ΔIC (Figure 5.2).

Since FEV_1 measurements are the primary quantitative criterion used to categorize severity of COPD, correlation analysis was performed between FEV_1 (% predicted) and various kinetic parameters (τ_P , G_P and G_{TOT}) in the COPD group. The remaining parameters used to describe \dot{V}_{O_2} kinetics, such as the amplitude and time delay components, were not included in the analysis as they were either not significantly different between the groups or were expected to be

different between the groups (as in the amplitude terms, which are a function of the power output used). Negative associations were observed between FEV₁ (% predicted) and τ_P ($r = -0.207$, $P=0.66$), G_P ($r = -0.20$, $P=0.67$) and G_{TOT} ($r = -0.194$, $P=0.68$), but these correlations were not statistically significant.

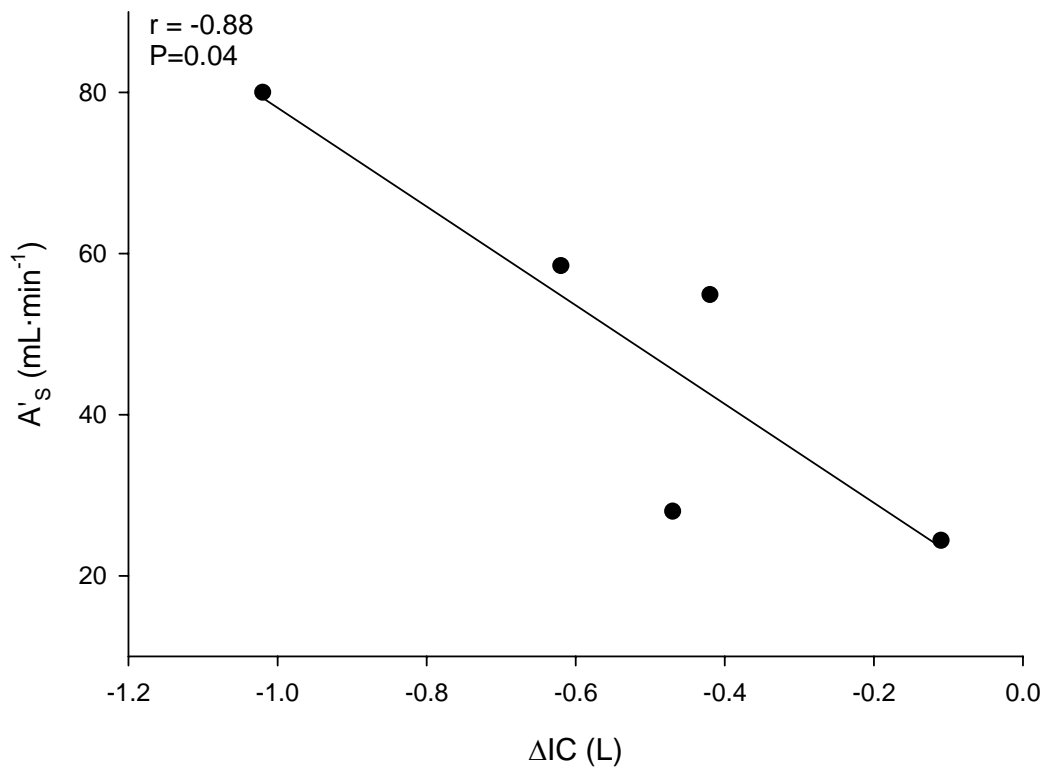


Figure 5.2. The relationship between the amplitude of the slow component of oxygen uptake kinetics (A'_s) and dynamic lung hyperinflation in the patients with chronic obstructive pulmonary disease. Dynamic hyperinflation was quantified as the change in inspiratory capacity (ΔIC) from rest to the end of constant-load exercise. A greater decrease in IC (increasingly negative value for ΔIC) indicates a larger magnitude of lung hyperinflation.

DISCUSSION

The primary findings of the present study include the observation of a slow component of \dot{V}_{O_2} in 5 of the 7 COPD patients studied and a slowing of phase II on-transient kinetics during heavy exercise in the COPD group compared to

healthy control group. Additionally, the phase II gain and overall gain of the \dot{V}_{O_2} response (G_P and G_{TOT} , respectively) were significantly elevated in the COPD patients. These results provide new information about \dot{V}_{O_2} kinetics within the heavy-intensity exercise domain for COPD patients.

Previous studies examining \dot{V}_{O_2} kinetics in patients with COPD have focused exclusively on the gas exchange responses to moderate-intensity constant-load exercise performed below the BLT (Nery et al., 1982; Palange et al., 1995; Otsuka et al., 1997; Puente-Maetsu et al., 2000; Puente-Maetsu et al., 2001; Somfay et al., 2002). A summary of the major findings of these study are as follows: 1) the phase II τ is slowed in patients with COPD compared to healthy controls (Nery et al., 1982; Palange et al., 1995; Somfay et al., 2002); 2) τ is speeded following endurance training in COPD patients (Otsuka et al., 1997; Puente-Maetsu et al., 2000); and 3) the effect of hyperoxia on τ is equivocal, with one study showing faster phase II kinetics when breathing hyperoxic air (Palange et al., 1995), while another study showed no effect of hyperoxia on \dot{V}_{O_2} kinetics in patients with COPD (Somfay et al., 2002). In the present study, τ_P was significantly greater in the COPD patients compared to controls, indicating that phase II kinetics during heavy-intensity exercise are slowed in the former.

It is well known that phase II \dot{V}_{O_2} kinetics are slowed in older compared to younger individuals during moderate-intensity exercise (Cunningham et al., 1993; Babcock et al., 1994), as well as during heavy- to severe-intensity exercise (Sabapathy et al., 2004). The slower on-transient kinetics with ageing have been attributed to inadequate O_2 delivery or muscle perfusion, and to age-related reductions in muscle oxidative metabolism (Babcock et al., 1994). Slower heart

rate kinetics (an estimate of cardiac output kinetics) (Chilibeck et al., 1996) and microvascular blood flow kinetics (DeLorey et al., 2004; DeLorey et al., 2005) in older compared to younger adults suggest that convective O_2 delivery may play a key role in the age-related slowing of \dot{V}_{O_2} kinetics at the onset of exercise. Factors intrinsic to the muscle such as age-related reductions in enzymatic activities of succinate dehydrogenase, citrate synthase and 3-hydroxyacyl-CoA dehydrogenase (Coggan et al., 1992), and a lower oxidative capacity in the vastus lateralis muscle of older subjects (Conley et al., 2000) could also contribute to the slowed \dot{V}_{O_2} on-kinetics with ageing. It is likely that factors related to the disease, compounded with normal age-related changes in muscle metabolism results in the further slowing of the on-transient response in COPD patients compared to healthy older adults.

A decline in habitual physical activity in patients with COPD due to breathlessness and/or muscular fatigue could cause a classic de-conditioning response that in turn further slows τ_P beyond what may be expected with normal ageing. Bed-rest induced de-conditioning is known to result in a greater O_2 deficit during constant-load exercise, implying slower on-transient kinetics (Convertino et al., 1984). Otsuka and colleagues (1997) demonstrated that while 8 wk of endurance training resulted in a reduction of τ_P in patients with COPD (63.5 ± 7.8 s to 53.2 ± 8.0 s), τ_P was again significantly longer (73.4 ± 14.9 s) than that measured immediately post-training during a follow-up session conducted 5 mo after training. These results show that inactivity has a detrimental effect on the factors controlling τ_P and may, in part, explain the slowing of phase II kinetics in COPD patients in the present study. Certainly, a reduced capillary to fibre ratio (Whittom et al., 1998) and a reduction in oxidative enzyme capacity in the skeletal muscles of COPD patients compared to healthy controls (Maltais et al.,

1996) could impair O₂ delivery and utilisation and slow \dot{V}_{O_2} on-transient kinetics. Such detrimental changes in muscle vascularisation and oxidative metabolism have been noted with reductions in, or the cessation of physical activity (Mujika and Padilla, 2001).

There are a number of other factors that could also explain the slowing of the phase II response time. Slower heart rate kinetics in patients with COPD compared to healthy controls could have contributed to the slowing of the phase II \dot{V}_{O_2} response (Nery et al., 1982; Puente-Maetsu et al., 2000). Additionally, gas exchange abnormalities at the lung such as ventilation to perfusion mismatching, diffusion impairment at the lungs, increased intrathoracic pressure swings during breathing and increased pulmonary vascular resistance could all potentially affect the efficient delivery of O₂ to the working muscle during a period of rapid cardiovascular and metabolic adjustment. It is suggested that the increased work of breathing in COPD patients (Evison and Cherniack, 1968) is likely to contribute to the slowing of phase II kinetics in COPD patients by redirecting blood flow to the respiratory muscles, thereby compromising O₂ delivery to the active skeletal muscle.

The elevated work of breathing may also explain the significantly higher gain components (G_P and G_{TOT}) observed in the COPD patients compared to healthy control subjects in the present study. While G_{TOT} during heavy-intensity exercise is expected to exceed that observed for moderate-intensity exercise (<10 mL·min⁻¹·W⁻¹) because of the \dot{V}_{O_2} slow component (Gaesser and Poole, 1996), G_P tends to remain relatively unchanged (Table 5.2, healthy subjects) or may even decrease at very high work intensities (Wilkerson et al., 2004). It is possible that the increased work of breathing in COPD patients adds to the metabolic cost of

exercise above that incurred by the active skeletal muscle, raising the O_2 cost beyond the value expected for a given power output. Baarends et al. (1997) reported that mechanical efficiency during moderate-intensity cycling in patients with severe COPD (N=33) was reduced and that those with the lowest mechanical efficiency (<17%, N=21) tended to have an increased $\dot{V}_E / \dot{V}_{O_2}$ compared to those with relatively normal efficiency. These investigators hypothesised that an increased work of breathing contributed to the decreased mechanical efficiency.

Richardson and colleagues (2004) also reported a reduced mechanical efficiency in COPD patients during single-leg knee extensor exercise, where the relatively small active muscle mass does not impose a central or ventilatory limitation to exercise tolerance. In the study by Richardson et al. (2004), biopsy analysis of the vastus lateralis muscle revealed a greater proportion of type II fibres in the COPD patients compared to healthy control subjects. These findings led the investigators to conclude that the reduced muscular efficiency in patients with COPD could be attributed to morphological characteristics of the active muscle. Type II muscle fibres are thought to be less metabolically efficient, with a lower phosphorylation and contractile-coupling efficiency than type I fibres (Crow and Kushmerick, 1982; Willis and Jackman, 1994). Although net efficiency has recently been shown to be similar in type I and type II fibres (Barclay and Weber, 2004), it is likely that the mechanical constraints associated with dynamic activity in humans (principally contraction frequency) permit type I fibres to operate closer to their maximum efficiency than type II fibres (Coyle et al., 1992). Thus, an elevated number of type II fibres recruited during cycle ergometry in patients with COPD compared to healthy subjects could explain the greater G_p observed.

It is interesting that although the physiological responses to high-intensity constant-load exercise are often studied when assessing the effectiveness for various interventions in patients with COPD (Puente-Maetsu et al., 2000; Casaburi et al., 2004; O'Donnell et al., 2004), no attempt has been made to formally characterise the kinetic components of gas exchange within this intensity domain in this patient population. Thus, the present study is the first to document the existence of a \dot{V}_{O_2} slow component during heavy-intensity constant-load exercise in patients with moderate COPD.

While an earlier study demonstrated that the onset of the slow component appeared to occur later in healthy older subjects than in younger individuals (Sabapathy et al., 2004), TD_S was not significantly different between the two groups in the present study. Currently, there have not been any studies conducted where the determinants of the slow component onset have been examined. However, it is feasible that the slow component only becomes distinguishable from the primary phase response at a time when phase II has attained or is approaching its asymptotic value (Özyener et al., 2001). Thus, the predominance of the phase II amplitude masks the slow component onset, implying that TD_S is not indicative of the true onset of the slow component. This hypothesis could also explain the later onset of the slow component in older subjects with slower phase II kinetics than in younger individuals (Sabapathy et al., 2004). However, the results of the present study would contradict this hypothesis since TD_S , while occurring ~15 s later in COPD patients compared to the healthy controls, was not significantly different between the two groups. Future studies, where a greater number of exercise transitions are used to reduce the confidence of TD_S parameter estimation and more participants are recruited to improve statistical power, are required to clarify this issue.

The mechanism(s) responsible for causing the \dot{V}_{O_2} slow component have yet to be fully elucidated. It is known that the slow component arises primarily from the working muscle (Poole et al., 1991). Moreover, the slow component is probably caused by the recruitment of additional motor units, possibly innervating type II fibres, to supplement fatiguing muscle fibres (Krustrup et al., 2004). Since muscular fatigue is a common symptom limiting exercise performance in patients with COPD (Killian et al., 1992), it is likely that the slow component in these individuals is also caused by the recruitment of additional muscle fibres. Evidence in COPD patients demonstrating abnormal muscle metabolism and morphology, such as the release of lactate at lower power outputs during exercise when compared to healthy controls (Casaburi et al., 1991; Maltais et al., 1996), a selective loss of type I fibres (Jakobsson et al., 1990; Whittom et al., 1998), and slower PCr recovery kinetics (Tada et al., 1992), suggest that the slow component amplitude may even be augmented. It has also been suggested that in healthy individuals, the increased work of breathing may contribute to a small portion of the slow component (Gaesser and Poole, 1996). This may have a greater relevance in COPD patients because of the elevated work of breathing during exercise in these patients. In the present study, A'_s correlated significantly with ΔIC , suggesting that a greater degree of DH was associated with a larger slow component amplitude. The increase in end-expiratory lung volume accompanying DH places a high elastic load on the inspiratory muscles and would also alter their length-tension relationship (shortening of the inspiratory muscles), decreasing their efficiency, thereby increasing the work of breathing. Thus, DH during high-intensity exercise could elevate the work of breathing, augmenting the slow component in COPD patients. This hypothesis is supported by evidence demonstrating that the addition of inspiratory resistance during high-

intensity constant-load exercise in healthy individuals increased the slow component amplitude by ~23% (Carra et al., 2003).

The smaller A'_S values observed in the COPD patients compared to healthy controls in the present study is consistent with the lower absolute power outputs used during constant-load cycling in these patients. However, G_{TOT} was significantly greater in the COPD patients. In the healthy subjects, G_{TOT} exceeded $10 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$ (while G_P was $<10 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$), indicating that the \dot{V}_{O_2} slow component was responsible for increasing the O_2 cost of heavy-intensity exercise in this group. In contrast, the gain was already elevated at the phase II-slow component transition (i.e., G_P was $>10 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$) in the COPD patients. However, the slow component did add further to the O_2 cost of exercise since the gain increased by approximately $0.9 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$ from the start of the slow component to the end of exercise. In the healthy older subjects, this increase amounted to approximately $2.1 \text{ mL}\cdot\text{min}^{-1}\cdot\text{W}^{-1}$. This suggests that the slow component accounted for a significantly greater proportion of the overall \dot{V}_{O_2} response in the healthy older group compared to the COPD group. Indeed, the slow component did comprise a greater proportion of the end-exercise \dot{V}_{O_2} value in the healthy subjects (18%) than in the COPD patients (10%).

The results appear to contradict earlier statements asserting that the slow component amplitude may be relatively greater in COPD patients compared to healthy individuals. However, an explanation for the observation of a relatively smaller slow component amplitude in the COPD group lies in the manner by which the work intensity for the constant-load bouts was determined. The \dot{V}_{O_2} slow component is only evident at work intensities above the BLT and increases

as a function of both power output and time (Gaesser and Poole, 1996). Therefore, it is more appropriate when calculating the power output used for constant-load tests measuring \dot{V}_{O_2} kinetics during heavy- to severe-intensity exercise to select work intensities based on a percentage of the difference between the power output achieved at the BLT or GET and W_{peak} , otherwise termed “delta” ($\Delta\%$). For example, 50% of the difference between the power output achieved at the GET and W_{peak} ($\Delta 50\%$) has been used in a number of studies investigating the \dot{V}_{O_2} slow component (Bearden and Moffatt, 2000; Koppo and Bouckaert, 2000; Sabapathy et al., 2004).

In the present study, the GET occurred at a significantly higher percentage of W_{peak} in the COPD patients (~55% of W_{peak}) compared to healthy controls (~43% of W_{peak}). Thus, the 70% W_{peak} power outputs used would represent a smaller $\Delta\%$ value in the COPD patients than in the control subjects. Consequently, it is reasonable to expect that the contribution of the slow component to the overall \dot{V}_{O_2} response to be relatively smaller in the COPD group. This may also explain the absence of a slow component in two of the seven subjects with COPD, whose GET occurred at relatively high percentages of W_{peak} (64% and 58% of W_{peak} , group range: 47%-64% of W_{peak}). Additionally, it is likely that the GET occurs at a higher percentage of W_{peak} in the COPD patients because incremental exercise tests are symptom-limited and therefore terminated “pre-maturely”; the COPD patients only attained 74% of age-predicted $\dot{V}_{O_2 peak}$ during the incremental exercise test, while the healthy subjects achieved 112% of age-predicted $\dot{V}_{O_2 peak}$. In support of this hypothesis, end-exercise \dot{V}_{O_2} during the constant-load exercise bouts attained values

equivalent to \dot{V}_{O_2} peak (mean: 102% \dot{V}_{O_2} peak; range: 91%-120%) in the patients with COPD. In some individuals, end-exercise \dot{V}_{O_2} even exceeded \dot{V}_{O_2} peak.

In conclusion, this study demonstrated that most patients with COPD were able to exercise at intensities high enough to elicit a \dot{V}_{O_2} slow component. Moreover, the significant positive correlation between the slow component amplitude and the degree of dynamic hyperinflation suggests that the work of breathing may contribute more to the slow component in patients with COPD than in healthy individuals. This conclusion must be interpreted with caution since IC was not measured in the healthy control group, and it is known that end-expiratory lung volume can also increase during high-intensity exercise in some healthy older individuals in whom lung recoil is reduced (Johnson et al., 1994). Differences between COPD patients and healthy controls in the amplitude of the slow component can be accounted for by the significantly different absolute power outputs used and also the method of determining the work intensities. It is suggested that even if a $\Delta\%$ power output were to be used in populations that are symptom-limited during exercise, the physiological "stress" may not be sufficiently normalised for valid comparisons to be made with respect to the slow component (particularly when comparing different populations). Nevertheless, high-intensity constant-load exercise is commonly used to assess the effectiveness of various interventions in COPD (Casaburi et al., 1991; Somfay et al., 2001; O'Donnell et al., 2004). Furthermore, it is recommended that the duration of the constant-load exercise tests should range from 4 to 7 min (Casaburi, 2005), long enough for a slow component to become evident. Thus, it is worthwhile characterising gas-exchange kinetics during high-intensity constant-load exercise in patients with

COPD undergoing various therapeutic interventions. The results of such investigations could potentially improve the level of interpretation of studies. Certainly a more formal and systematic characterisation of gas-exchange kinetics in the high-intensity exercise domain is warranted in COPD patients.

REFERENCES

- Adachi, H., A. Koike, A. Niwa, A. Sato, T. Takamoto, Marumo, F and M. Hiroe (2000). Percutaneous transluminal coronary angioplasty improves oxygen uptake kinetics during the onset of exercise in patients with coronary artery disease. *Chest*. 118: 329-335.
- American Thoracic Society (1994). Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med*. 152: 1107-1136.
- Baarends, E. M., A. M. Schols, M. A. Akkermans and E. F. Wouters (1997). Decreased mechanical efficiency in clinically stable patients with COPD. *Thorax*. 52: 981-986.
- Babcock, M. A., D. H. Paterson and D. A. Cunningham (1994). Effects of aerobic endurance training on gas exchange kinetics of older men. *Med Sci Sports Exerc*. 26(4): 447-452.
- Babcock, M. A., D. H. Paterson, D. A. Cunningham and J. R. Dickinson (1994). Exercise on-transient gas exchange kinetics are slowed as a function of age. *Med Sci Sports Exerc*. 26(4): 440-446.
- Barclay, C. J. and C. L. Weber (2004). Slow skeletal muscles of the mouse have greater initial efficiency than fast muscles but the same net efficiency. *J Physiol*. 559: 519-533.
- Bearden, S. E. and R. J. Moffatt (2000). \dot{V}_{O_2} kinetics and the O_2 deficit. *J Appl Physiol*. 88: 1407-1412.
- Bell C, Paterson DH, Babcock MA, and Cunningham DA (1998). Characteristics of the \dot{V}_{O_2} slow component during heavy exercise in humans aged 30 to 80 years. *Adv Exp Med Biol*. 450: 219-222.

- Carra, J., R. Candau, S. Keslacy, F. Giolbas, F. Borrani, G. P. Millet, A. Varray and M. Ramonatxo (2003). Addition of inspiratory resistance increases the amplitude of the slow component of O_2 uptake kinetics. *J Appl Physiol.* 94: 2448-2455.
- Casaburi, R. (2005). Factors determining constant work rate exercise tolerance in COPD and their role in dictating the minimal clinically important difference in response to interventions. *J COPD.* 2: 131-136.
- Casaburi, R., C. Chen, J. Porszasz and B. J. Whipp (2004). Work rate selection for constant work rate exercise testing for interventional studies in COPD. *Am J Respir Crit Care Med.* 169: A770.
- Casaburi, R., A. Patessio, F. Ioli, S. Zanaboni, C. F. Donner and K. Wasserman (1991). Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis.* 143: 9-18.
- Chilibeck, P. D., D. H. Paterson, W. D. F. Smith and D. A. Cunningham (1996). Cardiorespiratory kinetics during exercises of different muscle groups and mass in old and young. *J Appl Physiol.* 81(3): 1388-1394.
- Coggan, A. R., R. J. Spina, D. S. King, M. A. Rogers, M. Brown, P. M. Nemeth and J. O. Holloszy (1992). Histochemical and enzymatic comparison of the gastrocnemius muscle of young and elderly men and women. *J Gerontol.* 46: 71B-76B.
- Conley, K. E., S. A. Jubrias and P. C. Esselman (2000). Oxidative capacity and ageing in human muscle. *J Physiol.* 526: 203-210.
- Convertino, V. A., D. J. Goldwater and H. Sandler (1984). \dot{V}_{O_2} kinetics of constant-load exercise following bed-rest-induced deconditioning. *J Appl Physiol.* 57: 1545-1550.

- Coyle, E. F., L. S. Sidossis, J. F. Horowitz and J. D. Beltz (1992). Cycling efficiency is related to the percentage of type I muscle fibers. *Med Sci Sports Exerc.* 24: 782-788.
- Crow, M. T. and M. J. Kushmerick (1982). Chemical energetics of slow- and fast-twitch muscles of the mouse. *J Gen Physiol.* 79: 147-166.
- Cunningham, D. A., J. E. Himann, D. H. Paterson and J. R. Dickinson (1993). Gas exchange dynamics with sinusoidal work in young and elderly women. *Respir Physiol.* 91: 43-56.
- DeLorey, D. S., J. M. Kowalchuk and D. H. Paterson (2004). Effect of age on O₂ uptake kinetics and the adaptation of muscle deoxygenation at the onset of moderate-intensity cycling exercise. *J Appl Physiol.* 97: 165-172.
- DeLorey, D. S., J. M. Kowalchuk and D. H. Paterson (2005). Adaptation of pulmonary O₂ uptake kinetics and muscle deoxygenation at the onset of heavy-intensity exercise in young and older adults. *J Appl Physiol.* 98: 1697-1704.
- Evison, H. and R. M. Cherniack (1968). Ventilatory cost of exercise in chronic obstructive pulmonary disease. *J Appl Physiol.* 25(1): 21-7.
- Gaesser, G. A. and D. C. Poole (1996). The slow component of oxygen uptake kinetics in humans. *Exerc Sport Sci Rev.* 24: 35-70.
- Grassi, B., D. C. Poole, R. S. Richardson, D. R. Knight, B. K. Erickson and P. D. Wagner (1996). Muscle O₂ uptake kinetics in humans: implications for metabolic control. *J Appl Physiol.* 80: 988-998.
- Hebestreit, H., A. Hebestreit, A. Trusen and R. L. Hughson (2005). Oxygen uptake kinetics are slowed in cystic fibrosis. *Med Sci Sports Exerc.* 37: 10-17.

- Hughson, R. L., M. E. Tschakovsky and M. E. Houston (2001). Regulation of oxygen consumption at the onset of exercise. *Exerc Sport Sci Rev.* 29: 129-133.
- Jakobsson, P., L. Jorfeldt and A. Brundin (1990). Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD), with and without chronic respiratory failure. *Eur J Appl Physiol.* 3: 192-196.
- Johnson, B. D., M. S. Badr and J. A. Dempsey (1994). Impact of the aging pulmonary system on the response to exercise. *Clin Chest Med.* 15: 229-246.
- Killian, K. J., P. LeBlanc, D. H. Martin, E. Summers, N. L. Jones and E. J. M. Campbell (1992). Exercise capacity and ventilatory, circulatory and symptom limitation in patients with chronic airflow limitation. *Am Rev Respir Dis.* 146: 935 - 940.
- Koga, S., T. Shijori and N. Kondo (2005). Measuring \dot{V}_{O_2} kinetics: The practicalities. In *Oxygen Uptake Kinetics in Sport, Exercise and Medicine*. A. M. Jones and D. C. Poole (Eds). London, Routledge: 39-61.
- Koppo, K. and J. Bouckaert (2000). In humans the oxygen uptake slow component is reduced by prior exercise of high as well as low intensity. *Eur J Appl Physiol.* 83: 559-565.
- Krustrup, P., K. Söderlund, M. Mohr and J. Bangsbo (2004). The slow component of oxygen uptake during intense, sub-maximal exercise in man is associated with additional fibre recruitment. *Pflugers Arch.* 447: 855-866.
- Maltais, F., A.-A. Simard, C. Simard, J. Jobin, P. Desgagnés and P. LeBlanc (1996). Oxidative capacity of the skeletal muscle and lactic acid kinetics

- during exercise in normal subjects and in patients with COPD. *Am J Respir Crit Care Med.* 153: 288-293.
- Morton, R. H. (1986). A three component model of human bioenergetics. *J Math Biol.* 24: 451-466.
- Mujika, I. and S. Padilla (2001). Muscular characteristics of detraining in humans. *Med Sci Sports Exerc.* 33: 1297-303.
- Nery, L. E., K. Wasserman, J. D. Andrews, D. J. Huntsman, J. E. Hansen and B. J. Whipp (1982). Ventilatory and gas exchange kinetics during exercise in chronic airways obstruction. *J Appl Physiol.* 53(6): 1594-1602.
- O'Donnell, D. E., T. Fluge, F. Gerken, A. Hamilton, K. Webb, B. Aguilaniu, B. Make and H. Magnussen (2004). Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J.* 23: 832-840.
- Otsuka, T., N. Kurihara, T. Fuji, S. Fujimoto and J. Yoshikawa (1997). Effect of exercise training and detraining on gas exchange kinetics in patients with chronic obstructive pulmonary disease. *Clin Physiol.* 17: 287-297.
- Özyener, F., H. B. Rossiter, S. A. Ward and B. J. Whipp (2001). Influence of exercise intensity on the on- and off-transient kinetics of pulmonary oxygen uptake in humans. *J Physiol.* 533: 891-902.
- Palange, P., P. Galassetti, E. T. Mannix, M. O. Farber, F. Manfredi, P. Serra and S. Carlone (1995). Oxygen effect on O₂ deficit and \dot{V}_{O_2} kinetics during exercise in obstructive pulmonary disease. *J Appl Physiol.* 78: 2228-2234.
- Poole, D. C., W. Schaffartzik, D. R. Knight, T. Derion, B. Kennedy, H. J. Guy, R. Prediletto and P. D. Wagner (1991). Contribution of exercising legs to the

slow component of oxygen uptake kinetics in humans. *J Appl Physiol.* 71: 1245-1253.

Puente-Maetsu, L., M. L. Sáñez, P. Sáñez, A. Nuñez, F. González and B. J. Whipp (2001). Reproducibility of the parameters of the on-transient cardiopulmonary responses during moderate exercise in patients with chronic obstructive pulmonary disease. *Eur J Appl Physiol.* 85: 434-441.

Puente-Maetsu, L., M. L. Sanz, P. Sanz, J. M. Ruiz de Ona, J. L. Rodriguez-Hermosa and B. J. Whipp (2000). Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. *Eur Respir J.* 15: 1026-1032.

Richardson, R. S., B. T. Leek, T. P. Gavin, L. J. Haseler, S. R. Mudaliar, R. Henry, O. Mathieu-Costello and P. D. Wagner (2004). Reduced mechanical efficiency in chronic obstructive pulmonary disease but normal peak \dot{V}_{O_2} with small muscle mass exercise. *Am J Respir Crit Care Med.* 169: 89-96.

Sabapathy, S., D. A. Schneider, G. Comadira, I. Johnston and N. R. Morris (2004). Oxygen uptake kinetics during severe exercise: a comparison between young and older men. *Respir Physiol Neurobiol.* 139: 203-213.

Schneider, D. A., S. E. Phillips and S. Stoffolano (1993). The simplified V-slope method of detecting the gas exchange threshold. *Med Sci Sports Exerc.* 25: 1180-1184.

Sietsema, K. E. (1992). Oxygen uptake kinetics in response to exercise in patients with pulmonary vascular disease. *Am Rev Respir Dis.* 145: 1052-1057.

- Sietsema, K. E., I. Ben Dov, Y. Y. Zhang, C. Sullivan and K. Wasserman (1994). Dynamics of oxygen uptake for submaximal exercise and recovery in patients with chronic heart failure. *Chest*. 105: 1693-1700.
- Somfay, A., J. Pórszász, S. M. Lee and R. Casaburi (2001). Effect of oxygen on hyperinflation and exercise endurance in non-hypoxemic COPD patients. *Eur Respir J*. 18: 77-84.
- Somfay, A., J. Pórszász, S.-M. Lee and R. Casaburi (2002). Effect of hyperoxia on gas exchange and lactate kinetics following exercise onset in nonhypoxemic COPD patients. *Chest*. 121: 393-400.
- Tada, H., H. Kato, T. Misawa, F. Sasaki, S. Hayashi, H. Takahashi, Y. Kutsumi, T. Ishizaki, T. Nakai and S. Miyabo (1992). ³¹P-Nuclear magnetic resonance evidence of abnormal skeletal muscle metabolism in patients with chronic lung disease and congestive heart failure. *Eur Respir J*. 5: 163-169.
- Wasserman, K., J. E. Hansen, D. Y. Sue, R. Casaburi and B. J. Whipp (1999). *Principles of exercise testing and interpretation*. Baltimore, Lippincott, Williams & Wilkins.
- Whipp, B. J. (1994). The slow component of O₂ uptake kinetics during heavy exercise. *Med Sci Sports Exerc*. 26: 1319-1326.
- Whipp, B. J., S. A. Ward, N. Lamarra, J. A. Davis and K. Wasserman (1982). Parameters of ventilatory and gas exchange dynamics during exercise. *J Appl Physiol*. 52: 1506-1513.
- Whipp, B. J. and K. Wasserman (1972). Oxygen uptake kinetics for various intensities of constant-load work. *J Appl Physiol*. 33: 351-356.
- Whittom, F., J. Jobin, P.-M. Simard, P. LeBlanc, C. Simard, S. Bernard, R. Belleau and F. Maltais (1998). Histochemical and morphological

characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc.* 30(10): 1467-1474.

Wilkerson, D. P., K. Koppo, T. J. Barstow and A. M. Jones (2004). Effect of work rate on the functional 'gain' of Phase II pulmonary O_2 uptake response to exercise. *Respir Physiol Neurobiol.* 142: 211-223.

Willis, W. T. and M. R. Jackman (1994). Mitochondrial function during heavy exercise. *Med Sci Sports Exerc.* 26: 1347-1354.

ABBREVIATED TERMS

A	Amplitude of the oxygen uptake response (subscripts B, C, P and S refer to baseline unloaded cycling, and the cardiodynamic, primary and slow components, respectively)
BLT	Blood lactate threshold
COPD	Chronic obstructive pulmonary disease
ECG	Electrocardiograph
FEV ₁	Forced expiratory volume in 1 s
FVC	Forced vital capacity
G	Gain, indicating the oxygen cost per minute per unit increment in power output (subscripts P and TOT refer to the primary component and overall or total response)
GET	Gas exchange threshold
IC	Inspiratory capacity
O ₂	Oxygen
r	Coefficient of correlation
R ²	Coefficient of determination

RER	Respiratory exchange ratio
SEE	Standard error of the estimate
SEM	Standard error of the mean
t	Time
TD	Time delay (subscripts C, P and S refer to the cardiodynamic, primary and slow components, respectively)
t_{dis}	The value from the t -distribution (two-tailed) for a given degrees of freedom value
\dot{V}_{O_2}	Oxygen uptake
W _{peak}	Peak power output
95% CI	95% confidence interval
Δ	Delta; change
τ	Tau or time constant; time taken to reach 63% of the final amplitude in an exponential function (subscripts C, P and S refer to the cardiodynamic, primary and slow components, respectively)

**C
H
A
P
T
E
R

6**

Conclusions
Summary of the Findings

[Blank Page]

The wide range in disease severity and degree of functional impairment, as well as multiple determinants of exercise intolerance that characterise patients with chronic obstructive pulmonary disease (COPD) pose a challenge when attempting to optimise therapeutic interventions for individuals with this disease. With respect to exercise as a therapeutic intervention, “nowhere is the gap wider between what we know and what we do than in the area of physical activity, and nowhere is the potential pay-off greater” (Koplan, 2000). Indeed, exercise has become a fundamental component of pulmonary rehabilitation, with the benefits of physical training in patients with COPD well documented (Troosters et al., 2005; Pedersen and Saltin, 2006). Additionally, research has also been conducted into the efficacy of various training modes in an effort to optimise the delivery of exercise training and maximise the benefits for the patients. Recently, intermittent exercise (IE) has been proposed as an alternative training modality that, like continuous exercise (CE) training, is dynamic and engages a relatively large skeletal muscle mass (Coppoolse et al., 1999; Vogiatzis et al., 2002). Thus, the primary aim of this thesis was to develop a better understanding of the physiology and perceptual responses associated with the performance of CE and IE in patients with moderate COPD.

In Study 1, the physiological and perceptual responses to an acute bout of IE were compared to CE in patients with moderate COPD. Exercise intensity was standardised to 70% of peak power output achieved during incremental cycling for both exercise modes. Exercise tolerance and total work performed were significantly greater but the metabolic, respiratory and perceptual perturbations were significantly lower during IE compared to CE. The lower gas-exchange responses (particular attention was paid to oxygen uptake, \dot{V}_{O_2}) observed during the IE bouts were shown to be due to the exponential shape of the on-transient (phase II) \dot{V}_{O_2} response. The

comparisons between CE and IE were further developed in Study 2, where the adaptations to 8 wk of CE and IE training were examined. Other studies have compared CE and IE training in patients with COPD, reporting similar adaptations when total work performed was not significantly different between the training modes (Vogiatzis et al., 2002; Vogiatzis et al., 2005). However, in these studies, IE was performed at a higher relative intensity compared to CE. While the ability to tolerate high work intensities is one of the practical benefits of IE, it is unclear from these studies if the similar training adaptations between the training modes were due to the similar total work performed or because IE training was relatively more intense than CE training. In order to address this potentially confounding experimental design, the present study prescribed IE and CE training at the same relative intensity and ensured that the training groups were matched for total work completed.

The initial training intensity was fixed at 50% of peak power output for both training groups and subsequently increased by 5% per week in the last 6 wk of training. A lower initial exercise intensity compared to that used in Study 1 was chosen to ensure that those performing CE were able to complete 30 min of exercise. In Study 1, subjects were only able to tolerate an average of 11 min of CE. It was important that both groups exercised for the prescribed duration, as this would ensure that the total work performed by each group within a training session was the same. The results from Study 2 agree with previous studies (Vogiatzis et al., 2002; Vogiatzis et al., 2005), in that improvements in exercise capacity and tolerance with training were similar for the CE and IE groups when total work completed was standardised between the groups. Moreover, symptoms of breathlessness and leg fatigue were significantly lower during IE training than during CE training.

The results of Studies 1 and 2 suggest that IE may be superior to CE as a mode of training for patients with COPD. The adaptations to IE and CE are similar when total work for the two training modes is controlled. The greater total work achieved during acute bouts of IE could allow for a greater volume of training to be performed, while lower ratings of breathlessness and limb fatigue associated with IE may improve adherence to training in COPD patients. Furthermore, the greater options associated with IE protocol design (exercise to rest ratios, as well as a greater range of tolerated intensities) permit it to be applied to patients with varying degrees of functional impairment.

Studies 3 and 4 were concerned primarily with examining some of the factors that may contribute to exercise intolerance in patients with COPD. In healthy older individuals, maximal calf blood flow (CBF) is significantly correlated with peak oxygen uptake (\dot{V}_{O_2} peak), suggesting that the ability to regulate blood flow may be a limiting factor to exercise capacity in these individuals (Snell et al., 1987; Martin et al., 1991). In patients with COPD, a reduction in \dot{V}_{O_2} peak secondary to a decline in physical activity, may also be accompanied by a loss in the maximal ability of the peripheral vasculature to increase muscle blood flow. Thus, the purpose of Study 3 was to examine the relationship between exercise capacity and peak CBF responses in patients with moderate COPD compared to healthy age-matched control subjects. The results of this study demonstrated that peak hyperemic CBF and peak conductance, measured via venous occlusion plethysmography, was not significantly different between COPD patients and healthy control subjects. Moreover, \dot{V}_{O_2} peak was significantly correlated with peak calf blood flow and peak conductance in the control group but not in the COPD group. The results suggest that the loss of exercise capacity in patients

with moderate COPD cannot be attributed to an impairment in vasodilatory capacity of the lower limbs.

In healthy individuals, high-intensity exercise (above the blood lactate threshold, BLT) is associated with the development of a slow component of \dot{V}_{O_2} (Gaesser and Poole, 1996). Since the progressive increase in \dot{V}_{O_2} over time during constant-load exercise has the potential of driving \dot{V}_{O_2} to maximum values, the \dot{V}_{O_2} slow component has been implicated in the fatigue process by potentially limiting the capacity for prolonged activity at high work intensities. There is currently no information addressing \dot{V}_{O_2} kinetics in COPD patients for exercise intensities performed above the BLT, where a slow component of \dot{V}_{O_2} is usually evident. Thus, the purpose of Study 4 was to compare the dynamic changes in \dot{V}_{O_2} (kinetics) observed at the onset of high-intensity constant-load exercise in COPD patients and healthy age-matched control subjects. This study demonstrated that most patients with COPD were able to exercise at intensities high enough to elicit a \dot{V}_{O_2} slow component.

An interesting finding in Study 4 was the significant positive correlation between the slow component amplitude and the degree of dynamic hyperinflation observed in patients with COPD. Although the slow component is known to arise primarily from within the working muscle (Poole et al., 1991), the work of breathing has also been implicated in its development (Carra et al., 2003). Thus, the increased work of breathing may contribute more to the slow component in patients with COPD than in healthy individuals. Another interesting result is that while a slow component of \dot{V}_{O_2} was observed in the majority of subjects in Study

4, the opposite result was reported in Study 2. There is no clear explanation for the discrepancy in these findings and further work characterising the \dot{V}_{O_2} kinetic response during high-intensity exercise in patients with COPD is warranted.

REFERENCES

- Carra, J., R. Candau, S. Keslacy, F. Giolbas, F. Borrani, G. P. Millet, A. Varray and M. Ramonatxo (2003). Addition of inspiratory resistance increases the amplitude of the slow component of O₂ uptake kinetics. *J Appl Physiol.* 94: 2448-2455.
- Coppoolse, R., A. M. W. J. Schols, E. M. Baarends, R. Mostert, M. A. Akkermans, P. P. Janssen and E. F. M. Wouters (1999). Interval versus continuous training in patients with severe COPD: a randomized clinical trial. *Eur Respir J.* 14: 258-263.
- Gaesser, G. A. and D. C. Poole (1996). The slow component of oxygen uptake kinetics in humans. *Exerc Sport Sci Rev.* 24: 35-70.
- Koplan, J. P. (2000). Healthy Aging.
http://www.cdc.gov/nccdphp/aag/aag_aging.htm
- Martin, W. H., T. Ogawa, W. M. Kohrt, M. T. Malley, E. Korte, P. S. Kieffer and K. B. Schechtman (1991). Effects of aging, gender, and physical training on peripheral vascular function. *Circulation.* 84: 654-664.
- Pedersen, B. K. and B. Saltin (2006). Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports.* 16 (Suppl 1): 3-63.
- Poole, D. C., W. Schaffartzik, D. R. Knight, T. Derion, B. Kennedy, H. J. Guy, R. Prediletto and P. D. Wagner (1991). Contribution of exercising legs to the slow component of oxygen uptake kinetics in humans. *J Appl Physiol.* 71: 1245-1253.
- Snell, P. G., W. H. Martin, J. C. Buckley and C. G. Blomqvist (1987). Maximal vascular leg conductance in trained and untrained men. *J Appl Physiol.* 62: 606-610.

Troosters, T., R. Casaburi, R. Gosselink and D. Decramer (2005). Pulmonary rehabilitation in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 172: 19-38.

Vogiatzis, I., S. Nanas and C. Roussos (2002). Interval training as an alternative modality to continuous exercise in patients with COPD. *Eur Respir J.* 20: 12-19.

Vogiatzis, I., G. Terzis, S. Nanas, G. Stratakos, D. C. M. Simoes, O. Georgiadou, S. Zakyntinos and C. Roussos (2005). Skeletal muscle adaptations to interval training in patients with advanced COPD. *Chest.* 128: 3838-3845.

ABBREVIATED TERMS

BLT	Blood lactate threshold
CBF	Calf Blood Flow
CE	Continuous exercise
COPD	Chronic obstructive pulmonary disease
IE	Intermittent exercise
\dot{V}_{O_2}	Oxygen uptake

[Blank Page]

**A
P
P
E
N
D
I
X
A**

Sample Information Sheet and Consent Form

[Blank Page]



SUBJECT INFORMATION SHEET AND CONSENT FORM

Chief Investigators: **Dr Norman Morris**
School of Physiotherapy and Exercise Science
Tel: 07 5552 8921

Professor Lewis Adams
School of Physiotherapy and Exercise Science
Tel: 07 5552 8992

Associate Investigator: **Surendran Sabapathy**
School of Physiotherapy and Exercise Science
Tel: 07 5552 8281
E-mail: S.Sabapathy@griffith.edu.au

Project title

Efficacy of intermittent and continuous exercise training in individuals with COPD.

Purpose of the study

Thank you for volunteering to participate. The purpose of this study is to examine the optimal and safest method of exercise training for individuals with chronic obstructive pulmonary disease (COPD).

Duration of involvement

Your total involvement will be approximately 12 weeks. The training study will be conducted in the Physiology of Exercise Laboratory, located within the School of Physiotherapy and Exercise Science at Griffith University's Gold Coast campus.

Description of study

On commencing the study, you will be familiarised with the procedures being undertaken in the experiment including a maximal exercise test to determine peak oxygen uptake and submaximal exercise tests (see brief description of procedures). Your first visit to the School of Physiotherapy and Exercise Science will allow us to explain and familiarise you with the purpose and procedures that will be used during the experiment. We will also take a full medical history and ask you to perform a lung function assessment. At the completion of the

familiarisation session, and when you are satisfied that you wish to participate in the study, you will be asked to sign an informed consent form. During this period, and throughout the experiment, you will be able to ask questions on any of the procedures to be performed. Following this visit, and once you have agreed to participate in the study, you will complete a maximal exercise test (see brief description of procedures) to determine your exercise capacity on an agreed day. A specialist physician will conduct a medical examination (note that there will be no cost to you for the medical examination) prior to the test and monitor your progress throughout the test.

Individuals that fit within our selection criteria will then be invited to participate in the training program. Prior to commencing the training program participants will be required to visit the laboratory on four separate occasions. During the first of these visits, the maximal exercise test will be repeated; in the subsequent visits, participants will be asked to perform submaximal exercise tests on a cycle ergometer as well as 6-minute walk tests.

Brief description of experimental procedures

- The **maximal exercise test** to determine exercise capacity and peak oxygen uptake will be conducted on a stationary cycle. A doctor will monitor your heart rate and your blood pressure throughout the test. During the maximal exercise test you will breathe through a sterilised 'scuba type' mouthpiece to enable us to collect the air that you breathe out. The test will take approximately 12 minutes. The pedal resistance of the bike will be gradually increased throughout the test and you will be encouraged to cycle for as long as you can. The test will be stopped if you are in discomfort, or when you are unable to maintain a cycling cadence of 40 rpm or if the doctor indicates that the test should be terminated.
- The **submaximal exercise test** will last approximately 10 minutes and during this test you will again breathe through a sterilised 'scuba type' mouthpiece to enable us to collect the air that you breathe out. During the test you will cycle at a submaximal load (around 70% of your maximum). Your heart rate and blood pressure will be measured as in the incremental exercise test. Blood samples may be taken prior to and immediately following the submaximal exercise test. Blood samples will be taken by a registered nurse, a medical practitioner, or an individual certified to perform venipuncture under sterile conditions. Prior to the

commencement of the exercise test, a catheter will be inserted into your forearm under sterile conditions. The risks and benefits of this procedure will be re-explained and you can refuse this or any other procedure at any time. When the catheter is introduced you will feel a moment of discomfort. The catheter will be taped into place to prevent movement during the exercise test. Following exercise, the catheter will be removed and the site dressed. In total approximately 10mL of blood will be taken before and after the test.

- The **6-minute walk test** will involve you walking around a prescribed circuit for the duration of 6 minutes. The purpose of this test is to assess the maximum distance that you can walk in 6 minutes at a self-selected pace.
- At the end of the assessment period (pre-training tests), you will be given a questionnaire (**St. George's Hospital Respiratory Questionnaire**) to take home. You are asked to complete this questionnaire and return it when you attend your first training session.
- Once the pre-training tests are completed, you will participate in **8 weeks of exercise training** involving either 30 minutes of continuous exercise or 60 minutes of intermittent exercise (1-minute exercise and 1-minute rest intervals). The exercise training sessions will be held 3 times per week and the training intensity will be approximately 50% of that achieved during the maximal exercise test. The training intensity will be gradually increased over the 8-week period. During each training session your heart rate and rhythm, and blood pressure will be continuously monitored.
- At the end of the training program, you will be required to repeat the pre-training tests and complete another questionnaire.

Foreseeable Risks

There is minimal risk of misadventure during supervised exercise sessions. The American College of Sports Medicine indicates that the mortality rate associated with maximal exercise testing in a clinical population is approximately 1 per 20,000 exercise tests (American College of Sports Medicine, 1995). To minimise the potential risk associated with a maximal exercise test, each test will be conducted in a fully equipped stress-testing laboratory and be directly supervised

by a specialist physician. The fully equipped stress-testing laboratory at Griffith University is benchmarked to the Accident and Emergency Department of Pindara Hospital.

The procedures used during the exercise test present only minimal risks. To our knowledge, there are no risks associated with sub-maximal exercise testing with no deaths or serious medical complications reported (American College of Sports Medicine, 1995). All exercise training sessions will be directly supervised.

Benefits

The benefits to you for participation in the study are that you will receive a detailed medical examination and assessment of your physical work capacity. You may also improve your fitness levels and health as a result of following the exercise program, although no guarantee of this is made by any of the investigators. A specialist physician will conduct the medical examination. All exercise tests will be conducted by an experienced exercise physiologist. An experienced exercise physiologist will also supervise all exercise training sessions.

Confidentiality

Your involvement in the present study will be strictly confidential. Only you and the chief investigators will have access to your results. In addition, data will be coded on the computer, so that the identity of each participant remains confidential.

Voluntary participation

Your participation in the study is on a purely voluntary basis. You may withdraw from the study at any point without penalty. We encourage you to ask questions at any time during the study. This will enable you to gain a better understanding of your health and of your exercise testing and training response.

Feedback

You will receive information in regard to your health status and exercise performance during each of your visits to the department. In addition, at the

conclusion of the study a morning tea will be held where you will receive a detailed report of your performance.

Complaints mechanism

If participants have any complaints concerning the manner in which a research project is conducted, this may be given directly to the researcher or the following independent parties:

- The University's Research Ethics Officer, Office for Research, Bray Centre, Griffith University, Kessels Road, Nathan, Qld 4111, telephone (07) 3875 6618; or
- The Pro Vice-Chancellor (Administration), Bray Centre, Griffith University, Kessels Road, Nathan, Qld 4111, telephone (07) 3875 7343

Finally, our thanks

On behalf of all the staff in the School of Physiotherapy and Exercise Science, we would like to thank you for participating in the research we are conducting at Griffith University.

PARTICIPANT'S COPY

Consent Form

I agree to participate in the project '**Efficacy of intermittent and continuous exercise training in individuals with COPD**' being conducted Dr Norman Morris and give my consent freely. I understand that the project/study will be carried out as described in the information sheet, a copy of which I have retained. I realise that whether or not I decide to participate is my decision and will not affect my continued association with Griffith University or the School of Physiotherapy and Exercise Science. I also realise that I can withdraw from the project '**Efficacy of intermittent and continuous exercise training in individuals with COPD**' at any time, and that I do not have to give any reasons for withdrawing. I have had all questions answered to my satisfaction.

Signatures:

Participant

Date

Investigator(s)

Date

INVESTIGATOR'S COPY

Consent Form

I agree to participate in the project **'Efficacy of intermittent and continuous exercise training in individuals with COPD'** being conducted Dr Norman Morris and give my consent freely. I understand that the project/study will be carried out as described in the information sheet, a copy of which I have retained. I realise that whether or not I decide to participate is my decision and will not affect my continued association with Griffith University or the School of Physiotherapy and Exercise Science. I also realise that I can withdraw from the project **'Efficacy of intermittent and continuous exercise training in individuals with COPD'** at any time, and that I do not have to give any reasons for withdrawing. I have had all questions answered to my satisfaction.

Signatures:

Participant

Date

Investigator(s)

Date

[Blank Page]

**A
P
P
E
N
D
I
X
B**

Medical History Questionnaire

[Blank Page]

MEDICAL HISTORY QUESTIONNAIRE

Name: _____

Address: _____

Phone: () _____ (W)

Phone: () _____ (H)

Age: _____

DOB: _____

Please read the following questions very carefully. If you have any difficulty please advise the medical practitioner.

1. **Family history.** Indicate if any of your immediate family (parents, brothers, sisters, grandparents) has experienced any of the following, the age at which diagnosis occurred, and the person's relationship to you.

Relationship & Age

High Blood Pressure _____

High Cholesterol _____

Heart Disease _____

Stroke _____

Diabetes _____

Cancer _____

2. **Personal medical history.** Indicate symptoms that apply to you.

- Pain or discomfort in chest following exercise, eating or exposure to cold
- Frequent heart palpitations or flutter
- Pain in lower lungs when walking or climbing stairs
- Unusual shortness of breath
- Very poor exercise tolerance
- Frequent dizziness
- Chronic cough
- Frequent colds or flu
- Frequent headaches
- Frequent aches or pains in joints
- Frequent backache
- Other current symptoms that exercise may affect

3. Are you presently experiencing, or have you ever been treated by a doctor for any of the following?

Allergies: Hay fever, eczema, other rashes.

Yes

No

Details _____

4. **Lung problems**

(Asthma/Emphysema/Bronchitis/Shortness of Breath/Other)

Yes

No

Details _____

5. **Heart problems** (Rheumatic fever/Chest pains/Palpitations/Ankle swelling/Other)

Yes

No

Details _____

6. **Blood pressure problems**

Yes

No

Details _____

7. **Cholesterol problems**

Yes

No

Details _____

8. **Gut problems** (Ulcer/Abdominal pain/Diarrhoea/Constipation/Hernia/Other)

Yes

No

Details _____

9. **Unexplained weight loss**

Yes

No

Details _____

10. **Urinary problems** (Burning/Difficulty with control of urine)

Yes

No

Details _____

11. **Blood loss** (In Vomit/Sputum/Bowel action/Urine)

Yes

No

Details _____

12. **Easy bruising**

- Yes
- No

Details _____

13. **Endocrine problems** (Diabetes/Thyroid/Other)

- Yes
- No

Details _____

14. **Fitting, fainting, blackouts, loss of consciousness, muscle weakness, loss of sensation.**

- Yes
- No

Details _____

15. **Headaches**

- Yes
- No

Details _____

16. **Sight or hearing problems**

- Yes
- No

Details _____

17. **Nervous conditions**

- Yes
- No

Details _____

18. **Bone or joint injury**

(Back/Knee/Ankle/Hip/Shoulders)

- Yes
- No

Details _____

19. **Other joint problems**

- Yes
- No

Details _____

20. **Work related injuries**

- Yes
- No

Details _____

21. **Are you exposed to a noisy or dusty environment?**

- Yes
- No

Details _____

22. **How often do you take over the counter medications such as aspirin, etc?**

- Daily
- Weekly
- Occasionally
- Never

23. **Medication.** Are you taking any medication prescribed by your Doctor or other Health Care provider? If so, list details, i.e., type of drugs, dosage.

24. **Sleeping patterns.** How many hours do you sleep on average per night?

_____ hours

25. Do you ever have trouble falling asleep?

- Yes
- No
- Occasionally

26. **Smoking status**

- Never smoked
- Quit smoking more than ten years
- Quit smoking less than ten years
- Currently smoke (number of years _____)

27. If currently smoking, how many cigarettes do you currently smoke per day?

28. **Physical activity.** How many times per week do you exercise for at least 20-30 minutes continuously?

- Do not have a regular program
- Once per week
- 2-3 times per week
- 4-5 times per week
- more than 5 times per week

29. **Alcohol consumption.** In the past two weeks list how many days you consumed an alcoholic beverage.

- Did not drink in the past 6 months
- Did not drink in the past 2 weeks
- 1-2 days
- 3-4 days
- 5-7 days
- 8-10 days
- 11-14 days

30. In the past two weeks list how many drinks on average you had per day.

- Did not drink in the past 6 months
- Did not drink in the past 2 weeks
- 1 drink
- 2-3 drinks
- 4-6 drinks
- 7 or more drinks

**A
P
P
E
N
D
I
X
C**

**St. George's Hospital Respiratory Questionnaire
(SGRQ) & General Scoring Information**

St. George's Hospital Respiratory Questionnaire
Dr. Paul W. Jones, Division of Physiological Medicine,
Department of Medicine, St. George's Hospital Medical School
All Rights Reserved
Reproduced with permission of the Medical Outcomes Trust

[Blank Page]

THE ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand any thing. Do not spend too long deciding about your answers.

Name: _____

Age: _____

Sex: Male / Female

I.D. no.: _____

Date: _____

PART 1

QUESTIONS ABOUT HOW MUCH CHEST TROUBLE YOU HAVE HAD OVER THE LAST YEAR. PLEASE TICK IN ONE BOX FOR EACH QUESTION.

	Most days a week	Several days a week	A few days a month	Only with chest infections	Not at all
1) Over the last year, I have coughed:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2) Over the last year, I have brought up phlegm (sputum):	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3) Over the last year, I have had shortness of breath:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4) Over the last year, I have had attacks of wheezing:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5) During the last year, how many severe or very unpleasant attacks of chest trouble have you had:					
			More than 3 attacks	<input type="checkbox"/>	
			3 attacks	<input type="checkbox"/>	
			2 attacks	<input type="checkbox"/>	
			1 attack	<input type="checkbox"/>	
			No attacks	<input type="checkbox"/>	
6) How long did the worst attack of chest trouble last: (Go to Question 7 if you had no severe attacks)					
			A week or more	<input type="checkbox"/>	
			3 or more days	<input type="checkbox"/>	
			1 or 2 days	<input type="checkbox"/>	
			Less than a day	<input type="checkbox"/>	
7) Over the last year, in an average week, how many good days (with little chest trouble) have you had:					
			No good days	<input type="checkbox"/>	
			1 or 2 good days	<input type="checkbox"/>	
			3 or 4 good days	<input type="checkbox"/>	
			Nearly every day is good.	<input type="checkbox"/>	
8) If you have a wheeze, is it worse in the morning:					
			No	<input type="checkbox"/>	
			Yes	<input type="checkbox"/>	

PART 2**SECTION 1:**

HOW WOULD YOU DESCRIBE YOUR CHEST CONDITION? (PLEASE TICK ONE BOX ONLY)

- The most important problem I have
- Causes me quite a lot of problems
- Causes me a few problems
- Causes no problems

IF YOU HAVE EVER HAD PAID EMPLOYMENT, PLEASE TICK ONE OF THESE:

- My chest trouble made me stop work altogether
- My chest trouble interferes with my work or made me change my work
- My chest trouble does not affect my work

SECTION 2: QUESTIONS ABOUT WHAT ACTIVITIES USUALLY MAKE YOU FEEL BREATHLESS THESE DAYS. FOR EACH ITEM, PLEASE TICK IN THE BOX FOR EITHER TRUE OR FALSE AS IT APPLIES TO YOU.

- | | | | | |
|------------------------------------|--------------------------|------|--------------------------|-------|
| Sitting or lying still | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| Getting washed or dressed | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| Walking around the house | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| Walking outside on the level | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| Walking up hills | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| Playing sports or games | <input type="checkbox"/> | True | <input type="checkbox"/> | False |

SECTION 3: SOME MORE QUESTIONS ABOUT YOUR COUGH AND BREATHLESSNESS THESE DAYS. FOR EACH ITEM, PLEASE TICK IN THE BOX FOR EITHER TRUE OR FALSE AS IT APPLIES TO YOU.

- | | | | | |
|---|--------------------------|------|--------------------------|-------|
| My cough hurts | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| My cough makes me tired | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| I am breathless when I talk | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| I am breathless when I bend over | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| My cough or breathing disturbs my sleep | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| I get exhausted easily | <input type="checkbox"/> | True | <input type="checkbox"/> | False |

SECTION 4: QUESTIONS ABOUT OTHER EFFECTS THAT YOUR CHEST TROUBLE MAY HAVE ON YOU THESE DAYS. FOR EACH ITEM, PLEASE TICK IN THE BOX FOR EITHER TRUE OR FALSE AS IT APPLIES TO YOU.

- | | | | | |
|--|--------------------------|------|--------------------------|-------|
| My cough or breathing is embarrassing in public | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| My chest trouble is a nuisance to my family, friends or neighbours | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| I get afraid or panic when I cannot get my breath | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| I feel that I am not in control of my chest problem | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| I do not expect my chest to get any better | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| I have become frail or invalid because of my chest | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| Exercise is not safe for me | <input type="checkbox"/> | True | <input type="checkbox"/> | False |
| Everything seems too much of an effort | <input type="checkbox"/> | True | <input type="checkbox"/> | False |

SECTION 5: QUESTIONS ABOUT YOUR MEDICATION. IF YOU ARE RECEIVING NO MEDICATION GO STRAIGHT TO SECTION 6. TO COMPLETE THIS SECTION PLEASE TICK IN THE BOX FOR EITHER TRUE OR FALSE AS IT APPLIES TO YOU.

- My medication does not help me very much True False
- I get embarrassed using my medication in public True False
- I have unpleasant effects from my medication True False
- My medication interfere with my life a lot True False

SECTION 6: THESE ARE QUESTIONS ABOUT HOW YOUR ACTIVITIES MIGHT BE AFFECTED BY YOUR BREATHING. FOR EACH QUESTION, PLEASE TICK TRUE IF ONE OR MORE OF THE PARTS OF THE QUESTION APPLIES TO YOU BECAUSE OF YOUR BREATHING. OTHERWISE TICK FALSE.

- I take a long time to get washed or dressed True False
- I cannot take a bath or shower, or I take a long time True False
- I walk slower than other people, or I stop for rests True False
- Jobs such as housework take a long time, or I have to stop for rests True False
- If I walk up one flight of stairs, I have to go slowly or stop True False
- If I hurry or walk fast, I have to stop or slow down True False

My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf True False

My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim True False

My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports .. True False

SECTION 7: WE WOULD LIKE TO KNOW HOW YOUR CHEST TROUBLE USUALLY AFFECTS YOUR DAILY LIFE. PLEASE TICK EITHER TRUE OR FALSE (REMEMBER THAT TRUE ONLY APPLIES TO YOU IF YOU CANNOT DO SOMETHING BECAUSE OF YOUR BREATHING)

- I cannot play sports or games True False
- I cannot go out for entertainment or recreation True False
- I cannot go out of the house to do the shopping True False
- I cannot do housework True False
- I cannot move far from my bed or chair True False

HERE IS A LIST OF OTHER ACTIVITIES THAT YOUR CHEST TROUBLE MAY PREVENT YOU DOING (YOU DO NOT HAVE TO TICK THESE, THEY ARE JUST TO REMIND YOU OF WAYS IN WHICH YOUR BREATHLESSNESS MAY AFFECT YOU):

- Going for walks or walking the dog
- Doing things at home or in the garden
- Sexual intercourse
- Going out to church, or place of entertainment
- Going out in bad weather or into smoky rooms
- Visiting family or friends or playing with children

PLEASE WRITE IN ANY OTHER IMPORTANT ACTIVITIES THAT YOUR CHEST TROUBLE MAY STOP YOU DOING:

NOW, WOULD YOU TICK IN THE BOX (ONE ONLY) WHICH YOU THINK BEST DESCRIBES HOW YOUR CHEST AFFECTS YOU:

- It does not stop me doing anything I would like to do
- It stops me doing one or two things I would like to do
- It stops me doing most of the things I would like to do
- It stops me doing everything I would like to do

THE ST. GEORGE'S HOSPITAL RESPIRATORY QUESTIONNAIRE

GENERAL SCORING INFORMATION

SUMMARY

Three component scores are calculated: **Symptoms; Activity; Impacts.**

One **Total** score is also calculated.

PRINCIPLE OF CALCULATION

Each questionnaire response has a unique empirically derived 'weight'. The lowest possible weight is zero and the highest is 100. For each component the weights for all positive responses are summed. The score is calculated by dividing the summed weights by the maximum possible score for that component and expressing the results as a percentage.

SYMPTOMS

This consists of all the questions in Part 1. The weights for Questions 1-8 are summed. It will be noted that the questionnaire requests a single response to Questions 1-7. If multiple responses are given to a question then averaging the weights for the positive responses for that question is acceptable.

The maximum possible score is 662.5.

ACTIVITY

This is calculated from the summed weights for the positive responses to Section 2 and Section 6 in Part 2 of the questionnaire.

The maximum possible score is 1209.1.

IMPACTS

This is calculated from Sections 1, 3, 5 and 7. Again it will be noted from the questionnaire that a single response is required from the two parts of Section 1 and the last part of Section 7. If multiple responses are given to a question, then averaging the weights for the positive responses for that question is acceptable.

The maximum possible score is 2117.8.

TOTAL

The Total score is calculated by summing all the positive responses in the questionnaire and expressing the result as a percentage of the maximum possible score for the entire questionnaire.

The maximum possible score is 3989.4.

[Blank Page]