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ENDURANCE EXERCISE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

by

SUSAN M. REVILL

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy of the Loughborough University of Technology

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ABSTRACT

The series of experiments described in this thesis examine two relatively unexplored aspects of the exercise response in patients with chronic obstructive pulmonary disease (COPD), namely respiratory muscle performance and whole body endurance exercise.

Incremental threshold loading (ITL) was used to examine respiratory muscle performance. The technique imposes a threshold load to inspiration which must be overcome prior to the onset of airflow. An electronic solenoid valve was used to impose standardised increments in threshold load in 12 patients with moderately severe COPD. The peak mouth pressure (peak Pm) and pressure-time product ($\int$Pdt) were assessed and found to be repeatable after one practice test (mean differences (SE) between tests were 0.4 (2.3) cm H_2O, and 110 (201) $cmH_2O.s^{-1}$ respectively). Using the solenoid valve, ITL was quick and simple to perform and acceptable to the majority of patients.

The respiratory muscle performance was reduced in the patients examined, and though the external work achieved was repeatable (i.e. peak Pm and $\int$Pdt) the internal work, reflected by the cardio-respiratory response to the test, was more variable. The $\dot{V}O_2$ and $\dot{V}_E$ attained at peak Pm were (mean (SD)) 367 (65) $ml.min^{-1}$ and 24.2 (6.2) $l.min^{-1}$ respectively. The ITL provoked a small increase in blood lactate concentration (mean increase 0.32 (0.21) and 0.15 (0.24) $mmol.l^{-1}$, at 2 and 4 min post test).

The ITL was compared to treadmill exercise in the same group of patients. The oxygen cost of the ITL test was high and equated to 30% of the $\dot{V}O_{2peak}$, whilst the ITL blood lactate response equated to 40% of the whole body response. There was a significant relationship between peak Pm and treadmill exercise ventilation ($r=0.702$, $p<0.025$). This relationship improved following a bronchodilator, as did the exercise ventilation and $\dot{V}O_2$ (during both ITL and whole body exercise). However, there were no significant improvements in the external work achieved (treadmill time, peak threshold load or shuttle distance walked). This suggested factors additional to the ventilatory limit were important in the exercise limitation in COPD e.g. deconditioning. This finding, in addition to the improved relationship between the components of the exercise response (respiratory muscle performance and exercise ventilation), suggested exercise training could be introduced to maximise the bronchodilator changes and address the possibility of deconditioning.

In order to assess the effects of exercise training in COPD, a standardised field test for the assessment of endurance capacity was developed. The test was complementary to the incremental shuttle walk test (ISWT), incorporating a 10 m shuttle circuit, and an audio-signal to control pace. The exercise intensity was determined from the individual maximal performance achieved during the ISWT. The endurance field test performance was assessed in 10 patients with COPD at 3 levels of exercise intensity, which related to 75%, 85% and 95% of the $\dot{V}O_{2peak}$ predicted from the ISWT. The endurance field test performance was compared to the laboratory assessment of endurance, and was found to provoke similar heart rate responses and subjective ratings of breathlessness and exertion.

The field test was repeatable after one practice walk (mean difference (SE) 15 (6) s, between tests 2 and 3). To assess the sensitivity of the test, and the effects of an intervention, 19 patients with COPD underwent a course of pulmonary rehabilitation. Endurance capacity was not significantly different at the start and end of a 5 week control period (mean difference(SE) 4 (10) s), however following rehabilitation there were substantial improvements in endurance capacity (419(71)s,160% improvement).

The endurance shuttle walk test was simple to perform, and possessed good repeatability and sensitivity to the therapeutic intervention. The test was complementary to the incremental shuttle test and did not involve additional resources, apart from a set of pre-recorded cassette tapes. The intensity of the endurance exercise was easily determined from the $\dot{V}O_{2peak}$ predicted from the ISWT.

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Finally, my thanks go to the patients who willingly gave their time and effort participating in all of the studies.

PUBLICATIONS

Unless otherwise acknowledged or referenced to the published literature the work reported in this thesis is that of the author. Parts of the work have been reported in the following publications:-

1) The effect of ipratropium bromide on the shuttle walk test. SM Revill, MDL Morgan, AE Hardman. Eur Respir J 1994; 7: 324s.

2) Metabolic and cardio-respiratory responses to inspiratory threshold loading in COPD. SM Revill, MDL Morgan, AE Hardman. Thorax 1995; 50: 440P.

3) Incremental threshold loading and maximal systemic exercise in chronic airflow limitation. SM Revill, MDL Morgan. Am Rev Respir Dis 1995; 151: A573.

4) The effect of bronchodilation on maximal systemic exercise capacity and inspiratory threshold loading in chronic airflow limitation. SM Revill, MDL Morgan. Am Rev Respir Dis 1995; 151: A573.

5) A shuttle walking test to assess endurance capacity in patients with chronic airflow limitation. SM Revill, MDL Morgan, AE Hardman. Thorax 1995; 50 (Suppl 2): S30.

6) A paced field test of endurance capacity for patients with chronic obstructive pulmonary disease (COPD). SM Revill, MDL Morgan, AE Hardman. Eur Respir J 1996; 9 (Suppl 23): 388s (P2429).

7) Variability in the cardio-respiratory response to three levels of treadmill endurance exercise in patients with chronic obstructive pulmonary disease (COPD). SM Revill, MDL Morgan, AE Hardman. Eur Respir J 1996; 9 (Suppl 23): 388s (P2430).

8) A comparison of the cardio-respiratory effects of incremental and endurance exercise in COPD. SM Revill, MDL Morgan, AE Hardman. Am J Respir Crit Care Med 1997; 155 (4): A598.

9) Evaluation of walking endurance in COPD: Use of a standardised endurance shuttle field test. SM Revill, SJ Singh, MDL Morgan. (Abstract accepted for the 1997 European Society congress).

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LIST OF ABBREVIATIONS

BS	Breathlessness score
BTPS	Body temperature and pressure saturated
COPD	Chronic obstructive pulmonary disease
CRDQ	Chronic respiratory disease questionnaire
EELV	End expiratory lung volume
ESWT	Endurance shuttle walk test
fR	Respiratory frequency
FEV_1	Forced expired volume in 1 second
FRC	Functional residual capacity
FVC	Forced vital capacity
HR	Heart rate
ISWT	Incremental shuttle walk test
ITL	Incremental threshold loading
MVV	Maximal voluntary ventilation
MWT	Minute walk test
$PaCO_2$ /O_2	Partial pressure of gas in arterial blood
Pdi	Transdiaphragmatic pressure
$\int Pdt$	Pressure-time product
PEEPi	Intrinsic positive end-expiratory pressure
PE_{max}	Maximal expiratory pressure
$P_{ET}CO_2$	End-tidal carbon dioxide
PI_{max}	Maximal inspiratory pressure
Pm	Mouth pressure
P_{oes}	Oesphageal pressure
RER	Respiratory exchange ratio
STPD	Standard temperature and pressure dry
Ti	Inspiratory time
TLC	Total lung capacity
T_{lim}	Time to fatigue
TT_{DI}	Tension-time index
T_{Tot}	Duration of breathing cycle

TV	Tidal volume
$\dot{V}CO_2$	Carbon dioxide production
Vd/Vt	Deadspace to tidal volume ratio
$\dot{V}_E$	Ventilation
$\dot{V}O_2$	Oxygen consumption
$\dot{V}/\dot{Q}$	Ventilation/perfusion

Chapter 1

INTRODUCTION

The series of studies reported in this thesis are concerned with two important, though relatively neglected, aspects of the exercise response in chronic obstructive pulmonary disease (COPD), namely respiratory muscle performance and whole body endurance exercise. Exercise performance and respiratory muscle function are affected adversely by COPD, thus objective assessment which is sensitive and reliable is important for the evaluation of disability and for monitoring disease progression. Both respiratory muscle performance and the whole body endurance response in COPD are still poorly understood, therefore additional physiological characterisation and the development of new assessment methods will assist in the application of appropriate and effective treatment regimens.

Dynamic hyperinflation of the lungs during exercise is common in patients with moderate and severe COPD (Gibson 1996) and imposes an additional burden on the respiratory muscles. Changes in dynamic hyperinflation (assessed from changes in end-inspiratory lung volume) were found to be important determinants of exercise breathlessness in patients with moderate to severe COPD (O'Donnell 1993, Belman 1996). Thus the response of the respiratory muscles may constitute an important component of the whole body exercise response in COPD. Decramer (1994) suggests respiratory muscle endurance may have a significant role in the ventilatory limitation during exercise. Since many existing pharmacological and exercise training interventions have the potential to affect both respiratory muscle and whole body exercise performance, suitable objective measurements, which possess specificity and sensitivity to change, are important in the assessment and clinical management of patients with COPD.

Assessment of how the respiratory muscles respond to an additional inspiratory load, similar to that encountered from dynamic hyperinflation during exercise, is desirable. A simple and reliable test to enable the

objective measurement of dynamic performance would help establish the degree of impairment, monitor disease progression and assess therapeutic intervention. The technique of incremental threshold loading (ITL) provides the opportunity to determine respiratory muscle strength and endurance, under dynamic conditions, in response to standardised increments in respiratory muscle work rate. The standardised, incremental nature of the applied work rate is analogous to an incremental and progressive whole body exercise test. As such, ITL would also allow the examination of the cardio-respiratory and metabolic responses to the respiratory exercise.

The first two experimental chapters of this thesis examine ITL in a group of patients with COPD. The threshold load was imposed by a recently developed electronic solenoid device. The fundamental questions examined by the study were: 1) can the solenoid valve device provide a simple, repeatable and well tolerated method of assessing respiratory muscle performance in patients with COPD? 2) How do the measurements of ITL relate to other, more conventional measures of exercise performance? 3) can the measurement of respiratory muscle performance reflect changes associated with a common therapeutic intervention used in this patient group?

The first study describes the use of ITL in a group of patients with moderate to severe COPD. In addition to the descriptive purpose of the study, the aims were to quantify the repeatability of the test, and determine the cardio-respiratory and metabolic response to the task. The clinical relevance of ITL is largely unclear. How it relates to other tests of physical performance and measures of functional capacity is therefore important in understanding the measurement and its appropriate clinical application. Additionally, the sensitivity of the test is important, since any measurement which proves insensitive to change will have limited application. In order to address these two issues, the group of patients from the first part of the study performed additional tests of whole body exercise, and repeated all tests following a single dose of an inhaled bronchodilator. The study was carried out in a

double-blind, randomised, cross-over manner with nebulised placebo and ipratropium bromide. The purpose of the second part of the study was to examine how ITL related to conventional measurements of whole body exercise performance, and to determine the test sensitivity to the intervention of an inhaled bronchodilator.

The intervention of the inhaled bronchodilator revealed two important changes in the exercise response of this patient group, namely a closer coupling of events contributing to the exercise performance, i.e. respiratory muscle performance and exercise ventilation, and increases in the exercise ventilatory capacity during both the whole body and respiratory muscle exercise (ITL). However these improvements were not accompanied by any significant increases in the peak exercise work rates. The finding that isolated improvements in the ventilatory capacity do not lead to improvements in the exercise capacity of patients with COPD, suggested other therapeutic interventions, such as exercise training, could be introduced in order to maximise these improvements. In addition, the oxygen cost of the ITL test was found to constitute a large proportion of the maximum oxygen consumption in this patient group, which emphasised the need to introduce treatment strategies to optimise energy efficiency during physical exertion. The results of the second study therefore suggested additional investigations of the whole body exercise response and the role of exercise training in COPD. Thus the remaining experimental chapters of the thesis examine whole body endurance capacity in COPD, with the development of a standardised field test of walking endurance and an examination of the effects of an exercise training intervention (pulmonary rehabilitation) in this patient group.

Field based walking tests are popular assessment methods of exercise performance in COPD. The 12 and 6 minute walking tests (McGavin 1976, Butland 1982) are self-paced and measure the distance covered in a prescribed time. Recently a standardised, incremental and externally paced field walking test has been described (Singh 1992). Although limited in the

amount of physiological information which may be collected, field tests have a number of advantages which make them attractive as an alternative, or an adjunct to laboratory based clinical exercise tests. They are quick and simple to perform, and are less costly than laboratory tests requiring only minimal equipment and a single operator. They employ a universal mode of exercise - free walking, and the absence of complex equipment and robust exercise machines make them less daunting for the patient, and free from the apprehension which may lead to under-performance. However there are concerns with the performance of the self-paced field tests. A number of studies have demonstrated the effects of operator encouragement (Guyatt 1984), learning effects from repeat measurement (Knox 1988) and the effects of attitudes and beliefs on performance (Morgan 1983). Additionally the prescribed time limit may influence performance (individual judgement of walking pace) and compromise the nature of the test in reflecting endurance capacity.

The development of the shuttle walking test (Singh 1992) addressed a number of the concerns associated with the self-paced tests. It has a standardised walking pace and clearly defined end-points. It is less variable on repeat testing and requires only one practice walk. The standardised walking pace of the test will act to improve intra- and inter-subject comparison. The work rate is incremental and as such provides a measure of symptom limited maximal exercise capacity. However, a number of studies have demonstrated endurance capacity is particularly sensitive to interventions of both high and low intensity exercise training in COPD (Holle 1988, Niederman 1991, Punzal 1991, Singh 1996). Thus, there existed a strong argument for the development of a standardised, constant-paced field endurance test for the assessment of exercise training interventions in patients with COPD.

The aims of the third and fourth experimental studies were to: 1) develop a standardised, constant-paced, field walking test to assess endurance capacity in patients with COPD; 2) examine the cardio-respiratory and

metabolic responses to different intensities of endurance exercise in COPD; 3) assess the validity of the field test against the laboratory based assessment of endurance capacity. The purpose of the field test developmental study was to design a test which complemented the shuttle walk test, where the maximal performance achieved during the incremental shuttle test would determine the exercise intensity of the endurance field test. Additionally, the new test would be externally paced, utilise the same 10 m shuttle course and use an audio signal to control walking speed. The test would allow endurance capacity to be assessed to a constant walking pace without a prescribed time limit.

In order to explore the cardio-respiratory and metabolic responses to endurance exercise, and assess the validity of the new field test against conventional measures of exercise performance, patients were also required to walk at a constant pace on a treadmill. Three different intensities of exercise were examined, which related to 75%, 85% and 95% of the individual $\dot{V}O_{2peak}$. In comparing the patients performance during the field endurance test against the laboratory based assessment it was possible to reveal if the field test was a valid indicator of endurance capacity.

The final study of the thesis examines an intervention of pulmonary rehabilitation on the endurance capacity in this patient group. Any new test will be of limited value if it lacks sensitivity to change. Therefore the sensitivity of the newly developed field test was examined in a group of patients following a 7 week course of pulmonary rehabilitation. In order to incorporate a control period, patients were recruited 6 to 8 weeks prior to their commencement of the Hospital rehabilitation course, which contained educational and exercise training components. The endurance field test was performed at the start of the control period (no change to usual treatment), and repeated at the start and end of the rehabilitation course. Additionally, the between day repeatability of the test was assessed.

1.1 Organisation of the thesis

There are five experimental chapters in this thesis. The first two chapters examine incremental threshold loading as a measure of respiratory muscle performance in a group of patients with COPD. Chapter 4 describes the technique and the cardio-respiratory and blood lactate response to the test. It also examines the repeatability of the test. Chapter 5 examines how ITL relates to conventional measures of whole body exercise, and the effect of an inhaled bronchodilator on the outcome of the test.

The following experimental studies examine the measurement of whole body endurance exercise in COPD. Chapter 6 describes the development of a standardised field test for the assessment of endurance capacity. In order to describe the cardio-respiratory and metabolic changes associated with endurance exercise in COPD, the same group of patients from the developmental study underwent laboratory assessment of endurance exercise. This also enabled the relationships between the field and treadmill responses to be examined. The results from this study are presented in chapter 7.

Finally, in order to evaluate the sensitivity of the field test to a clinical intervention, and to quantify the short term variability of the test an exercise training study was undertaken. Patients were assessed at the start and end of a control period, and following a 7 week course of pulmonary rehabilitation. The findings of this study are described in chapter 8.

Chapter 2

REVIEW OF THE LITERATURE

2.1 INTRODUCTION

The general aim of this thesis was the development of simple assessment methods to examine two relatively unexplored components of the exercise response in COPD, namely respiratory muscle performance and endurance exercise. One of the principal symptoms of COPD is breathlessness, which increases progressively with disease severity. With increasing dyspnoea, patients tend to avoid exertion and enter into what Young (1983) defines as a 'dyspnoea spiral' where deconditioning occurs as a result of adopting a more sedentary lifestyle. Exercise imposes an additional ventilatory burden to the already compromised respiratory muscle function (Belman 1993) whilst the development of dynamic hyperinflation, during exercise, has been identified as a key determinant of exercise dyspnoea (O'Donnell 1993). Whilst there is increasing interest in the role of the respiratory musculature during exercise, and evidence of deconditioning and peripheral muscle weakness, tests of respiratory muscle performance are poorly understood and not widely applied. Additionally, there is a lack of concensus concerning the most appropriate methods for the assessment of the whole body exercise response and therapeutic interventions, such as pulmonary rehabilitation.

The term COPD covers a spectrum of symptoms and pathological change within the lungs, therefore the first part of this review describes the pathology of the disease. Additionally, the risk factors and aspects of clinical management are considered. A wide range of clinical measurements may be applied in the diagnosis, and assessment of the functional abnormalities arising from the condition. The measurements most relevant to the experimental work of the thesis, namely the assessment of exercise capacity and respiratory muscle performance, will be considered in detail. Throughout this review the rationale for the experimental work will be developed.

2.2 PATHOLOGY

2.2.1 Terminology

Diseases of the chest may be classified into two broad physiological categories: 1) restrictive i.e. restrict lung expansion either as a result of changes to the lung parenchyma or changes to the thoracic cage; 2) obstructive i.e. obstruct airflow as a result of changes to the airways. Within the obstructive classification are three main pathological types, though patients may demonstrate a combination of changes. The major conditions associated with the obstructive classification are asthma, chronic bronchitis and emphysema.

A consensus to adopt a single term to embrace all three conditions does not exist at present. Asthma remains largely distinct whilst chronic obstructive airways disease (COAD), chronic obstructive pulmonary disease (COPD) and chronic obstructive lung disease (COLD) are used synonomously for chronic bronchitis with airflow obstruction and for emphysema. The experimental work contained within this thesis is concerned with the exercise performance of patients with chronic bronchitis with airflow obstruction, and patients with emphysema, and the term COPD is adopted throughout.

2.2.2 Chronic obstructive pulmonary disease

Chronic obstructive bronchitis is primarily a disease of the airways, with changes in the larger airways (> 2 mm in diameter) a predominant feature. Lesions in the small airways (< 2 mm) are increasingly recognised in the early stages of the disease, and are a major feature of mild airflow obstruction. Alternatively, emphysema is considered a disease of the parenchyma (gas exchanging tissue) and is defined as permanent, abnormal enlargement of the airspaces distal to the terminal bronchioles accompanied by destruction of their walls and without obvious fibrosis (American Thoracic Society (ATS) 1995). In most patients with chronic obstructive bronchitis there may be varying degrees of emphysema since

tobacco smoke is the common (though not necessarily the exclusive) trigger to both conditions.

Chronic obstructive bronchitis

The Lancet (Editorial 1965) published a statement from the Medical Research Council outlining the definition and classification of chronic bronchitis based on the outcome of a key symposium in 1958 (Ciba Symposium 1959) and work from the previous decade. The statement included a definition for chronic obstructive bronchitis:- 'chronic bronchitis in which there is persistent, widespread narrowing of the intra-pulmonary airways, at least on expiration, causing increased resistance to airflow'. The term chronic bronchitis is used to denote chronic or recurrent bronchial mucus hypersecretion for 3 months or more in each of two successive years when other causes have been excluded (Editorial 1965). More recent statements from the American Thoracic Society (1995) define COPD as a disease state characterised by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperactivity, and may be partially reversible.

The pathological changes associated with chronic obstructive bronchitis include hypertrophy of the mucus secreting glands mainly in the larger bronchi with increased numbers of mucus secreting cells (goblet cells) within the walls of the gland (Seaton 1989). There is strong evidence the small airways (< 2 mm in diameter) are particularly affected in the early stages of the disease (Thurlbeck 1990). Inflammatory processes are present in the respiratory bronchioles, and there may be varying degrees of mucus plugging, globlet cell metaplasia, increased smooth muscle and fibrotic changes in bronchioles less than 2 mm in diameter. The pathological changes are progressive, and associated with increasing functional impairment.

The concept of small airways disease was described by Hogg (1968) who proposed the bronchioles (or small airways) as the main site of increased airflow resistance. Additionally, lesions within the small airways are believed to be the most important cause of mild chronic airflow obstruction (Thurlbeck 1990). However, Thurlbeck emphasises the lesions that are important in mild airflow obstruction may not be important in patients with severe COPD, and other (rare) forms of bronchiolitis (inflammation of the small airways) are associated with irritants other than tobacco smoke.

The functional consequences of the changes associated with chronic obstructive bronchitis are narrowing of the lumen of the airways due to the excess mucus, and thickening of the airway walls due to enlarged glands, inflammatory oedema and increased amounts of airway smooth muscle. The narrowing of the airways leads to increased airflow resistance thus imposing a greater resistive load to breathing. In addition, the obstructed airways lead to gas trapping and hyperinflated lungs which imposes a greater mechanical load to breathing. Increased airway reactivity may be present in a significant number of patients, Thurlbeck (1990) suggests this may be present in 25% of patients, although estimates vary.

Chronic cough and persistent sputum expectoration are the major features. Most patients have a history of smoking. Sputum is usually mucoid but becomes purulent with an exacerbation. Exacerbations of the disease occur more frequently as the disease progresses, and are associated with increased and purulent sputum, increased cough, wheeze and dyspnoea. In the later stages of the disease increasing dyspnoea is a feature, initially associated with exertion. Hypercapnia may develop with increasingly severe hypoxemia when central cyanosis is apparent. Polycythaemia may be present when there is long standing hypoxaemia. Cor pulmonale with right heart failure and oedema can often develop during an exacerbation or infection, though it may persist and become a chronic feature. There appears to be a spectrum of response to the occurrence of hypoxia, with those most

sensitive developing pulmonary hypertension and right heart failure early on in the disease (Seaton 1989).

Respiratory muscle function is often compromised from a combination of factors including the increased resistive and mechanical loads, changes in muscle configuration as a result of lung hyperinflation, muscle weakness from malnutrition and possibly, in some cases, muscle fatigue (Rochester 1991). Airway resistance is elevated in both inspiration and expiration. The expiratory airflow limitation causes airtrapping and is responsible for most of the hyperinflation. Rochester (1991) notes both residual volume (RV) and functional residual capacity (FRC) are often markedly increased (e.g. to 70% and 85% of predicted total lung capacity (TLC) respectively), thus patients breathe at much higher lung volumes than healthy individuals, where FRC is more usually < 50% of TLC. The forced expiratory volume in one second (FEV_1) is reduced as a result of the narrowed airways and increased resistance, the reduction increasing with the severity of the disease. Since smoking is a significant factor in the development of chronic obstructive bronchitis and emphysema, many patients with chronic obstructive bronchitis may have coexistent emphysematous changes. These changes can only be quantified at post mortem, although lung function measurements may reveal gas exchange and blood gas abnormalities commonly associated with the condition.

Emphysema

Emphysema is defined in structural or pathologic terms, and is characterised by abnormally large airspaces and destruction of the alveolar walls and capillary bed, which consequently leads to a reduction in the gas exchanging capacity and elastic recoil properties of the lung. Individuals with genetically inherited alpha-1-antitrypsin deficiency are particularly susceptible to emphysema if they smoke. Alpha-1-antitrypsin modulates the activity of some of the protease enzymes, which are responsible for tissue degradation (Thurlbeck 1990). Without protease inhibition there would be widespread tissue damage. In the healthy, non smoking individual there is

usually a balance between protease activity and inhibition from antiproteases. In some individuals alpha-1-antitypsin is deficient, and the normal protease activity overwhelms any antiprotease activity. In smokers protease production is increased, which will greatly aggravate the problems in antiprotease deficient individuals. Smoking is the greatest risk factor to the development of acquired emphysema, and to a lesser extent occupational dust exposures.

There are three commonly recognised forms of emphysema identified from the primary location of the pathological changes and these are described by Thurlbeck (1990) as follows: panacinar emphysema where the abnormally large airspaces are found evenly distributed across the acinar units; centriacinar emphysema where the abnormal airspaces are found initially in association with the respiratory bronchioles; and paraseptal emphysema where the abnormal airspaces run along the edge of the acinar unit where it abuts a fixed structure. Additionally emphysematous changes may be associated with the margins of a pre-existing scar. Larger air-filled spaces (> 1 cm^3) which may form from areas of overdistended emphysema are termed bullae. The common types of emphysema (panacinar and centriacinar) have differing distributions within the lung. Panacinar is found in both the upper and lower lobes and tends to be maximal at the base where it is associated with alpha-1-antitrypsin deficiency, whilst centriacinar tends to be located in the upper zones of both the upper and lower lobes.

In the emphysematous lung there is a loss of elastic recoil and therefore a reduction in expiratory pressure and increased resistance as a result of the loss of support for the surrounding lung which then encroaches on the airway lumen (Pare 1991). With the increased airway resistance there is usually an accompanying reduction in expiratory airflow. The loss of elastic recoil and increased airway resistance leads to gas trapping (hyperinflation) and an increase in the TLC, and to a greater extent the subdivisions RV and FRC (Gibson 1996). With increasing loss of elastic recoil, forced expiration may cause premature airway collapse trapping gas beyond the collapsed or

narrowed airway segment, in which case the forced vital capacity (FVC) is reduced (Pare 1991). The vital capacity (VC) measured under relaxed conditions will often yield a larger volume than the FVC. The increased airway resistance and hyperinflated lungs lead to an increase in the work of breathing, and total respiratory muscle oxygen consumption may be 10 to 20 times the normal values (Rochester 1979).

The loss of alveoli in emphysema leads to a decrease in transfer factor whilst the maldistribution of inspired gas and blood flow are important consequences of the disease process. Mismatching of ventilation and blood flow ($\dot{V}/\dot{Q}$ mismatch) lead to reductions in gas exchange, which may be reflected in abnormal blood gases (Belman 1993). Regions of wasted ventilation (limited or no blood perfusion) are referred to as deadspace, and the deadspace to tidal volume ratio (Vd/Vt ratio) is increased. Areas of perfusion in excess of ventilation lead to a reduction in the mixed venous PaO_2. There may be varying degrees of both wasted ventilation and wasted perfusion present (Belman 1993).

The main symptom of emphysema initially noticed by the patient is usually shortness of breath. Cough and sputum may be present but are usually associated with coexistent chronic bronchitis. Reduced body weight is often present. Common signs of the disease are low body weight, obvious dyspnoea, pursed lip expiration, use of accessory respiratory muscles, hyperinflated chest, and diminished breath sounds though some expiratory wheezes may be heard on forced expiration (Seaton 1989).

2.2.3 **Risk factors for COPD**

There are a number of risk factors associated with the development of COPD. Tobacco smoke is the single most important risk factor in adult life whilst passive smoking *in utero* and during childhood results in diminished lung function (Hanrahan 1992). The association between early childhood respiratory infections (especially lower respiratory tract infections) and the

development of COPD in later life is unclear. The message is confounded by environmental tobacco smoke exposure and lung function development in infancy (Tager 1993).

Atmospheric pollution was the major factor in the increase of mortality from chronic respiratory illness during the notorious London smog episode of 1952. This led to changes in legislation governing atmospheric pollution and a gradual decrease in both industrial and domestic smoke emissions. The relationship between sulphur dioxide and airborne particulates, so called 'black smoke', and increases in morbidity amongst adult patients with chronic respiratory illness led the World Health Organisation in 1992 to issue guidelines on the concentrations which might be expected to trigger such increases. Additionally the so-called 'summer' pollutants are beginning to receive attention. These are commonly the photochemical pollutants occurring around urban areas during periods of bright sunshine (e.g. ozone, nitrogen oxides and acid aerosols). However work has tended to focus on the effects on patients with asthma, and there is little evidence so far concerning the risk for people with COPD.

Chronic bronchitis is more prevalent in workers exposed to either inorganic or organic dusts or to noxious fumes (Seaton 1989). Focal dust emphysema is found in coal miners where coal dust deposits in the lung are incorporated into macrophages and aggravated in the respiratory bronchioles. Intense exposure may lead to accumulation of dust around the lobular pulmonary arterioles and veins (Morgan 1991). In non-smoking coal miners there is an increased prevalence of bronchitis, with an increasing gradient of occurrence in increasingly dusty conditions. In miners who smoke the effects of dust versus smoking cannot be distinguished, both dust and smoking increase bronchial gland dimensions, with mucus hypersecretion and increased cough and expectoration (Morgan 1991).

2.3 RESPIRATORY MUSCLE PERFORMANCE IN COPD

2.3.1 Normal function

To appreciate the changes in the mechanical properties of the respiratory system and the disturbances in respiratory muscle function as a result of COPD the following is a brief overview of the sequence of events which take place during breathing in the healthy individual.

During rest the diaphragm is the most important inspiratory muscle. Anatomically, the structure of the muscle may be described in terms of a central tendon and muscular domes with attachments to the lower six ribs, to the xiphisternum and pericardium, and, via the arcuate ligaments and diaphragmatic crura, to the lumber vertebrae (Gibson 1989). The muscle separates the thoracic from the abdominal cavity. The level of the diaphragm varies with posture, it is at its highest in the chest when supine, and assumes a slightly lower position when standing.

During inspiration the muscle fibres shorten and the diaphragm moves downward. The changes in muscle length are accommodated mainly by increasing and decreasing the area of the upper surface of the diaphragm in direct contact with the inner surface of the ribcage. This is known as the area of apposition, where the lower ribcage is expanded as a result of the insertion of the diaphragm into the ribcage, and the changes in abdominal pressure as a result of diaphragm descent (Gibson 1996). During inspiration abdominal pressure increases and pleural pressure decreases (becomes more negative). Air enters the lungs as a result of the decrease in pleural pressure.

To achieve inspiration the diaphragm has to overcome a number of impedances to move the chest wall. These consist mainly of the elastic resistance of tissue and the alveolar gas/liquid interface and the frictional resistance to gas flow (Nunn 1987). The more minor sources of impedance arise from the inertia of gas and tissue and the friction of tissue deformation. Quiet expiration is a passive mechanism, the result of inspiratory muscle

relaxation and the elastic recoil of the respiratory structures and the surface tension forces at the gas/liquid interface within the lungs. The compliance of the respiratory system is described in terms of the change in lung volume per unit change in transmural pressure ($1.kPa^{-1}$) and is the reciprocal sum of the compliance of the lungs and of the thoracic cage (ribcage and diaphragm). Factors affecting compliance are lung volume (and recent ventilatory history), pulmonary blood volume, age and disease. The neutral position of the respiratory system, where the inward acting deflationary forces (elastic recoil) within the lungs are counter-balanced by the outward recoil of the thoracic cage, occurs at end-expiration and the lung volume approximates the functional residual capacity (FRC). In paralysis the true relaxation volume (Vr) is approximately 400 ml lower than FRC, with diaphragmatic muscle tone accounting for the difference in volumes (Nunn 1987).

The main determinant of the resistance to airflow is the lumen size of the branching airways. Airway patency is regulated via the parasympathetic nervous system controlling bronchomotor tone. Resistance to airflow can be assessed by the simultaneous measurement of gas flow and the driving pressure gradient (usually alveolar pressure assessed from intrathoracic pressure changes) though more usually resistance is inferred from timed-volume measurements (e.g. FEV_1) and expiratory gas flow (Nunn 1987).

Although the diaphragm is responsible for the greater part of inspiration at rest, other muscles, termed the accessory muscles of respiration, show electrical activity during various stages of respiration. Rhythmic electrical activity has been recorded from the anterior and medial scalene muscles in the neck, and from the inspiratory intercostal muscles during rest (Gibson 1989). The scalene muscles help to fix the first and second ribs and assist in upper rib elevation. During deep or forced inspiration the diaphragm contracts maximally and an increasing number of intercostal muscles are recruited in addition to the scalene muscles and the sternomastoids. Other muscles, recruited to varying degrees depending on the level of ventilation, include the erectores spinae, latissimus dorsi, the pectoral muscles and the

serratus anterior (Gibson 1989). Forced expiration is associated with contraction of the expiratory intercostal muscles and the muscles of the abdominal wall. The anteriolateral muscle group of the abdominal wall is able to compress the abdominal viscera and the external oblique muscles are able to depress and compress the lower part of the thorax so further aiding expiration (Gibson 1989).

Measurements of respiratory muscle strength are based on the assessment of inspiratory and expiratory pressure generation, and may be divided into those which assess global function reflecting the contraction of most or all of the respiratory muscles, and measurements which specifically isolate diaphragm function. Additionally measurements are made during periods of airflow (dynamic) or no airflow (static). The measurement of mouthpressure during maximal inspiratory (PI_{max}) or expiratory (PE_{max}) efforts against an occluded mouthpiece is the simplest measure of global muscle strength.

The pressure difference across the diaphragm (transdiaphragmatic pressure, Pdi) is assessed from the pressure differential which exists between the oesophagus and the abdomen. Pleural pressure is estimated from an oesophageal balloon catheter, and abdominal pressure from a catheter positioned in the stomach. Milic-Emili (1964) recorded an inverse relationship between Pdi and lung volume, and Pdi should always be expressed at the lung volume at which it is measured. Expiratory pressures assessed at TLC include the forces exerted by the elastic recoil of the respiratory system, and conversely inspiratory pressures assessed at RV will include elastic inflationary forces. These effects will be minimised for measurements at FRC. Maximal diaphragmatic strength may be assessed from a variety of voluntary manoeuvres which vary in complexity e.g. the Müller manoeuvre and short sharp nasal sniffs. Electrical, or magnetic stimulation of the phrenic nerve provides a measure of involuntary diaphragmatic contraction (twitch Pdi), and thus avoids interference from other muscle activity.

2.3.2 **Respiratory muscle dysfunction in COPD**

The function of the respiratory muscles is profoundly disturbed in COPD (Rochester 1979). Increases in airway resistance, decreases in dynamic compliance and loss of elastic recoil lead to hyperinflation of the lungs and chest wall which greatly increases the work of breathing (Pride 1995). As a consequence of lung hyperinflation the inspiratory muscles, especially the diaphragm, are shortened and the curvature of the diaphragm is reduced (i.e. assumes a flatter position). This results in the inspiratory muscles assuming a disadvantageous position on the length-tension curve, such that the maximum pressure developed during inspiration is substantially reduced (Rochester 1979). In addition the zone of apposition is decreased, thus the ability of the diaphragm to expand the ribcage is reduced. As a consequence patients with COPD show increased use of ribcage muscles and the inspiratory accessory muscles e.g. the sternomastoid, which becomes more pronounced during periods of increased ventilation (Gibson 1996).

The effects of lung hyperinflation on respiratory muscles other than the diaphragm appear to be less profound. X-ray studies and skeletal muscle measurements have revealed a degree of shortening (5 to 8%) in the scalene muscles, the sternomastoids and the external intercostals compared to healthy control subjects, but this is markedly less than the 30 - 40 % shortening found in the diaphragm (Sharp 1986). In addition animal studies indicate the diaphragm bears a much higher fraction of the increased work load than do the other respiratory muscles. Using a series of inspiratory resistances in canines Robertson (1977) was able to demonstrate large increases of blood flow and oxygen consumption by the diaphragm compared to much smaller changes found in the intercostal and scalene muscles. The author concluded this represented preferential changes in favour of the diaphragm.

The mechanism of lung hyperinflation is thought to arise from the loss of elastic recoil (static hyperinflation) which tends to increase the relaxation volume of the lungs (Vr), and the development of prolonged expiratory time

constants, as a result of increased airway resistance which tends to increase FRC (dynamic hyperinflation) (Pride 1995). Dynamic hyperinflation is often present at rest, and increases further on exercise and during acute exacerbations associated with increasing airway obstruction (Gibson 1996). The elevation in end-expiratory lung volume above the true relaxation volume of the respiratory system results in the persistence of an elastic recoil pressure at end-expiration i.e. it is no longer effectively zero, thus giving rise to the development of an intrinsic positive end-expiratory pressure, (PEEPi). The elevated end-expiratory pressure imposes an additional 'threshold load', which the inspiratory muscles must overcome prior to the lowering of alveolar pressure and the onset of inspiratory air flow. The development of PEEPi places a significant extra burden on the inspiratory muscles already operating under disadvantageous force-length conditions and abnormal geometry (Pride 1995).

There are mixed reports concerning any adaptive mechanisms of the respiratory muscles as a result of the chronic resistive and mechanical loading. Measurements at post mortem have revealed reduced diaphragm weight, thickness, area and volume (Steele 1973, Thurlbeck 1978), whilst other studies have shown thicker diaphragms with similar or increased surface areas compared to normal controls (Ishikawa 1973, Scott 1976). De Troyer (1991) concluded the majority of studies indicated a loss of diaphragm weight and thickness in COPD, and there are several confounding factors including loss of body weight and other, as yet unidentified, factors which contribute to the muscle changes. Indirect measurements of diaphragm muscle length reveal a 30 - 40% shortening (Sharp 1986), though when corrected for the absolute lung volumes at which the measurements were made Arora (1987) argued the differences to normal controls are only small. Studies in hamsters with experimentally induced emphysema have revealed adaptive changes in the chronically shortened diaphragm such that the length-tension curve of the muscle is 're-set', i.e. undergoes a left-hand shift, producing similar tensions at shorter fibre lengths compared to the normal diaphragm (Supinski 1982). Gibson

(1996) notes the mechanism of any likely muscle adaptation to hyperinflation in humans is still speculative, however patients with severely hyperinflated lung volumes are still able to generate inspiratory pressures from voluntary manoeuvres and phrenic nerve stimulation.

In addition to the increased resistive (increased airway resistance) and mechanical (hyperinflation) loads, there are a number of blood biochemical changes which may produce less than ideal conditions for the already compromised respiratory muscle function. The oxygen cost of breathing ($\dot{V}O_{2resp}$) is elevated in COPD and at higher levels of ventilation is proportionately much greater than in normal subjects (Rochester 1979). Roussos (1982) determined the oxygen cost of breathing from the rate of work performed ($\dot{W}$) and the efficiency (E), such that $\dot{V}O_{2resp} = (\dot{W})/E$. If the lungs are stiff or airways obstruction is present, the work performed to inflate the lung will increase. In addition, when the load is increased respiratory muscle efficiency will be reduced therefore increasing the $\dot{V}O_{2resp}$ for a given work rate. A reduced efficiency was demonstrated in patients with emphysema, where for the same degree of ventilation the oxygen cost was greater than in normal subjects, and breathing through resistances was more costly than isocapnic hyperventilation (McGregor 1961). Reduced oxygen delivery is a consequence of chronic hypoxaemia, however there is evidence of a compensatory adjustment in diaphragm blood flow and oxygen extraction to satisfy diaphragmatic metabolic requirements (Rochester 1979). However more recent work (in canines) suggests the development of an oxygen debt during periods of repeated maximal diaphragm contractions (Bellemere 1983).

In the long term a combination of hypoxaemia, hypercapnia, an elevated energy demand due to the increased work of breathing, and decreased muscle efficiency are factors which will predispose the respiratory muscles towards fatigue (Roussos 1982). Poor nutritional status is common in severe COPD increasing the likelihood of glycogen depletion and shifting the balance towards anaerobic metabolism. Increases in blood lactate

concentration of approximately 1 mmol.l^{-1} have been measured in normal individuals following the imposition of high, fatiguing resistances (Eldridge 1966). However for the patient with chronic disease there are likely to be multiple confounding factors including electrolyte and mineral deficiencies, impaired muscle membrane function, reductions in energy metabolite concentrations, the effects of hypoxia, hypercapnia, acid-base imbalance and recurrent infection (Gibson 1996).

Measurements of respiratory muscle strength are reduced in patients with COPD and hyperinflation (Black 1968). However when corrected for the abnormally high lung volumes Sharp (1986) suggested muscle strength was fairly well preserved. In severe COPD there is evidence of an elevated general metabolic rate (Donahoe 1989), and reduced body weight (with insufficient calorific intake to satisfy the increased energy demands) is common (Ferguson 1993). Additionally electrolyte imbalance and mineral depletion will accompany poor nutritional status. Respiratory muscle weights closely parallel body weight, and concurrent reductions in respiratory muscle strength have been measured in patients with low body weights (Rochester 1986). Rochester (1991) suggests inspiratory muscle strength in COPD is determined not only by the degree of mechanical disadvantage to the diaphragm but also by the presence or absence of generalised muscle weakness.

In summary, the pathological changes leading to increased airway resistance and loss of elastic recoil with the resultant gas trapping and hyperinflation have a profound effect on the functioning of the respiratory muscles. In addition the confounding factors of low body weight, poor nutritional status, hypoxia, hypercapnia and recurrent infection associated with the later stages of this chronic condition are likely to contribute to the sub-optimal operating conditions.

2.3.3 **Assessment of respiratory muscle performance**

As the main function of the respiratory musculature is to generate changes in pressure, indirect assessment of respiratory muscle strength is achieved from the measurement of an individuals pressure generating capacity. As such, the assessment of respiratory muscle strength is fairly well established with the use of simple mouthpressure measurements (PI_{max} and PE_{max}). More complex techniques involve the use of oesophageal and abdominal pressure catheters, and electrical and magnetic muscle stimulation. However measurement of respiratory muscle performance (strength and endurance) during dynamic testing has not gained wide application. In an editorial, Decramer (1994) suggested its relevance in the clinical setting remains only partly understood even though respiratory muscle endurance may have a significant role in the ventilatory limitation during exercise.

The demands on respiratory muscle performance in COPD, already compromised as a result of increased resistive and mechanical loads, will increase during periods of ventilatory stress e.g. exercise, exacerbation of symptoms etc. As endurance cannot be inferred from measurements of strength, the use of dynamic tests enable respiratory muscle performance to be examined under stress. Dynamic tests of respiratory muscle performance include maximum voluntary ventilation (MVV), resistive and threshold loading, which impose an additional inspiratory load on the respiratory musculature.

The MVV test describes the upper limit of the body's ability to ventilate the lungs. It is conventionally measured from maximal volitional effort for short periods of time e.g. 12, 15 or 20 seconds and is expressed in litres per minute. The test reflects voluntary neural drive, airway resistance and respiratory muscle strength (Goldstein 1993). Studies using isocapnoeic hyperventilation have reported the maximum sustained ventilatory capacity for 15 minutes is 60% of the MVV for normal subjects (Keens 1977), whilst for patients with COPD it may be as high as 100% (Belman 1980). The difference between the MVV and the $\dot{V}_{Emax}$ during exercise is used as a

measure of breathing reserve. In healthy subjects this is usually >30%, whilst in subjects with COPD it is often reduced, and in severe cases ventilation during exercise may exceed the measured MVV (Belman 1993). The manoeuvre is highly dependant on motivation, effort and performance technique, therefore its use is less attractive where more reliable measures of respiratory muscle performance may be required.

Resistive loading involves the addition of alinear resistances to the inspiratory port of a two-way breathing valve. The resistance imposed is usually flow dependant. Much of the preliminary work examining diaphragm fatigue was performed with this type of inspiratory load. Using alinear resistances Roussos (1977) described a curvilinear relationship between Pdi (expressed as a fraction of the Pdi_{max} at FRC) and the time required to produce diaphragm fatigue (T_{lim}). The Pdi associated with an indefinite T_{lim} was approximately 40% of the Pdi_{max}. The study also found that quite high inspiratory loads could be tolerated indefinitely, and the authors suggested diaphragm fatigue should develop once the energy consumption of the respiratory muscles exceeded a critical value. Bellemere (1982) suggested, since inspiration is associated with active muscle contraction, an important component of respiratory muscle endurance is the ratio of inspiratory time to the total duration of the breathing cycle i.e. the duty cycle (Ti/T_{Tot}). Additionally the pressure generated, as a percentage of the maximum available pressure $Pdi_{max,}$ (Pdi/Pdi_{max}), was also important. This led Bellemere to propose a tension-time index (TT_{DI}) which incorporated both the duty cycle and the Pdi/Pdi_{max}.

The use of alinear resistive loads as a means of examining respiratory muscle performance requires careful control and standardisation of breathing pattern. This is a major drawback with any popularisation of the technique for routine clinical assessment. Moreover rigid standardisation of breathing pattern and inspiratory flow prevents the examination of the natural breathing strategies developed by healthy individuals, and patients with respiratory impairment, to overcome additional inspiratory loads.

The use of inspiratory threshold loading as a means of examining respiratory muscle performance may in some cases, also be influenced by the breathing pattern, depending on the application of the technique. The weighted plunger device, described by Nickerson (1982), has been used to measure T_{lim} (the length of time a particular load may be tolerated before the onset of fatigue) and sustainable inspiratory pressure (maximum load tolerated for 10 minutes) (Clanton 1985, Nickerson 1982). Both inspiratory flow and the duty cycle were found to have significant effects on the measurement of T_{lim} (Clanton 1985). However, when the technique was applied using an incremental and progressive loading protocol (which provides a measure of peak mouth pressure - peak Pm) it was uninfluenced by breathing pattern (Martyn 1987, Morrison 1989). In addition, threshold loading using an incremental protocol, which allowed subjects to develop an individual response to the increasing inspiratory loads, was more reproducible compared to the T_{lim} test (McElevaney 1989).

The ideal protocol and method with which to assess respiratory muscle performance is unresolved. As with the assessment of whole body exercise performance it is unlikely a single protocol or method will suffice for all situations. MVV is beset with subject motivational problems whilst resistive loading requires a high degree of subject co-operation and breathing control. It is also recognised that if the resistance is too high endurance may be limited by CO_2 retention, and if it is too low subjects may hyperventilate (Nickerson 1982). Practical accessibility is important for both practitioner and patient. This is a constraint with resistive loading which requires patient feedback circuits. Alternatively incremental threshold loading, which does not require breathing regulation, allows the subject to develop an individual strategy to overcome the additional inspiratory load.

The use of a progressive and incremental loading protocol was a departure from the original description of the technique which described sustainable inspiratory pressure as a measure of ventilatory muscle endurance (Nickerson 1982). However, if endurance is considered the capacity for

sustained performance of a 'task', then the task may involve either a constant workload (usually identified as a fraction of the individual maximum workload achieved) or a workload that varies. Incremental threshold loading is influenced by muscle strength and therefore assesses both strength and endurance since performance is measured over a period of time. The T_{lim} test assesses how long an additional threshold load, which remains constant, can be endured. As a practical clinical test the requirement of breathing regulation during the T_{lim} test is a disadvantage.

The weighted plunger device consists of a plunger covering a large aperture within a chamber which is connected to the inspiratory port of a two-way mouthpiece valve (Nickerson 1982). Weights may be added to the plunger, which will only rise once a sufficient threshold pressure has been generated by the subject to lift the plunger from the aperture thus allowing air to flow during inspiration. The expiratory port is unimpeded. In the original description the device was shown to produce a constant inspiratory pressure independent of inspiratory flow. However, more recent studies have demonstrated higher loads (> 350 g) produce an inconsistent relationship between the weight on the plunger (threshold load) and the mouth pressure generated by the subject (Bardsley 1993, Eastwood 1995). Only partial opening of the plunger occurred at higher loads thus imposing an additional resistive load to inspiration. In addition, Clanton (1985) demonstrated the vertical displacement of the plunger was critical since the pressure load produced by the valve was highly dependent on its vertical orientation above the aperture.

As a result of the limitations with the original design of the weighted plunger apparatus Bardsley (1993) described an electronic, solenoid valve device which only triggered when the set threshold pressure had been generated by the subject. Once the threshold pressure had been achieved, the solenoid valve opened to allow unimpeded airflow. It avoided the manual application of weights to a plunger, therefore increases in threshold load (which are varied electronically by the operator) were smoother and quicker

to introduce. In a study on healthy individuals there was good reproducibility of peak Pm and the pressure-time product (∫Pdt, integration of pressure with time and an index of the oxygen cost of breathing, Collett 1985) using a one minute incremental loading protocol. Additionally, the measurements were uninfluenced by varying breathing patterns therefore precluding the use of external regulation. The application of a threshold load from the solenoid device differs to that presented by the weighted plunger. Once the initial threshold load from the solenoid valve has been overcome the load disappears and airflow proceeds unimpeded. The load from the weighted plunger persists throughout inspiration. The load presented by the solenoid valve may be likened to increasing PEEPi, - the intrinsic pressure associated with dynamic hyperinflation.

In terms of sensitivity to a therapeutic intervention both constant threshold loading tests (assessment of T_{lim}) and incremental threshold loading tests (measurement of peak Pm) have demonstrated improvements following inspiratory muscle training programmes in patients with COPD (Larson 1988, Goldstein 1989, Flynn 1989, Weiner 1992, Wanke 1994, Lisboa 1994). However, there is little evidence of the utilisation of the technique following other types of intervention such as inhalation therapy or general rehabilitation programmes.

Incremental threshold loading using the solenoid valve device has a number of potential qualities which are desirable for a simple test for the routine clinical situation. A linear and accurate response was demonstrated over a wide range of threshold pressures in a group of healthy individuals (Bardsley 1993). Performance was uninfluenced by breathing pattern and therefore excludes the requirement for cumbersome external regulation, and allows the natural strategies, developed by an individual to overcome the additional inspiratory loads, to be studied (Bardsley 1993). However the acceptability and performance of the device has not been tested in the clinical situation. Prior to any routine use the device and technique requires

assessment within the patient population it is likely to serve, to enable the variability (test - re-test) and the sensitivity to change to be quantified.

2.3.4 **Effects of therapy on respiratory muscle performance**

Although respiratory muscle function is compromised in patients with COPD its assessment is not always routinely applied, however simple measurements are becoming more common. A number of well established pharmacological therapies, and exercise training, have the potential to affect respiratory muscle function either directly or indirectly. This makes respiratory muscle assessment all the more important since therapeutic intervention is most effectively directed where there are appropriate and sensitive evaluation methods.

Bronchodilators

Inhaled bronchodilators act to reduce airway narrowing and therefore might be considered an indirect route to improving respiratory muscle function as a result of the reduction in the resistive and mechanical (hyperinflation) load. Assessment of the effectiveness of bronchodilator therapy tends to concentrate on the changes in lung function i.e. routine measurement of airflow (Calverley 1995). Several studies which have assessed changes in respiratory muscle function following bronchodilator therapy have produced conflicting results. Therapeutic doses of methylxanthines produced increases in Pdi and changes in the EMG power spectrum, suggesting a reduction in fatigue in COPD (Murciano 1984), whilst others have found no change (Moxham 1985, Foxworth 1988). However, more recent work has shown benefits in hyperinflated lungs and in diaphragm fatigue (Gauthier 1995).

Two recent studies with Beta-2-agonists (ß2-agonists) have demonstrated beneficial effects in the reduction of hyperinflation and consequent improvements in the muscle force reserve. These were accompanied by changes in breathing pattern and inspiratory muscle EMG activity (Duranti 1995), and reductions in exercise breathlessness (Belman 1996). Other

studies with ß2-agonists have shown improvements in static strength measurements (PI_{max}) (Gigliotti 1993) and respiratory muscle endurance (T_{lim}) (Nava 1992). Additional to the evidence for a reduction in the mechanical and resistive load on the respiratory musculature there is some evidence that methylxanthines, and to a lesser extent ß2-agonists, have an intrinsic effect on the contractility of the diaphragm (van Der Heijden 1996). However this is doubted by some investigators who attribute most of the changes in respiratory muscle function to the deflationary effects in the lung (Moxham 1985, Belman 1996).

Whatever the mechanism of improvements in respiratory muscle function reliance on spirometric evidence alone to evaluate the response to bronchodilators in COPD may undervalue their usefulness. Symptomatic relief is widely reported (Guyatt 1987a, Chrystyn 1988), whilst improvements in exercise tolerance (Chrystyn 1988, Hay 1992) and reductions in exercise breathlessness (Belman 1996) are also reported. In a study which examined the deflationary effects of ß2-agonists and consequent respiratory muscle changes during exercise, Belman (1996) suggested breathlessness should always be evaluated following bronchodilator administration. Belman (1996) examined 13 patients with moderate to severe COPD (mean FEV_1 1.20 l) and demonstrated reductions in exercise dynamic hyperinflation following bronchodilation, and concomitant improvements in inspiratory pressure reserve and neuroventilatory coupling (ratio of inspiratory effort to resultant mechanical event) were the main determinants of reduced exercise breathlessness. These findings further support the association between dynamic hyperinflation and exercise dyspnoea proposed by O'Donnell in 1993. Gibson (1996) summarises the likely mechanism of improvement with bronchodilator therapy as a reduction in the load/capacity ratio (i.e. ratio of the pressure generated during any given change in lung volume to the maximum pressure available) achieved from the combined effects of a reduced load and improved inspiratory muscle capacity accompanying partial reversal of hyperinflation.

Exercise training

Belman (1993) suggests improvements in exercise tolerance following a period of exercise training may be ascribed to one or more of the following factors: improved aerobic capacity and/or muscle strength, increased motivation, desensitisation to dyspnoea, improved ventilatory muscle function, and improved technique of performance. Casaburi (1991 and 1995) has suggested reductions in the lactic acidosis, following periods of high intensity exercise training, lead to concomitant reductions in ventilation in patients with mild to moderate airways disease. Many patients with more severe disease often fail to show a lactate response (Belman 1993), nevertheless useful improvements in exercise tolerance have been demonstrated in such patients (Punzal 1991, Niederman 1991, Carter 1988). What the predominant mechanism of improvement might be in these cases remains speculative. A reduction in the ventilatory requirement as a result of adopting a more efficient respiratory pattern of slower and deeper breathing has been proposed by Casaburi (1995). This mechanism was suggested following the preliminary results of a study which examined a range of respiratory variables in a group of patients with severe airway obstruction (FEV_1 <0.9 l) (Casaburi 1994).

If exercise training achieves a fall in the ventilatory demand for a given work rate the burden on the respiratory muscles will be reduced. Additionally, improvements in general mechanical skill and co-ordination decreases both the oxygen cost and ventilatory requirements of a given work rate, i.e. an improved efficiency for a given task performance. The improved mechanical skill might also extend to improved co-ordination and efficiency of the respiratory muscles. However there are few studies which have incorporated measures of respiratory muscle performance and efficiency into the examination of whole body training.

A study from Wanke (1994) examined the effects of combining inspiratory muscle training with general exercise training (cycle ergometer training) and compared this with general training alone. Forty-two patients with COPD

(mean FEV_1 1.33l) were split into the 2 groups. The inspiratory muscle training consisted of maximal static inspiratory efforts against an almost occluded mouthpiece, and endurance training with a threshold loading device. The author found no change in respiratory muscle strength (oesophageal and Pdi during a sniff manoeuvre) or endurance (T_{lim}) following cycle ergometer training alone, whilst there were significant improvements in these measurements for the combined training group. Both groups increased maximal cycle work rate and maximal oxygen consumption ($\dot{V}O_{2max}$), however the improvement was significantly greater in the group which had received the additional inspiratory muscle training.

Similar results were demonstrated by Weiner (1992) who examined changes in a group of 36 patients with more severe airway obstruction. The patients were split into 3 groups, inspiratory muscle training and cycle training exercise, cycle training and sham inspiratory muscle training, and a control group received no training. Respiratory muscle strength was assessed from maximal inspiratory and expiratory mouth pressures (PI_{max} and PE_{max}) and respiratory muscle endurance from incremental threshold loading with the measurement of peak Pm. The cycle training alone had no effect on the measures of respiratory muscle function whilst the combined training produced substantial improvements. Additionally, the combined training group improved 12 minute walking distance and endurance cycling significantly more than the cycle training only group.

The findings from the study of Weiner (1992) and those of Wanke (1994) suggest additional training specific for the respiratory muscles, is more advantageous to the whole body exercise response than generalised training alone for this patient group. However there are a number of additional issues which these two studies pose concerning the effect of generalised training on respiratory muscle performance: 1) cycle training alone does not improve respiratory muscle function even though both studies demonstrated significant improvements in whole body exercise performance; 2) the measurements of respiratory muscle function employed

were not sensitive enough to detect any subtle changes induced by the cycle training alone, and/or any such improvement may require a longer training period to become established; 3) changes in respiratory mechanical efficiency or work of breathing may have occurred but these were not examined.

It has been suggested by a number of workers that the oxygen cost of increased ventilation during exercise may become uneconomical and eventually act as a limiting factor in COPD (Levison 1968, Rochester 1979, Bye 1983), however methods to establish the oxygen cost of breathing are complex and timely. Incremental threshold loading presents the possibility of assessing respiratory muscle performance in a simple and standardised fashion, analogous to a whole body incremental exercise test. As such it would allow the examination of the cardio-respiratory and metabolic response to the task. If a therapeutic intervention has the potential to alter the efficiency of the respiratory musculature, either directly or indirectly, can the assessment of the cardio-respiratory and metabolic response to a simple task for the respiratory musculature reflect that change?

The possibility of improving respiratory muscle function by specific upper extremity training exercise has been examined by a number of workers. Celli (1994) demonstrated significant improvements in maximal inspiratory pressures in patients with COPD following unsupported arm training. Keens (1977) demonstrated a vigorous training regimen, consisting of swimming and canoeing, in patients with cystic fibrosis, produced similar improvements in the maximal ventilatory capacity as a programme of ventilatory muscle training. However other studies were unable to detect improvements in the measures of respiratory muscle performance employed (Ries 1988, Lake 1990).

In a training study which used low intensity peripheral muscle conditioning, including arm exercises and breathing techniques, Clark (1996) found hyperinflation of the lungs increased in the control group which had received

no training during the study period. The author speculated that the breathing techniques, taught during the various exercises, may have contributed to decreased airway narrowing which acted to inhibit further increases in hyperinflation in the actively training group. Additionally the training group improved work capacity for the same level of dyspnoea measured pre-training. The perception of breathlessness has been shown to be closely associated with dynamic hyperinflation during exercise in COPD (O'Donnell 1993 and 1997, Belman 1996). O'Donnell (1995) suggested a possible mechanism of reduced elastic and resistive loading, and/or improved ventilatory muscle strength for the relief of breathlessness following exercise training. Although assessment of whole body exercise provides insight into the symptoms associated with increased ventilatory stress, it involves many other muscle groups not related to breathing, therefore it may not be sufficiently sensitive to evaluate changes in ventilatory muscle function.

There is still considerable debate concerning the usefulness of specific respiratory muscle training in COPD and any transfer effects leading to improvements in whole body exercise and functional capacity (Goldstein 1993, Gosselink 1994). Although improvements in respiratory muscle strength and endurance have been demonstrated in a large number of studies and the improvements appear to be mode specific (Belman 1993), the functional advantages are still unclear. Improvements in exercise capacity have been demonstrated in two randomised, controlled studies (Larson 1988, Dekhuijzen 1991), which used a training programme of threshold loading, and Lisboa (1994) measured decreased breathlessness associated with activities of daily living following inspiratory muscle training in a placebo controlled study. The two studies (Weiner 1992, Wanke 1994) which found additional improvements from combining inspiratory muscle training with general exercise training have already been discussed.

In an editorial Gosselink (1994) suggests the strongest indication for inspiratory muscle training lies in its combination with general exercise training, though careful monitoring of the training intensity and consideration

of the type of training employed is necessary to achieve measurable change. Training using inspiratory threshold loading has been associated with increases in exercise capacity and improvements in breathlessness (Larson 1988, Lisboa 1994). More recently improvements in the disposable devices which deliver a training threshold load have occurred (Gosselink 1996a, Johnson 1996).

In conclusion, popular methods of therapeutic intervention used in this patient group, namely bronchodilator therapy and exercise training, have the potential to affect respiratory muscle performance, yet its assessment is not routinely applied. A simple and reliable test which does not require cumbersome external regulation and equipment, would make assessment more accessible. Additionally, greater clarity of the clinical relevance and application of the assessment of respiratory muscle performance, and its relationship to other conventional measures of exercise performance is required. Incremental threshold loading using the solenoid valve offers the potential for such a test, and with standardised increments in work rate would enable the energetics of the task to be examined.

Although there is increasing evidence of the role of the respiratory musculature in the response to exercise in COPD, many aspects of the whole body exercise response remain poorly understood. Deconditioning and skeletal muscle weakness are gaining recognition as potential factors in the limitation of whole body exercise in this patient group. Since measurements of lung function at rest are poor predictors of functional capacity, the assessment of the whole body exercise response is important in the quantification of disability and application of therapeutic interventions.

2.4 ASSESSMENT OF EXERCISE CAPACITY IN COPD

The indications for performing an exercise test in COPD are varied and include the objective measurement of an individuals exercise capacity, the evaluation of disability, dyspnoea and exercise related symptoms, the establishment of a differential diagnosis, guidelines for exercise prescription,

and assessment of a therapeutic intervention. There are a wide variety of exercise tests, laboratory based tests may be as comprehensive as resources allow, whilst field-based tests are quick, simple to apply, less intimidating for the patient and usually do not involve major resource commitments.

2.4.1 **The response to exercise in COPD**

The abnormal ventilatory mechanics and increased airway resistance act to reduce the ventilatory capacity, which is one of the most important factors in the exercise limitation of patients with COPD (Belman 1993). A limited breathing reserve is characteristic of the condition, where the difference between the maximum exercise ventilation and the MVV is less than 10 $l.min^{-1}$ (Wasserman 1993). The recognition of a ventilatory limit to exercise in patients with COPD was acknowledged by Jones (1971) in a study which examined the exercise responses in 50 men with the condition. Maximal exercise work capacity was reduced in comparison to predicted normal values, and low ventilatory capacities were measured, whilst the cardiovascular response for a given work rate was essentially normal. Whilst it is generally accepted the maximal ventilatory capacity is reduced, Spiro (1975) demonstrated, for a given oxygen uptake, ventilation was significantly higher in patients compared to age-matched controls. Spiro also demonstrated a reduced maximal oxygen uptake, consistent with the reduced peak work rate, compared to the control group. The true $\dot{V}O_{2max}$, where $\dot{V}O_2$ assumes a plateau despite an increasing work rate, is not usually attained in patients with COPD since exercise is symptom limited. More appropriately the 'symptom limited' $\dot{V}O_{2max}$ or peak $\dot{V}O_2$ ($\dot{V}O_{2peak}$) is reduced when compared with predicted normal values, or control subjects (Jones 1988).

Arterial oxygen desaturation is a fairly common finding during exercise in COPD, and is largely accounted for by a worsening of the $\dot{V}/\dot{Q}$ mismatch (Belman 1993). Marked inhomogeneity in the distribution of ventilation and perfusion leads to areas with a high $\dot{V}/\dot{Q}$ ratio, which act as deadspace, and

areas with low $\dot{V}/\dot{Q}$ ratios which act as venous admixture and contribute to arterial O_2 desaturation (Jones 1991). There is little evidence for a diffusion limitation in COPD (Belman 1993) though this may occur during periods of infection and inflammation.

In healthy individuals there is usually a reduction in the Vd/Vt during exercise. In COPD the reverse is true, the Vd/Vt ratio tends to increase during exercise. This acts to increase the ventilatory equivalent for carbon dioxide elimination ($\dot{V}_E$ /$\dot{V}CO_2$) and thus contributes to the sensation of dyspnoea (Jones 1991). In some patients this may be lessened by alveolar hypoventilation at the expense of a rising arterial CO_2 ($PaCO_2$). The concept of an arterial CO_2 set-point describes the widely differing alveolar ventilation requirements between patients who regulate a normal $PaCO_2$, and are less able to tolerate variation in $PaCO_2$ and pH, and patients who are able to tolerate a higher $PaCO_2$. The former patient is likely to experience a greater degree of breathlessness at any given metabolic rate since a higher degree of alveolar ventilation is required to maintain the $PaCO_2$ within tight limits (Wasserman 1993). The alveolar mass balance equation describes the level of ventilation ($\dot{V}_E$) for a given $PaCO_2$, and the effect of the Vd/Vt :

$$\dot{V}_E = \frac{k\dot{V}CO_2}{PaCO_2\ (1 - Vd/Vt)}$$

where k is a constant, $\dot{V}CO_2$ is carbon dioxide output, $PaCO_2$ is arterial CO_2 partial pressure, and Vd/Vt is the deadspace to tidal volume ratio and quantifies the efficacy with which CO_2 is expelled from the lung.

The work of breathing and the increased cost of ventilation in COPD was proposed by Levison (1968) as an important limiting factor of exercise. In a study which examined the response to exercise in both normal subjects and patients with COPD, Levison (1968) measured a disproportionate increase in the oxygen cost of breathing in the patient group. Rochester (1979) estimated the level of activity which might be sustained by two hypothetical patients with COPD and a normal subject, based on the amount of oxygen available to the body after the oxygen consumed by the respiratory muscles

had been subtracted. Based on a minute ventilation of 30 $l.min^{-1}$ a patient who maintains a normal $PaCO_2$ manages only minimal activity equivalent to slow walking, whilst the patient who tolerates hypercapnia is able to perform a higher rate of activity equivalent to light work, for example. The former patient is expending more energy eliminating CO_2 and therefore less is available for other muscular activity. However both types of patient have a much reduced work capacity compared to the normal subject, who at the same level of ventilation is capable of moderately heavy manual work. The oxygen cost of breathing in the normal subject is small in comparison to the patients with COPD and not a limiting factor at that level of ventilation. Bye (1983) described the concept of 'energy stealing' i.e. the respiratory muscles 'steal' blood flow and energy potentially available for other working muscles, and suggests it may be a rate limiting step in healthy individuals at very high ventilations.

The ventilatory and gas exchange kinetics, measured during moderate, constant-load exercise in patients with COPD, have been shown to be significantly different from the normal response (Nery 1982). The phase 1 increases (which describes the change from rest to exercise and represents the period in which mixed venous tensions have not changed) in ventilation ($\dot{V}_E$), carbon dioxide production ($\dot{V}CO_2$), $\dot{V}O_2$, heart rate (HR) and O_2pulse were significantly smaller, and the phase 2 kinetics (slow exponential rise to steady state) were significantly slower than in a normal control group. The authors attributed the slowed ventilatory kinetics during phase 2 to a slowed cardiovascular response in the patient group. Breathing 30% O_2 was found to accelerate the $\dot{V}O_2$ kinetics, and consequently reduced the O_2 deficit (difference between the minute $\dot{V}O_2$ and the average $\dot{V}O_2$ during a 10 minute bout of constant-load exercise) in mildly hypoxaemic COPD patients (Palange 1995). The authors suggested the observed improvements with O_2 supplementation were consistent with an enhancement of aerobic metabolism in skeletal muscles during moderate exercise.

There is generally a high heart rate reserve (predicted maximum heart rate minus the peak exercise heart rate) at peak exercise levels since most patients terminate exercise prematurely due to symptoms. However, a number of workers have found higher heart rates in comparison with normal individuals at equivalent $\dot{V}O_2$ or work rates. Matthews (1989) found consistently higher heart rates over a wide range of work rates compared to an age matched control group, and suggested it possibly represented a combination of both deconditioning and the increased energy demands of the ventilatory muscles. Spiro (1975) also measured significantly higher heart rates at equivalent, absolute levels of $\dot{V}O_2$, and postulated a reduced stroke volume as a result of raised pulmonary artery pressure, or the development of left ventricular dysfunction. Wasserman (1993) suggested a reduced stroke volume may partly explain the reduced oxygen-pulse which is commonly observed in COPD.

One of the main symptoms of exercise in COPD is breathlessness, though recent work has suggested symptoms of leg fatigue, and a combination of leg fatigue and dyspnoea occur more frequently. Killian (1992) compared each of the respective symptoms in a large group of patients with chronic airflow limitation and a control group. A greater proportion of patients rated leg fatigue in excess of dyspnoea (43%), whilst only 26% rated dyspnoea in excess of leg fatigue. The remainder of the group (31%) rated both symptoms equally. Similar findings were reported by Rampulla (1992) with proportions of 46% reporting fatigue at exercise termination and 36% reporting dyspnoea. These findings suggest fatigue of the peripheral muscles and general deconditioning also contribute to the exercise limitation in this group. Peripheral muscle weakness, in terms of reduced quadriceps and handgrip force, was confirmed in a study of 41 patients with COPD (Gosselink 1996b). The study also found quadriceps force and PI_{max} explained 45% of the variance in the 6 minute walk distance, whilst transfer factor, FEV_1 and quadriceps force explained 58% of the variance in $\dot{V}O_{2max}$. The authors concluded lung function and peripheral muscle force were important determinants of exercise capacity in COPD.

In a large retrospective study of over 4,617 subjects referred for clinical exercise testing, reduced peripheral and respiratory muscle strength (PI_{max} and PE_{max}) were measured in subgroups classified with respiratory disorders and cardiorespiratory conditions (Hamilton 1995). There were also significant relationships between symptom intensity and muscle strength and between maximal work capacity and muscle strength. The authors suggested the most likely cause for the systematic decline in peripheral muscle strength, observed in the presence of cardiorespiratory disorders, was a reduction in the level of habitual activity.

Reductions in muscle size and strength following limb immobilisation are generally well known, whilst differences between active and sedentary individuals in muscle strength and oxidative enzymes have been widely demonstrated (Jones 1991). Additionally steroid usage and diuretic therapy are important factors which may account for weakness in some patients, and theoretically hypoxaemia and hypercapnia may also impair muscle function (Jones 1991). Whilst patients experience increasing dyspnoea to a range of daily activities, a greater motivation and tolerance will be required to achieve the same level of activity. Alternatively, many patients will avoid activities which provoke dyspnoea and adopt a more sedentary lifestyle, which leads to further deconditioning and the downward spiral of dyspnoea described by Young (1983).

Wasserman (1993) acknowledges the contribution of cardiovascular and muscle deconditioning to the reduced exercise capacity in COPD, with the occurrence of anaerobic metabolism at low exercise levels and the contribution of lactic acidosis to the ventilatory burden. The increased concentration of hydrogen ions, as a result of lactic acid dissociation, stimulate the carotid bodies to increase ventilatory drive. Casaburi (1991) demonstrated a high intensity exercise training programme in patients with mild and moderate disease, and with evidence of an anaerobic threshold, reduced the exercise lactic acidosis and ventilation at set work rates compared to pre-training levels, and improved the total work capacity.

However Belman (1993) points out more severely affected patients often fail to demonstrate an anaerobic threshold or a significant exercise lactic acidosis, yet often show large improvements in submaximal exercise endurance following a course of exercise training.

2.4.2 **Laboratory-based exercise tests**

Laboratory tests include both incremental and constant workload tests. The incremental and symptom limited maximal test enables peak $\dot{V}O_2$, $\dot{V}_E$ and heart rate to be measured, with additional monitoring of pulse oximetry for arterial oxygen saturation (%SpO_2), ECG, dyspnoea and perceived exertion. There exists a number of incremental treadmill and cycle ergometer protocols for clinical assessment (American College of Sports Medicine, ACSM 1995). However, to date there are no consensus guidelines concerning the assessment of exercise capacity in COPD, or the respiratory patient in general. Many protocols have evolved from the investigation of cardiac disorders, with the Bruce protocol (1973) being popular in the UK. Its application in the respiratory patient is not recommended since the work rate increments are large and may quickly exceed the $\dot{V}O_2$ mechanisms in most patients (Jones 1988). Protocols with smaller increments are better suited for elderly subjects, and patients with respiratory disease, and the modified Balke or Naughton protocols are suggested by the ACSM guidelines (1995). Such protocols adopt a constant treadmill walking speed, individualised to each subject, with an increase in gradient of 2 - 3% every 2 to 3 minutes. Increments of 10 - 15 watts.min^{-1} are suggested for the cycle ergometer. Ideally the total test time should be 8 to 12 minutes for the symptom limited maximal test (Wasserman 1993) with the work rate increments adjusted accordingly.

Constant work rate tests may be used to elicit steady state conditions in the measured physiological variables (e.g. heart rate and $\dot{V}O_2$), measure endurance capacity, and discontinuous constant work rate tests, with intervening rest periods, used for the measurement of $\dot{V}O_{2max.}$ A constant work rate test at near (90%) maximal predicted values for either heart rate or

$\dot{V}O_2$ is the recommended challenge for exercise-induced asthma (Eggleston 1979). When measuring endurance capacity the intensity of exercise is usually set to a proportion of the maximal work rate or $\dot{V}O_{2max}$ determined from a maximal incremental test, and the endurance capacity is defined as the duration of exercise at the set work rate (Åstrand 1986). Constant work rate tests are ideal for measuring cardiovascular, ventilatory, and gas exchange kinetics, and using breath-by-breath analysis allows the measurement of time constants (rate of rise - the time for 63% of the final response to be reached) of the physiological responses (Wasserman 1994). Whipp (1972) examined the $\dot{V}O_2$ kinetics over a 6 minute constant work rate test and found that for work rates above the anaerobic threshold the $\dot{V}O_2$ failed to reach a plateau after 3 minutes. The rate of rise in the $\dot{V}O_2$ during 3 to 6 minutes of a constant-load test ($\Delta\dot{V}O_2$ (6-3)) was found to correlate with the magnitude of any lactic acidosis (Roston 1987). Analysis of the breath-by-breath measurement of CO_2 production and O_2 uptake during constant-load exercise can also be used to derive a noninvasive evaluation of the magnitude of blood lactate increase, by estimating the degree of lactic acid buffering by bicarbonate ions and the subsequent dissociation to CO_2 and H_2O (Wasserman 1994).

With the increasing sophistication of computerised exercise test systems it is easy to obtain a wide range of derived variables from the gas analysis, flow and volume measurements. However caution is suggested since the computer algorithms may be based on a number of assumptions which may not apply in all circumstances. For example, use of end-tidal CO_2 measurement as a substitute for $PaCO_2$, and used in the calculation of physiological deadspace (e.g. Vd/Vt) has been shown to be erroneous in COPD (Clark 1992, Lewis 1993).

There is evidence that the cardio-respiratory response to a maximal test is mode specific in healthy subjects, and unsupported walking on the treadmill may produce a $\dot{V}O_{2max}$ 5 - 10% greater than the cycle ergometer (ACSM

1995). In severe COPD, were it may be hypothesised the support for the upper body offered by the cycle ergometer may provoke a higher $\dot{V}O_{2peak}$ than the treadmill, there is no significant difference between the two forms of exercise (Mathur 1995). However, the same study demonstrated a significantly higher lactate concentration following cycle exercise compared to the treadmill test, which was in agreement with the findings of Cockcroft (1985) from a study on patients with COPD, and with studies on healthy individuals (Koyal 1976, Hermansen 1969). Cockcroft (1985) suggested the smaller muscle mass used in cycling may account for the differences in lactate concentration, since the mean metabolic rate per unit of contracting muscle is greater than for the equivalent treadmill work and thus engages anaerobiosis at a lower level of $\dot{V}O_2$. Additionally, Cockcroft (1984) found less oxygen desaturation during the cycle test compared to that during the treadmill exercise, and suggested the greater lactic acidosis, provoked by the cycling, stimulated a greater ventilatory response, therefore minimising the fall in PaO_2. Spence (1993) similarly found less desaturation during cycle exercise compared to corridor walking in patients with severe COPD.

The differences in the metabolic (lactate concentration and PaO_2) responses to cycle and treadmill exercise in severe COPD might influence the choice of exercise modality in specific circumstances. Where exercise prescription is based on the development of an anaerobic threshold, then a cycle exercise test may be more appropriate to elicit a higher lactate concentration. Alternatively, domiciliary oxygen prescription may rely on the demonstration of a certain level of oxygen desaturation during exercise, in which case walking exercise appears to be more specific for arterial desaturation. For the assessment of an exercise training programme Jones (1989) proposes treadmill testing is the most appropriate form of test if the training is based on walking. Additionally, Casaburi (1993) states it is important the exercise testing modality utilises the same muscles which were trained during the rehabilitation programme, since performance will be improved only in those muscle groups which undergo training.

Since exercise capacity is difficult to predict from resting measurements of pulmonary function (Jones 1971, Wasserman 1993), standardised methods of laboratory testing enables the exercise capacity to be quantified in terms of $\dot{V}O_{2peak}$, $\dot{V}_{Epeak}$, HR_{peak} and peak work rate, and the subjective response to be qualified. Additionally the subjective response, in terms of breathlessness and perceived exertion, may be quantified by use of the Borg rating scales (appendix 5). The Borg scales correlate well with exercise intensity (Borg 1982), are reproducible and show a similar degree of variability as $\dot{V}O_2$, $\dot{V}_E$ and HR in COPD over short periods of time (Silverman 1988). Over longer periods (5 weeks) the Borg ratings of dyspnoea were found to be less reproducible than $\dot{V}O_2$ and $\dot{V}_E$ in COPD (Mador 1995). Belman (1991a) also found increased variability with time after the physiological response to exercise had stabilised in COPD, and interpreted this as a sign of desensitisation to dyspnoea. Mahler (1992) demonstrated ratings of dyspnoea overlapped (with maximal respiratory pressures and lung function) but were independent factors in the evaluation of patients with COPD.

The reproducibility and learning effects of incremental maximal cycle ergometer tests were examined over a short term period (24 hours) in eleven patients with mild to moderate COPD (Cox 1989). Maximal work rate, $\dot{V}O_{2peak}$, HR_{peak} and the respiratory exchange ratio (RER) all showed good reproducibility with less than 5% variation between tests. $\dot{V}_{Epeak}$, $\dot{V}CO_{2peak}$ and breathing frequency (fR) were slightly less reproducible, with values of 6.6%, 6.0% and 8.3% respectively. Cox (1989) concluded there was good reproducibility of the test and no learning effects were apparent. However the study was performed in the Netherlands and the author conceded cycling was a common mode of transport within the population. Brown had published similar results in 1985 (in the USA), and in addition demonstrated slightly less variability between cycle tests carried out on the same day than the variability between days. The within-day variability of $\dot{V}O_{2peak}$ was approximately 4%, and the between day variability was approximately 7%. In a study on eight patients with severe COPD (mean FEV_1 0.69 l), Mathur

(1995) measured a between-day variability in $\dot{V}O_{2peak}$ of 6.8% for an incremental cycle test, and 8.2% for an incremental treadmill test.

Swinburn (1985) suggested at least 3 practice exercise tests be performed in patients with severe COPD prior to the evaluation of an intervention. The authors found wide variability between the performance (work rate) in three types of test carried out on four occasions in one week. Performance increased significantly between the 1st and 4th test, with the widest differences for a fixed height and rate step test, followed by an incremental cycle ergometer test, and least differences recorded with a 12 minute walking distance test. All the patients were admitted into hospital specifically for the performance of the study, and it may be argued there was a strong motivational element since each type of test was performed every day for three days (the 4th test was performed after 3 days of additional placebo treatment).

In summary, laboratory based tests of peak exercise capacity assist in the establishment of a diagnosis, they allow the objective assessment of the cardio-respiratory response to exercise, and enable signs and symptoms to be quantified. In addition they may be useful in the prescription of exercise allowing peak heart rates and the blood lactate response to be evaluated. However laboratory-based tests are costly and are likely to be limited to the larger investigative medical centres.

2.4.3 **Field tests of exercise performance**

Whilst laboratory exercise tests enable the gold standard measurement of aerobic fitness - the $\dot{V}O_{2max}$ (or $\dot{V}O_{2peak}$) to be measured directly, and assist in the diagnostic process, they are complex and costly, and not necessarily appropriate where a simple assessment of disability is required. The 12 and 6 minute walking tests (12 or 6 MWT), are self-paced walking tests which measure the distance covered in the respective times, and are widely used clinical field tests of disability for patients with COPD. More recently a shuttle

walk test (SWT) has been described which incorporates a standardised and incremental work rate (Singh 1992).

The 12 MWT was described by McGavin (1976). The reproducibility of the test, its relationship to resting lung function and maximal cycle ergometer performance were assessed in a group of patients with chronic bronchitis. The test was performed along a hospital corridor with the supervising doctor walking alongside, giving encouragement as necessary. The patient was instructed to 'walk continuously if possible but not to be concerned if he had to slow down or stop. The aim was to feel at the end of the test he could not have covered more ground in the time'. Additionally a maximal exercise test on a cycle ergometer and resting FEV_1 and FVC measurements were performed. Although significant, the correlation between the distance walked and $\dot{V}O_{2max}$ was only moderate (r=0.52), similarly with FVC (r=0.406), whilst there was no significant correlation with FEV_1. The authors assessed reproducibility over three tests and found a significant difference between the 1st and 2nd test, and a mean difference of +7.33 $\pm$4.22% between the 2nd and 3rd test (NS), and concluded the test should be carried out twice to achieve reproducible results.

Butland (1982) compared the 12 MWT to performance during 6 and 2 minute versions of the test, since 12 minutes was quite a taxing length of time for patients with more severe impairment. Two practice 12 MWT were performed by all patients before entry into the study. The timing and wording of encouragement were standardised, and the distance covered every two minutes was measured. Patients walked further during the first 2 minutes than any subsequent two minute period, though all tests (2, 6 and 12 MWT) were significantly correlated. The within day reproducibility of the 2 MWT was assessed, and a 7.3% increase in distance was measured over four tests. There was a greater spread of results using the longer tests which led the authors to conclude these were better discriminators of exercise tolerance. It was concluded the 6 MWT was a suitable compromise for a shorter duration test. Alternatively, the greater spread of results from the

longer tests may also indicate a variability in the patients' ability to pace themselves over a longer period. The variability in pacing is borne out in a study by Guyatt (1984) which found a significant difference between the distance covered during a 2 MWT and during the first 2 minutes of a 6 MWT, suggesting knowledge of the test duration might influence pacing.

The effect of encouragement on walking test performance was examined in a mixed group of patients (COPD and/or heart failure) (Guyatt 1984). Simple encouragement was found to significantly improve the 6 MWT by up to 30.5m, whilst repeated testing with no encouragement also produced an improvement though of a smaller magnitude. The effect of encouragement was similar in magnitude to improvements previously attributed to some pharmacological or physiological interventions (Guyatt 1984). The authors suggested consistency in the conduct of the test was important, and recommended two practice tests because of an initial training effect. Similarly, Knox (1988) described a learning effect over 12 walks, with a 33% increase in distance walked when the tests were carried out over a short period of time (12 tests in 3 consecutive days), and a 8.5% increase over 4 weeks. The authors concluded at least five practice walks were desirable when tests were to be performed on consecutive days, and four practice walks when tests were to be performed over a greater time period. Additionally a randomised cross-design, or a placebo group, should be considered for research studies as an additional control.

Other studies have also demonstrated learning and/or motivational effects with repeat testing. Swinburn (1985) measured a 16% improvement over four 12 MWT performed during one week, and recommended at least three practice attempts. Mungall (1979) measured a significant improvement over six 12 MWT performed over a longer period of time (the level of improvement was not stated) and again recommended 3 practice walks.

It is apparent the conduct of the test is important since both encouragement and the number of practice walks performed can significantly influence the

results. As Guyatt (1984) reports, a number of studies have measured apparent improvements following a clinical intervention, though much of the improvements noted may be accounted for by lack of protocol standardisation. The recommended number of practice walks ranges from one to five, with the choice influenced by the period of time over which the measurement is to be repeated. The number of practice attempts and the influence of the time period renders the test cumbersome in practice, reduces its simplicity, increases the cost and is more inconvenient for the patient.

Other variables which have been shown to be related to the performance of timed walk tests include attitudes and beliefs, dyspnoea ratings and quality of life scores (McGavin 1978, Morgan 1983, Mak 1993, Wegner 1994). Both Morgan (1983) and McGavin (1978) found Borg ratings of perceived exertion measured post test correlated significantly to the 12 MWT ($r = -0.49$ for both studies), and additionally patients' attitudes and beliefs concerning their respiratory condition and treatment accounted for a substantial proportion of the variance (Morgan 1983). Mak (1993) reported a strong correlation between the 6 MWT and perceived respiratory impairment (rated prior to exercise on the Medical Research Council breathlessness scale) ($r=-0.520$). Whilst there were poorer correlations with breathlessness and perceived exertion rated after the 6 MWT ($r= -0.35$, and $r = -0.30$ respectively).

Using factor analysis, Wegner (1994) found 6 MWT, dyspnoea and quality of life scores together acted as a significant, statistically independent variable on the characterisation of COPD. In contrast, quality of life measures were found not to relate to either a 6 MWT or a maximal cycle ergometer test in a study on 40 patients with COPD, whilst Borg ratings of dyspnoea at rest produced a significant correlation with the 6 MWT ($r= -0.41$) (Wijkstra 1994). The apparent effect of attitudes and beliefs on exercise performance would appear to be an important dimension for consideration during programmes of pulmonary rehabilitation, which aims to improve performance and understanding of the condition.

The question of what the timed walk test measures is important for its application and its potential sensitivity and specificity for a treatment intervention. The moderate relationships with measures of maximal exercise performance (McGavin 1976) indicate the test is more akin to a submaximal test than the maximal performance provoked during a conventional incremental test. Using a portable oxygen analyser Swinburn (1985) demonstrated a steady state in $\dot{V}O_2$ and $\dot{V}_E$ occurred after 6 minutes of a 12 MWT, a finding which has more in common with a submaximal endurance test. Additionally, in the same group of patients, higher $\dot{V}O_2$ and $\dot{V}_E$ values were measured during a step test than during the 12 MWT emphasising the submaximal nature of the test. Singh (1992) compared the peak heart rate achieved during a 6 MWT and the incremental shuttle walk test, and found it was 9 beats higher following the shuttle test, which supports the submaximal nature of the 6 MWT.

A patient's exercise performance must depend on various factors including motivation, endurance, respiratory function, cardiovascular fitness and neuromuscular function, all of which McGavin (1976) suggests govern 'everyday disability', and therefore confer the 12 MWT with the potential to establish everyday disability. Steele (1996) argues that walking tests may be a better measure of 'functional exercise capacity', defined as the patients ability to undertake physically taxing activities encountered in everyday life, that are not reflected by conventional exercise testing. However, Spiro (1977) notes since day to day activities are mostly of an irregular nature with a steady state rarely being achieved, an increasing work rate test is more likely to reveal or identify the causes of exercise limitation. The counter argument is an individual rarely utilises maximal capacity and most normal activity engages only differing proportions of the maximum capacity. In addition, endurance capacity, which measures repeated or sustained performance of a task (or tasks), is an essential part of normal functioning. Whilst an incremental maximal test defines the limit of exercise capacity and with full physiological monitoring reveals abnormality of response,

submaximal field testing has the potential to quantify useful employment of that capacity.

The self-paced nature of the timed walking tests may confer both advantages and disadvantages. Steele (1996) argues self-pacing is an important skill which is taught and needs to be measured in a naturalistic format following pulmonary rehabilitation and other similar interventions. Alternatively, Swinburn (1985) suggests self-pacing is a disadvantage which probably accounts for the test's dependence on attitude and motivation, and the effects of verbal encouragement on performance. Swinburn also questions the habitual nature of the walking speed adopted by the patient which may prevent the test from demonstrating the full beneficial effect of any treatment. Previous studies have demonstrated the variability in self-pacing adopted by patients (Butland 1982, Guyatt 1984) and this in part may be influenced by knowledge of the test duration. The use of self-pacing makes inter-subject comparison difficult, since different patients experience a different challenge depending on individual judgement of pace, and the adopted pace will reflect the employment of different relative levels of maximum capacity. Self-pacing may also lead to decreased test sensitivity and poor intra-subject comparison. A patient may achieve similar distances before and after an intervention, but poor judgement of pace over 6 or 12 minutes may disguise improvements in the patient's ability to exercise at a higher capacity.

The concerns over the use of self-paced, timed field tests have been discussed, however the test does possesses a number of qualities for the assessment of exercise performance. The simplicity and low cost of the test are evident, and it avoids the use of intimidating, complex equipment which may be daunting to the patient and lead to underperformance. The familiarity of the type of exercise is universal. Since walking is central to the achievement of normal daily functioning it is an appropriate activity to assess. Whilst the lack of relationship to routine measures of lung function may be viewed as a disadvantage, it also highlights the necessity to objectively evaluate exercise performance in COPD.

Many of the concerns over the use of the timed field walking tests arise from the absence of a standardised protocol, use of self-pacing, individual motivation and learning effects. The development of the incremental shuttle walking test (Singh 1992) addressed some of the shortcomings of the existing field tests, whilst its purpose was to provide a standardised, incremental field test of symptom limited maximum performance. The test incorporates external pacing, therefore eliminating variability in pace and improving intra- and inter-subject comparison, since all patients experience the same set work rate. The work rate is incremental, the speed of walking is increased every minute, and the protocol is standardised with clearly defined end-points. The external pacing reduces the effect of operator encouragement and reproducibility is improved since it requires only one practice test.

Whilst the advantages of assessing maximal capacity from an incremental maximal test have been examined, the evaluation of submaximal endurance performance with field walking tests has a place in the assessment of disability. The timed field walking tests, with and without the addition of maximal incremental tests, have been used widely as outcome measures following both pharmacological and rehabilitation interventions. Whilst maximum exercise capacity ($\dot{V}O_{2peak}$) often shows minimal improvement, submaximal endurance tests (either field or treadmill walking, or cycle ergometry) have been shown to be particularly sensitive to interventions of exercise training (Larson 1988, Zuwallack 1991, Niederman 1991, Punzal 1991, Goldstein 1994, Singh 1996). Thus, there are sound arguments for standardising the assessment of endurance capacity, and for the development of a field test which avoids many of the shortcomings associated with the existing timed walk tests.

Chapter 3

GENERAL METHODS

3.1 INTRODUCTION

To ensure consistency throughout all procedures and measurements were standardised in the experimental studies undertaken. A description of the standard methods and equipment used is given below.

3.2 Demographic details and subject examination

All subjects had the following details recorded at their first visit: date of birth; height; body weight; current medication; and smoking history. Body weight was measured using a beam balance (Marsden Ltd., Model 150) and height was measured using the stadiometer fixed to the balance scales. Outer clothes and shoes were removed. Height was measured according to the recommendations of the British Thoracic Society and the Association of Respiratory Technicians and Physiologists (BTS/ARTP) (1994). Body weight was re-checked periodically throughout study periods.

All subjects undergoing maximal exercise testing had a supine, standard 12-lead ECG recorded (Nihon Kohden, Cardiofax) and resting blood pressure measurement (Accuson, Freestyle), as a safety precaution. Any deviation from normal was assessed by the study supervisor. All exercise tests were carried out according to local safety guidelines and the guidelines issued by the American College of Sports Medicine (1995).

3.3 Lung Function Measurements

The FEV_1 and FVC were measured on a wedge-bellows spirometer (Vitalograph Ltd, R model), and performed according to the BTS/ARTP Guidelines (1994). Subjects were seated and performed a minimum of three technically acceptable tests, with at least a 30 second rest between manoeuvres. The highest value for each measurement was recorded for analysis (acceptability criteria: within 5% or 0.1 l of the next highest measurement). If the third attempt produced the highest measurement further

manoeuvres were performed until a plateau was reached (attempts limited to five). All volumes were expressed at body temperature and pressure saturated with water vapour (BTPS), and read to the nearest 0.025 l.

The accuracy and linearity of the Vitalograph was checked on a weekly basis using a 1 l syringe (Vitalograph Ltd), compared to the manufacturers tolerence limits and adjusted if necessary. It was checked for air leaks daily.

3.4 Heart Rate

During the laboratory based tests (incremental threshold loading and treadmill exercise tests) the heart rate was monitored continuously with a single lead ECG signal (Graseby Medical, Cardiac Monitor 304). The electrodes were applied to approximate the standard chest lead V5 (mid-line of right clavicle and 5th intercostal space, left anterior axilla). The monitoring electrodes were attached after preparing the areas with alcohol and light abrasion to improve electrical contact. The cardiac monitor displayed a continuously updated heart rate (measured from R-R wave time), a real-time ECG signal and a static baseline signal for comparison.

During the field walking tests the heart rate was monitored using a short range telemetry device (Polar Electro, Sports Tester PE3000). The device consists of a transmitter on a belt worn around the chest and a receiver worn around the wrist. The belt has two electrodes which are placed over the heart. Electrical contact is achieved by wetting the electrodes. The receiver has a memory for storing the heart rate signal and a stopwatch facility to enable synchronisation between the exercise period and monitoring. The heart rate was monitored continuously, and the 15 second average recorded for data analysis.

3.5 Respiratory gas analysis and ventilation measurement

Measurements of oxygen consumption and ventilation were made using the OxyconBeta system (Mijnhardt Ltd., Holland). This is a fully computerised breath-by-breath exercise testing system incorporating fast-response oxygen

(paramagnetic) and carbon dioxide (infra-red) gas analysers, and a flow-turbine mouthpiece valve which detects inspiratory and expiratory airflow. The subject was required to breathe through a flanged rubber mouthpiece attached to the flow-turbine valve. A noseclip was used and all connections checked for leaks prior to testing. Gas flow through the flow-turbine unit is measured continuously by electronic detection (photo-diodes) of the rotation of the turbine vanes in the mouthpiece valve. Samples of inspiratory and expiratory gas are diverted to the analysers for the measurement of oxygen and carbon dioxide concentration.

The system required a one hour warm-up period and was calibrated for gas analysis (room air, and 5% CO_2 in nitrogen) and volume (3 l syringe) prior to each test. The system has internal temperature and barometric pressure sensors to enable the correct gas volume measurement, and correction to BTPS and standard temperature and pressure dry (STPD) as appropriate. In order to remain consistent with clinical practice, all gas volume measurements were calculated to BTPS with the exception of $\dot{V}O_2$ and $\dot{V}CO_2$ which were calculated to STPD.

The test-retest reliability of the gas analysis measurements were assessed in a preliminary study with six healthy subjects (appendix 1). In addition, to ensure quality control of measurements over a wide operating range, one healthy subject (SMR) performed an incremental treadmill test (4 x 2 min test stages) on a regular basis during the study periods (appendix 2).

3.6 **Treadmill**

A treadmill was used throughout the studies (Jaeger LE 3000). The gradient and speed were adjusted from a programmable touch-pad keyboard. The treadmill speed was checked at the start and periodically throughout each study period (appendix 3).

3.7 Incremental Shuttle Walk Test

The incremental shuttle walk test is an incremental, externally-paced, symptom limited field test described by Singh (1992). The test consists of a 10 metre course demarcated by cones. The object of the test is to walk at a set-pace around the course to reach a symptom limited maximum. The pace is externally controlled by bleeps from a pre-recorded cassette tape. The test is progressive and maximal, with increments in walking speed every minute. There are a set of standardised instructions to the patient at the start of the tape, which explain the purpose of the test and how it should be performed. The bleeps indicate when turning should occur around the cones. The test is terminated for any one of the following reasons: too breathless to continue; too tired; unable to keep up the set pace.

The total distance walked was recorded, and patients asked to rate breathlessness and perceived exertion at the end of the test from Borg scales (1982). Heart rate was recorded throughout the test using the short range telemetry device (Sport Tester, Polar Electro, Finland).

3.8 Blood sampling

Samples of arterialised capillary blood were taken for the analysis of blood gases and pH, and for the measurement of lactate concentration. The samples were taken from the earlobe following vasodilation with a preparatory cream (Algipan, Wyeth laboratories). All traces of the cream were removed and the lobe was cleaned with alcohol and thoroughly dried before the ear was pieced with a lancet. For blood gas measurement 100 µl samples were collected in heparinised glass capillary tubes, placed on ice and analysed within 10 minutes on a Corning BGA machine (Corning UK). The machine was fully automatic with half hourly calibration cycles in addition to a one-point calibration following each analysis.

For the lactate analysis duplicate samples (20µl) were collected and immediately deproteinised in 100 µl iced perchloric acid (2.5%) to arrest metabolism and for subsequent storage at minus 70°C. The samples were

analysed at a later date using the fluorometric enzymatic micro-method described by Maughan (1982) (appendix 4). Quality control of the technique included regular analysis of commercially prepared Q.C. ampoules, with specified tolerance limits, to assess accuracy. Precision of the technique was assessed from the repeat analysis of a single blood sample. A coefficient of variation was calculated and a value of 3.3% was obtained (appendix 4).

3.9 Borg rating of breathlessness and perceived exertion

The sensations of breathlessness and perceived exertion were rated by all of the patients. Breathlessness was rated at rest and at the end of exercise, in addition to perceived exertion. Patients were asked specifically to rate how breathlessness they felt, and to rate how difficult the exercise felt, from the separate Borg scales. The Borg scale for breathlessness (1982) consists of a series of descriptors ranging from 'nothing at all' with a zero rating to 'maximal' rated at 10. Similarly the scale for perceived exertion has a series of scores from 6 to 20 and descriptors ranging from 'very, very light' to 'very, very hard' from which subjects choose the most appropriate (appendix 5).

3.10 The Chronic Respiratory Disease Questionnaire (CRDQ)

The questionnaire was used to assess the emotional and functional stability of patients with COPD throughout the study periods. It was administered at the start of any study period and repeated every two weeks. The questionnaire was designed to assess four areas of a patients' well-being: dyspnoea; fatigue; mastery (control of the disease); and emotional function (Guyatt 1987). The questionnaire consisted of 20 questions. The first question assessed the degree of breathlessness experienced during five activities identified by the patient. The remaining questions required the patient to select a numbered response from a range appropriate to the question. A comparison of the total score for each component was made between sequential administrations to examine functional stability. A significant change was deemed to have occurred if the total score had increased by at least 0.5 per question (maximum potential change for each component: dyspnoea 2.5; fatigue 2.0; emotion 3.5; mastery 2.0).

3.11 Subject recruitment, consent and ethical approval

Patients were recruited from the medical out-patient clinics or from the Glenfield Hospital pulmonary rehabilitation course. The study was initially explained to the patient and, if they expressed an interest, a date for a screening visit was made. They were also provided with an information leaflet to read in their own time. At the screening visit patients confirmed they had read the study information leaflet and any questions were answered. Signed consent was then sought with the patient fully aware of the study entailment, risks and benefits. It was also made clear that withdrawal from the study was allowed at any time without the need to express a reason and without jeopardy to future treatment.

Written submissions were made to the local ethical committee (Leicestershire Health) and approval was granted for all the studies undertaken.

3.12 Prediction values and conversion factors

Values pertaining to normal physiological function were calculated from a series of regression equations derived from studies of healthy populations. These are termed predicted values and were calculated for $\dot{V}O_{2max}$ (Bruce 1973), HR_{max} (Wasserman 1994), FEV_1 and FVC (Quanjer 1993), and PI_{max} (Black 1969). $\dot{V}_{Emax}$ was calculated from an equation developed from 50 patients with COPD (Spiro 1975). The regression equations are reproduced in appendix 6.

The traditional units for mouth pressures and other pressure measurements relating to changes within the thorax are cm H_2O. To remain consistent with clinical practice and for comparison with other published data the traditional units are used throughout. The conversion factor from cm H_2O to the SI unit kilopascal (kPa) is 0.098 (i.e. 1 cm H_2O = 0.098 kPa).

3.13 **Statistical Methods**

Parametric statistical methods were employed for data that was interval and/or ratio with sample sizes ≥10. Summary data is expressed as mean and standard deviation (SD), unless otherwise stated. Relationships between variables were examined using the Pearson Product Moment correlation coefficient (r), and the method of least squares was used for any regression analysis. Multiple linear regression was used to establish the determinants of exercise performance where there were two, or more, variables significantly related to a single factor. The Student's t-test was used to examine the differences between two correlated means, and analysis of variance (ANOVA) used for multiple comparisons (i.e. greater than 2). The post hoc Scheffé test was used to determine where significant differences occurred. To express the level of agreement between repeat measurements the mean difference between two variables, the standard error (SE) and the 95% confidence intervals were calculated according to the recommendations of Bland and Altman (1986). Relationships and differences were considered significant at the 5% level.

Non-parametric statistical methods were used for sample sizes < 10 and for non-continuous data. Both mean and median values have been calculated to summarise data. The Wilcoxon signed ranks test was used to assess the difference between correlated Borg scores and Friedman analysis of variance for multiple comparisons. The 5% level of significance was adopted throughout.

Chapter 4

EVALUATION OF INCREMENTAL THRESHOLD LOADING OF THE RESPIRATORY MUSCLES IN COPD

4.1 INTRODUCTION

The static measures of respiratory muscle function e.g. PI_{max} and PE_{max} make no account of the performance of the muscles under dynamic conditions, or during the increased ventilatory demands imposed by exertion. Assessment of the ability of the respiratory muscles to respond to such conditions is offered by incremental threshold loading (ITL). The method imposes a threshold load to inspiration which may be altered in an incremental manner analogous to the use of a cycle ergometer or treadmill during a whole body exercise test. As such, the technique also offers the potential for the examination of the metabolic and cardio-respiratory responses to quantifiable increases in respiratory work.

Many existing pharmacological and exercise training interventions have the potential to affect both respiratory muscle and whole body exercise performance. In order to evaluate changes in the functional capacity of the respiratory muscles arising from such interventions, simple and reproducible tests of respiratory muscle performance are desirable. Exercise training interventions may also influence the development of an exercise lactic acidosis. This is particularly important in COPD as its occurrence will burden the ventilatory system further as a result of the additional CO_2 and H^+ ions generated during the buffering process of the acid. There is little information regarding the contribution of the respiratory muscles to any lactic acidosis in COPD. Incremental threshold loading therefore provides the opportunity to examine changes in blood lactate following a period of increased ventilatory work.

An electronic threshold loading device utalising a solenoid valve has been described by Bardsley (1993). The device demonstrated a number of advantages over the weighted plunger method in a group of healthy individuals. It was found to be accurate and linear over a wide range of mouth pressures and was unaffected by breathing pattern. However the

device has not been assessed within the clinical setting in patients with COPD.

Thus the purpose of this initial study was twofold:

1. To examine the suitability of ITL, using the electronic solenoid valve device, as a simple method of assessing respiratory muscle performance, without external constraint, in a group of patients with COPD.

2. To assess the energetics of the task in terms of $\dot{V}O_2$, $\dot{V}_E$, heart rate and blood lactate concentration.

4.2 METHODS

4.2.1 Patients

Twelve patients (9 men, 3 women, mean age 61 years) with COPD were recruited from the out-patient clinics. The recruitment procedures and collection of demographic data conformed to the methods described in chapter 3. To ensure functional stability throughout the study, the Chronic Respiratory Disease Questionnaire (CRDQ) (Guyatt 1987) was administered at the start and every alternate week. Patients were requested to refrain from inhaled bronchodilators 4 hours prior to testing. None of the patients were on oral bronchodilators or theophyllines.

4.2.2 Study Design

The study involved performance of an ITL test on two separate visits (mean time between visits 15 days). The first visit was considered a practice session. All visits were at the same time of day. The baseline measurements were the same for each visit and included FEV_1 and PI_{max}. During the ITL test the breath by breath mouth pressure (Pm) was recorded in addition to the pressure-time product ($\int Pdt$), achieved by integrating Pm with respect to time. Measurements of $\dot{V}O_2$, $\dot{V}_E$ and HR were made at rest and throughout the test, and samples of blood collected before and after the test to determine lactate concentration. To assess test repeatability seven of the patients performed a third test during a further visit. The remaining patients had previous experience of ITL with the solenoid device and were therefore excluded from this limb of the study.

4.2.3 **Incremental Threshold Loading**

The solenoid valve device has been described in detail elsewhere (Bardsley 1993). It consists of a wide bore, 24 volt DC solenoid valve which opens when the required negative mouth pressure is attained, and closes on expiration. The mouth pressure was detected by a micro-transducer (Gould Instruments, Bilthoven, The Netherlands, model P50) located at the mouthpiece (figure 4.1). The output from the micro-transducer was fed into an amplifier and a display and alarm module (Gould, models 13-4615-50 and 13-4611-12). The threshold pressure can be varied and was selected on a digital display. When the mouth pressure reaches the value set on the digital display an internal relay is actuated, connecting 24V from a Farnell L30 power supply to the solenoid valve via a latching circuit, so holding the valve open. During expiration pressure in the mouthpiece rises, triggering the high pressure alarm which resets the latching circuit and closes the valve.

The FEV_1 and PI_{max} were measured before the threshold loading commenced. The PI_{max} was measured during a maximal inspiration from residual volume using a hand-held electronic mouth pressure meter, which incorporated a small air leak to reduce buccal pressure (Precision Instruments, DeVilbiss UK). A noseclip was used and the pressure sustained for 1 second was recorded, the best of three attempts was taken. If the third attempt produced the highest measurement, further attempts were made until a plateau was reached (limited to eight attempts). For the threshold loading, patients were seated in a hard-backed chair, asked to wear the noseclip and breathe through a flanged rubber mouthpiece. This was attached to the solenoid device and the flow-turbine measurement head of the gas analysis system (figure 4.1). Patients were asked to relax and breathe at a comfortable rate and depth. Tidal volume (TV) and breathing frequency (fR) were unrestricted and expiration was not loaded.

The initial load and size of the one minute increments were determined individually for each patient, based on the measurement of PI_{max}. The aim was to achieve the maximum threshold load within approximately 10 minutes, thereby avoiding fatigue and premature cessation of the test prior to

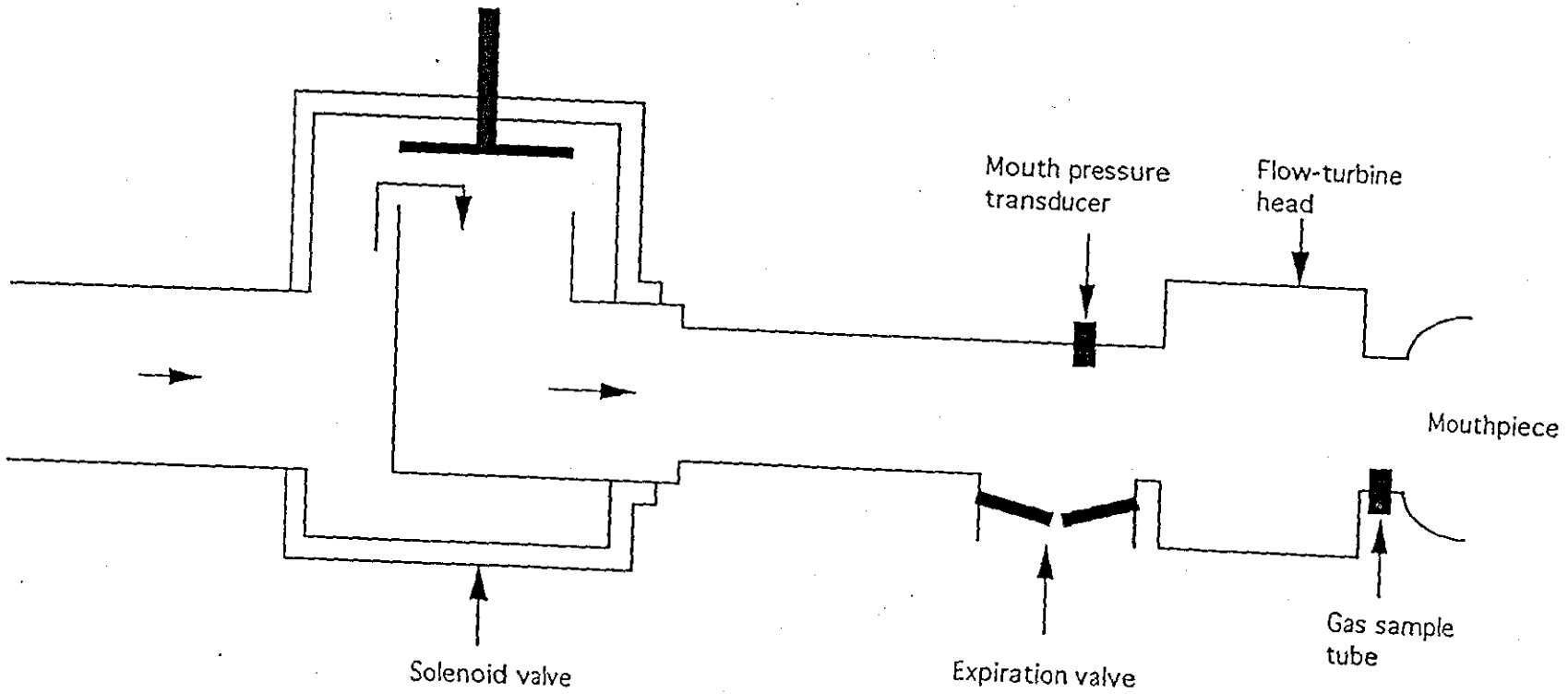


Figure 4.1 Schematic diagram of solenoid valve and flow turbine head

the achievement of maximal workloads. Thus a patient with a low PI_{max}, e.g. 55 cm H_20 would start at a threshold load of 10 cm H_20 followed by 5 cm H_20 increments every minute. The test finished when the patient was unable to reach the set threshold pressure required to open the solenoid valve. The peak mouth pressure achieved was taken as the highest pressure achieved for a full minute. Throughout the test the breath by breath Pm, and the $\int Pdt$ were recorded on a paper-strip chart (Gould, model 13-4615-09). Patients were asked to rate breathlessness and perceived exertion at the start and end of the test from Borg scales.

4.4.4 **Cardio-respiratory and metabolic measurements**

The breath-by-breath, computerised gas analysis system (described in chapter 3), was used throughout. Prior to the first threshold load, patients relaxed for 10 minutes with the mouthpiece and nose clips, breathing through the unrestricted apparatus. During the last five minutes of the rest period measurements of $\dot{V}_E$, $\dot{V}O_2$, $\dot{V}CO_2TV$, fR, $\dot{V}CO_2$ to $\dot{V}O_2$ ratio (RER) and end-tidal CO_2 ($P_{ET}CO_2$) were recorded, and heart rate (HR) was measured from a single lead ECG. The breath by breath analysis was averaged over the last 30 seconds of each minute. The same cardio-respiratory measurements were made throughout the threshold loading test.

Prior to the start of the test a small sample of blood (2 x 20 µl) was collected from the earlobe for measurement of the baseline lactate concentration, as described in chapter 3. Further blood samples were collected at 4 minutes post-testing. Previous studies which have examined respiratory muscle lactate production have used shorter sampling times, therefore to examine the effect of time, samples were also taken at 2 minutes after the end of the test from six patients. The blood was stored at minus 70°C and analysed later according to the method described by Maughan (1982) (appendix 4).

4.3 **RESULTS**

Three patients showed a deterioration in symptoms during the study from the onset of common colds (change in CRDQ scores and fall in FEV_1). Testing on these patients was suspended until they returned to baseline levels. One

patient was unable to tolerate the noseclip for the duration of the test and was therefore eliminated from the analysis. The baseline FEV_1, PI_{max} measurements and anthropometric details of the group are presented in table 4.1

4.3.1 **Performance of incremental threshold loading**

An example of the inspiratory pressure wave form and the ∫Pdt signal from a representative threshold loading test is shown in figure 4.2. All patients for whom data are presented, found the threshold loading technique acceptable. The mean maximal performance is shown in table 4.2, and the Borg ratings of perceived exertion and breathlessness at rest and at peak performance are shown in table 4.3. The Pm response was found to be linear over the range of set threshold pressures (-5 to -100 cm H_20), with a correlation coefficient of 1.000 (figure 4.3). The ∫Pdt increased in a regular manner, and there was a good correlation with the threshold pressure (r=0.980) (figure 4.4).

Evaluation of the relationship between peak ITL performance and baseline measurements revealed a significant relationship between peak Pm and PI_{max} (r=0.65, p=0.03, figure 4.5), but only a weak relationship with FEV_1, (r=0.42, p>0.05), and no relationship with FVC (r=0.267, p>0.05). There was no significant relationship between the pressure-time product and FEV_1 (r=0.119, p>0.05), or with PI_{max} (r=0.378, p>0.05).

4.3.2 **Cardio-respiratory responses to threshold loading**

The cardio-respiratory response to the threshold loading is shown in table 4.4. There were significant increases in $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}_E$, TV and HR, and a significant decrease in the $P_{ET}CO_2$ at the end of the test ($p<0.05$). The mean increases from resting levels for $\dot{V}O_{2peak}$, $\dot{V}_E$ and HR were 118 (52) (47%) $ml.min^{-1}$, 11.4 (6.5) (89%) $l.min^{-1}$ and 12.4 (6.0) (16%) $beat.min^{-1}$ respectively. The increase in $\dot{V}_E$ was achieved primarily by an increase in the TV rather than any change in the fR.

Table 4. 1 Summary of patient characteristics.

	Mean (SD)	Range	% of predicted
FEV_1 (l)	1.28 (0.33)	0.80 - 1.78	43 (12)
FVC (l)	3.21 (0.54)	2.48 - 4.60	86 (13)
(FEV_1/FVCx100) (%)	40 (10)	26 - 55	-
PI_{max} (cm H_2O)	78.4 (23.5)	40.7 - 126.5	81 (21)
Age (y)	61 (6.6)	50 - 71	-
Height (m)	1.72 (0.07)	1.58 - 1.80	-
Weight (kg)	73.1 (13.4)	54.2 - 96.0	-

n=12, 9 men, 3 women

Mean (SD) and range for baseline lung function and anthropometric details of the patient group. Lung function measurements are also expressed as % of values predicted for a normal population.

Figure 4.2 Example of mouth pressure recording

Table 4.2 Peak performance during incremental threshold loading

	Mean (SD)	Range
peak Pm (cm H_2O)	52 (23)	20 - 100
$\int$Pdt (cm $H_2O.s^{-1}$)	1410 (867)	400 - 2750
% of PI_{max}	65 (21)	41 - 127
Time (min)	8.5 (3.0)	4.0 - 14.0

n=11

Mean (SD) and range for peak performance and total test time.

Table 4.3 Borg scores for breathlessness and perceived exertion

		Mean (SD)	Median	Range
BS	rest	1.3 (1.1)	1	0 - 3
	peak	4.5 (2.2)	5	0 - 7
RPE	peak	16.7 (2.4)	17	11 - 19

n=11

Mean (SD), median and range of Borg ratings for breathlessness (BS) at rest and at peak threshold load, and for perceived exertion (RPE) at peak load.

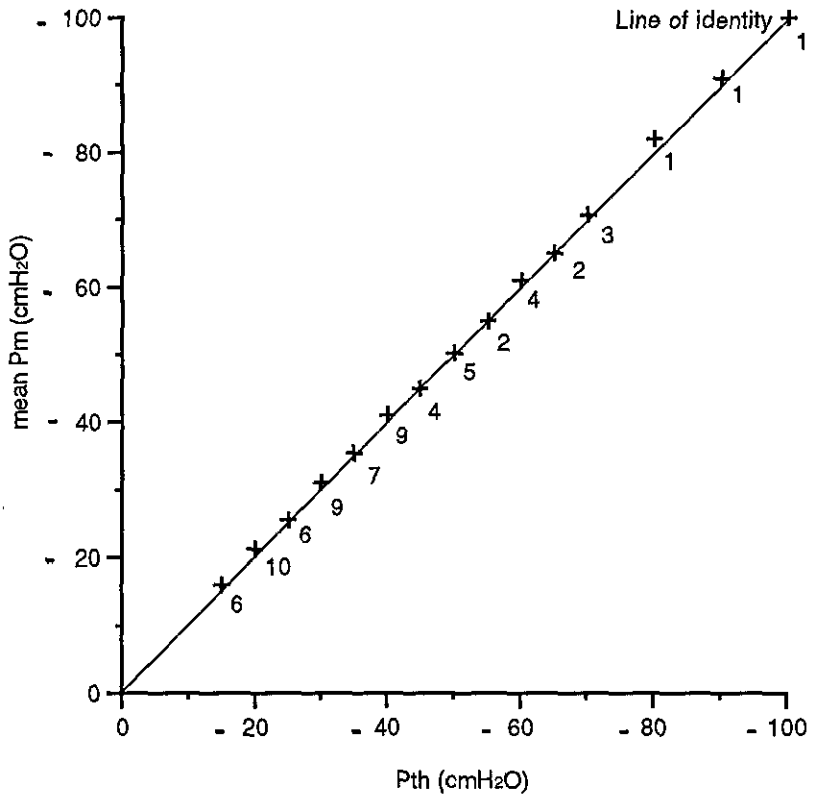


Figure 4.3 Relationship between mean mouth pressure (Pm) and set threshold pressure (Pth). The figures indicate the number of values for each point. NB standard error bars hidden by data points.

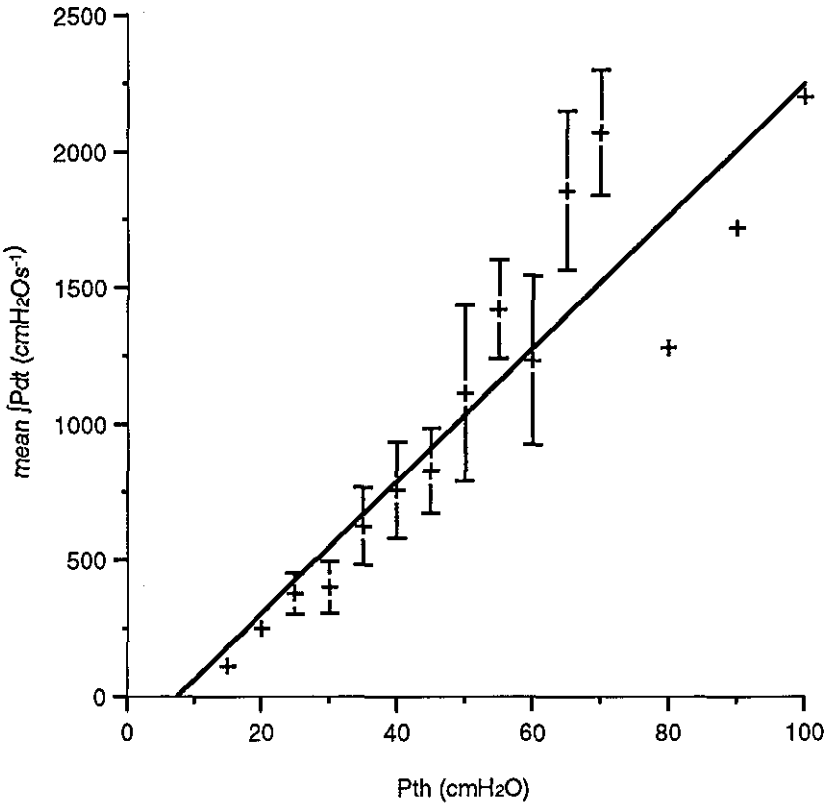


Figure 4. 4 Relationship between mean pressure-time product (∫Pdt) and threshold pressure (Pth). The linear regression line has been drawn.

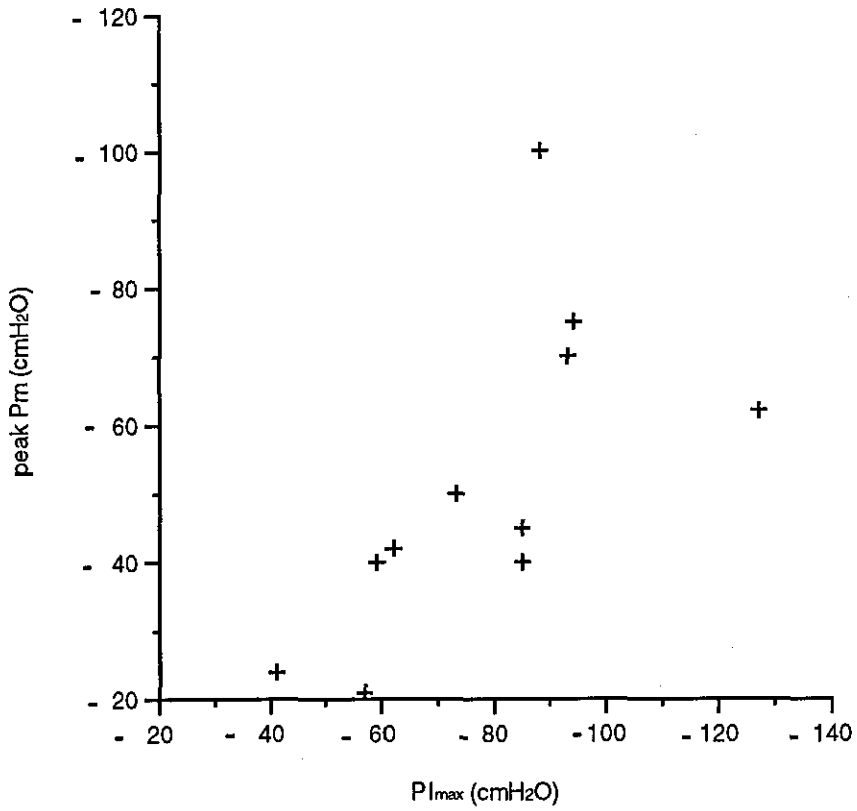


Figure 4.5 Relationship between peak mouth pressure (peak Pm) and maximal inspiratory mouth pressure (PI_{max}).

Table 4.4 Cardio-respiratory measurements during incremental threshold loading

	$\dot{V}O_2$ ($ml.min^{-1}$)	$\dot{V}CO_2$ ($ml.min^{-1}$)	$\dot{V}_E$ ($l.min^{-1}$)	TV (ml)	fr ($breath.min^{-1}$)	$P_{ET}CO_2$ (kPa)	RER	HR ($beat.min^{-1}$)
Rest	250 (24)	222 (25)	12.8 (2.6)	847 (292)	16.3 (4.2)	4.21 (0.68)	0.92 (0.10)	77 (15)
	212 - 302	186 - 267	9.6 - 18.5	564 - 1572	10 - 22	2.99 - 5.38	0.79 - 1.02	56 - 102
Peak Load	367 (65)*	359 (62)*	24.2 (6.2)*	1628 (501)*	15.5 (4.9)	3.46 (0.46)*	0.98 (0.13)	89 (18)*
	296 - 540	293 - 503	13.8 - 33.4	1078 - 2441	6 - 21	2.39 - 4.18	0.82 - 1.15	58 - 122

n=11, * $p < 0.05$ (peak c.f. rest)

Mean (SD) and range for cardio-respiratory measurements at rest and at peak threshold load.

The relationship between $\dot{V}O_{2peak}$ and peak Pm was weak with a correlation coefficient of 0.510, $p>0.05$. There was no relationship between $\dot{V}O_{2peak}$ and $\int Pdt$ ($r=0.122$, $p>0.05$). Two patterns emerged from the individual responses in $\dot{V}O_2$ to increasing threshold loads. Two patients had a fairly linear increase in $\dot{V}O_2$ with increasing threshold load, whilst the more typical response was a jump in $\dot{V}O_2$ during the initial load, followed by small and fluctuating increases until the peak load was reached. The mean response in $\dot{V}O_2$ and $\dot{V}_E$ to progressive threshold loads is illustrated in figure 4.6.

4.3.3 **Lactate response to threshold loading**

All patients had samples collected at 4 minutes post-loading, and six patients had an additional sample collected at 2 minutes post-loading to assess any time effect. The mean concentrations at baseline, 2 and 4 minutes post-loading are shown in table 4.5, and the mean increases from baseline (Δ) are also given. There was no significant difference between the baseline and 4 minute measurement, however the difference between baseline and the 2 minute concentration was of borderline significance ($p=0.05$). There was a significant relationship between the lactate concentration and the peak Pm ($r=0.800$, $p<0.05$), figure 4.7.

4.3.4 **Test repeatability**

To examine the variability of the technique seven of the patients had an additional test on a further visit, giving a total of three tests performed on separate occasions (table 4.6a). Analysis of variance of repeat measures showed there was no significant difference between Pm, $\int Pdt$, $\dot{V}O_{2peak}$ and $\dot{V}_E$ measured at peak threshold load on the three test occasions ($p>0.05$). The mean differences between the three tests and the 95% confidence intervals are shown in table 4.6b. The smallest differences for peak Pm and $\int Pdt$ occurred between tests 2 and 3, suggesting the test repeatability improved following one practice test. There was a significant correlation between the differences in peak Pm for tests 2 and 3 and the mean of the measurements ($r=0.765$) (figure 4.8). The $\dot{V}O_{2peak}$ and $\dot{V}_E$ measurements at

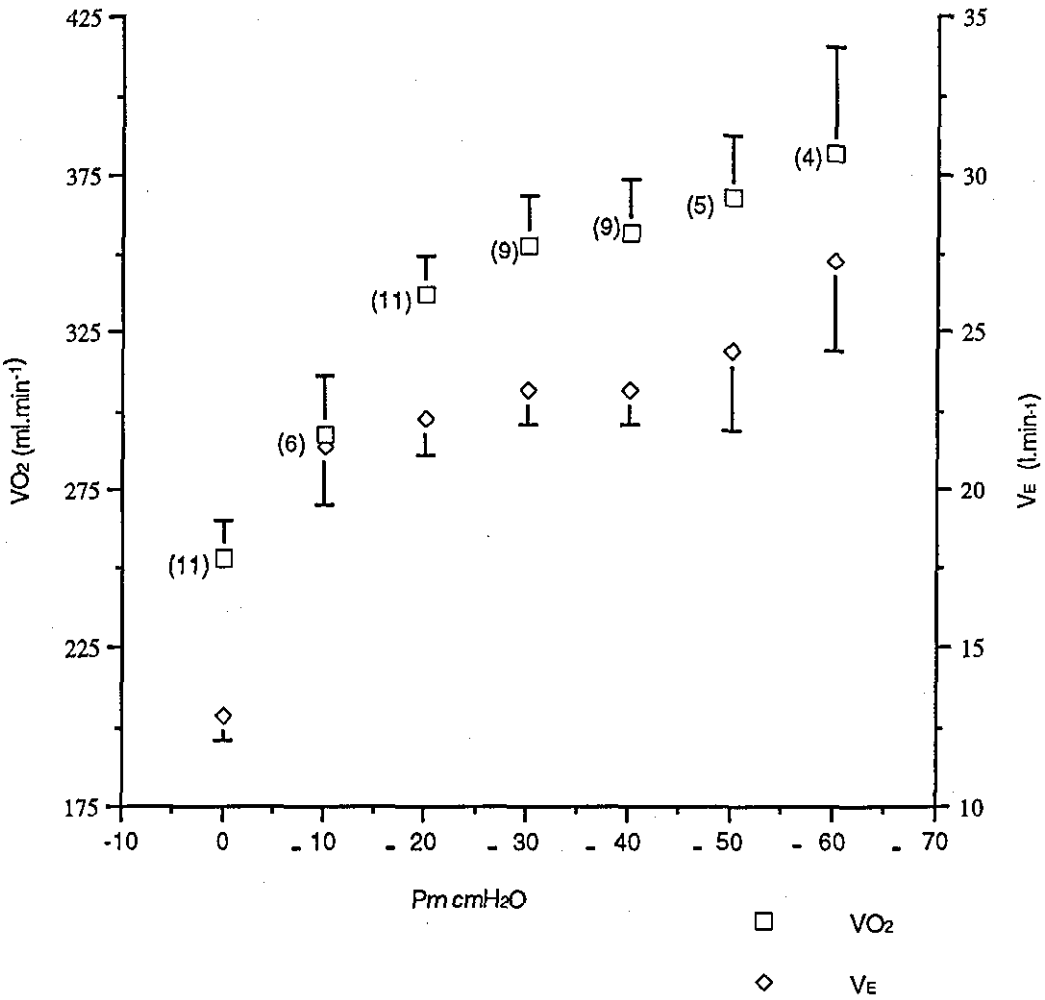


Figure 4.6 Mean (SE) VO_2 and V_E with increasing mouth pressure (Pm). () indicates the number of values at each threshold load.

Table 4.5 Capillary blood lactate response to incremental threshold loading

	Baseline	*2 mins*	*4 mins*	*Δ 2 min*	*Δ 4 min*
Lactate ($mmol.l^{-1}$)	0.68 (0.29)	1.04 (0.29)*	0.82 (0.26)	0.32 (0.21)*	0.15 (0.24)
	0.29 - 1.76	*0.64 - 1.31*	*0.49 - 1.18*	*0.07 - 0.56*	*0.00 - 0.70*

2 min n=6, 4 min n=10 * p=0.05 (post test c.f. baseline)

Mean (SD) and range of blood lactate concentrations at baseline, 2 and 4 minutes post loading. The mean increases from baseline levels (Δ) are also shown.

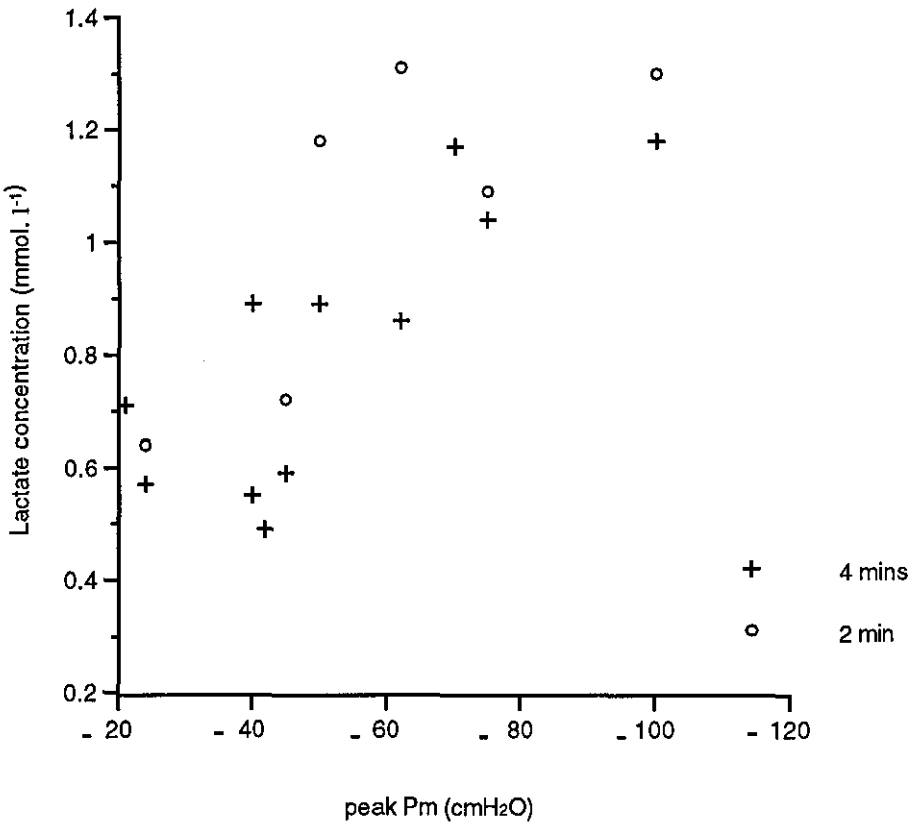


Figure 4.7 Blood lactate response to ITL

Assessment of Test Repeatability

Table 4.6a Peak performance during repeat incremental threshold loading tests

	peak Pm ($cm\ H_2O$)	$\int Pdt$ ($cm\ H_2O.s^{-1}$)	$\dot{V}O_{2peak}$ ($ml.min^{-1}$)	$\dot{V}_{E\ peak}$ ($l.min^{-1}$)
Trial 1	48.7 (7.6)	1646 (293)	399 (19)	26.4 (3.7)
Trial 2	52.1 (8.2)	1473 (247)	417 (35)	24.3 (2.7)
Trial 3	52.6 (10.0)	1363 (297)	370 (31)	22.0 (2.4)

n=7

Mean (SD) peak values achieved during ITL performed at three separate visits.

Table 4.6b Mean differences between repeat tests.

Test	peak Pm ($cm\ H_2O$)	$\int Pdt$ ($cm\ H_2O.s^{-1}$)	$\dot{V}O_2peak$ ($ml.min^{-1}$)	$\dot{V}_E$ ($l.min^{-1}$)
2 - 1	3.4 (2.6) -2.9 - 9.8	-173 (218) -707 - 361	12 (34) -83 - 108	-1.5 (2.3) -8.0 - 5.0
3 - 1	3.9 (3.7) -5.3 - 13.0	-283 (225) -833 - 268	-22 (15) -64 - 20	-3.1 (2.0) -8.6 - 2.5
3 - 2	0.4 (2.3) -5.3 - 6.1	-110 (201) -603 - 383	-35 (37) -127 - 56	-2.2 (1.4) -2.2 - 9.8

n=7

Mean differences (SE) and 95% confidence intervals between repeat tests.

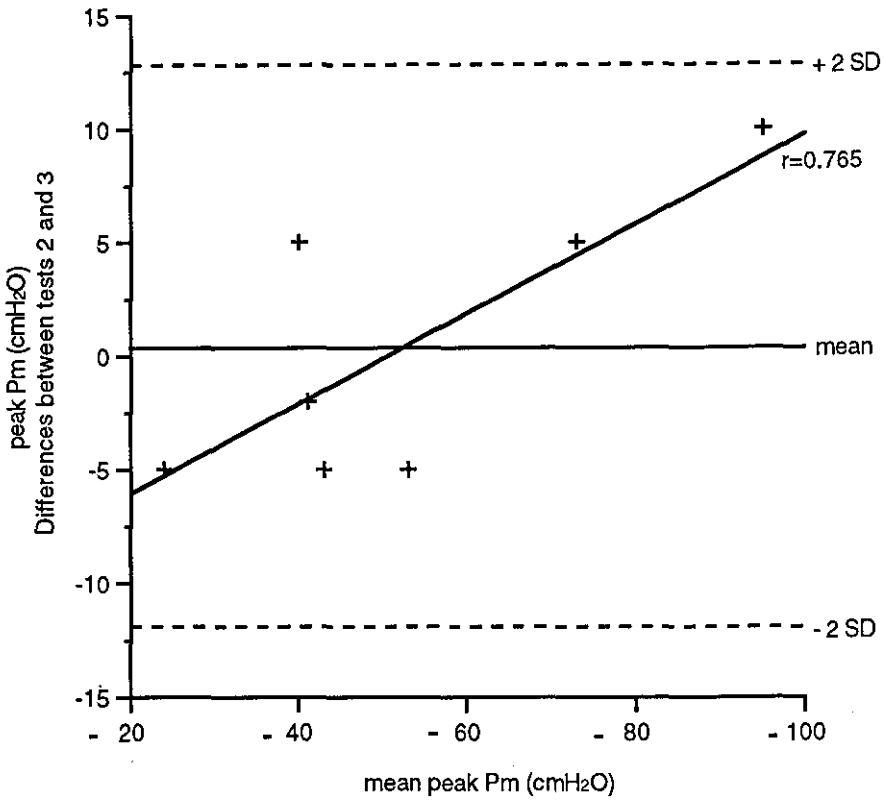


Figure 4.8 Differences between peak mouth pressure (peak Pm) (tests 2 and 3) and the mean of the two values.

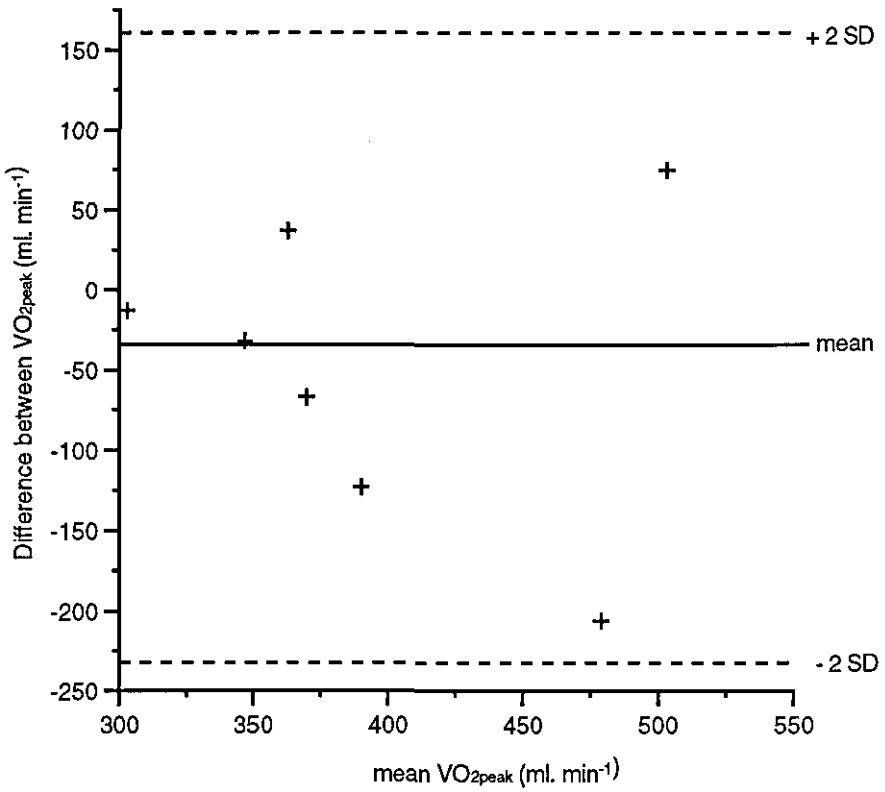


Figure 4.9 Differences between peak oxygen consumption (VO_{2peak}) (tests 2 and 3) and the mean of the two values.

peak load show a wide variability between tests (figure 4.9 illustrates the differences between repeat $\dot{V}O_{2peak}$ measurements). The limits of agreement (i.e. mean difference ± 2 sd), which provide an estimate of the widest deviation likely to be observed, were -233 to 163 ml.min^{-1} for $\dot{V}O_{2peak}$ and -9.8 to 5.4 l.min^{-1} for $\dot{V}_E$, for tests 2 and 3.

4.4 DISCUSSION

The incremental threshold loading test using the solenoid valve device was simple to administer and acceptable to all the patients. The one patient who failed to complete the test did so because of an intolerance of the noseclip and not as a result of the loading sensation experienced during inspiration. In the initial developmental study, which assessed the response of the solenoid valve in a group of healthy subjects, the mouth pressure response was found to be accurate and linear over a wide range of threshold pressures (Bardsley 1993). A linear response was maintained with the group of patients examined in this study, which presented a wide range of airflow obstruction from moderate to severe. The workload protocol of one minute increments (size of increment individually determined for each patient according to the baseline PI_{max}) achieved the maximum threshold load within approximately 10 minutes, thus ensuring the test did not exhaust patients prematurely, and was quick and simple to apply.

The increase in $\dot{V}_E$ during ITL was achieved primarily by increasing TV whilst fR remained unchanged. This pattern of change has also been reported in normal subjects (Yanos 1990). However, it is in contrast to the findings from Kelson (1978) in a study of six patients with COPD. A decrease in fR and a less than compensatory increase in TV were measured, resulting in an overall drop in $\dot{V}_E$ and an increase in $P_{ET}CO_2$. The threshold loading was at a constant load of 40 cm H_20 (40 to 57% of individual PI_{max}), and was maintained for at least 10 minutes. The author concluded that adequate ventilation may not be sustainable when high loads (relative to PI_{max}) were presented for prolonged periods of time.

The change in the breathing pattern during the threshold loading was different from that which usually occurs during either disease exacerbation or during whole body exercise in COPD. During exercise patients with COPD increase fR in addition to increasing TV (Spiro 1975), and tachypnea is a feature of disease exacerbation (Pride 1995). The failure to reproduce similar changes in the breathing pattern to those seen during naturally occuring instances of increased mechanical load in COPD i.e. exercise or exacerbation, represents a limitation of the threshold loading test.

The protocol adopted in the current study was different from the constant-load test employed by Kelson (1978). It was incremental, starting with low threshold loads which increased every minute, and the average time of the test was 8.5 minutes, therefore the higher loads were tolerated for shorter periods. Respiratory muscle fatigue has been shown to occur during the application of loads of 60 - 75% of PI_{max} in normal subjects (Roussos 1977). Fiz (1990) demonstrated that respiratory muscle strength (PI_{max}) decreased in patients with COPD after constant threshold loads, equivalent to 65% of PI_{max}, were applied to exhaustion. The authors suggested this reflected the occurrence of high frequency fatigue following the application of high threshold loads.

The results from the current study demonstrate patients with COPD are able to increase ventilation during incremental and progressive threshold loading of relative short duration, however this response may change with endurance loading. The finding suggests patients are able to respond appropriately to short periods of increased mechanical load e.g. dynamic hyperinflation during exercise, whereas the findings from other workers (Kelson 1978) suggest prolonged periods of increased loading in COPD, e.g. as a result of infection or exacerbation of symptoms, may interfere with the ability to maintain adequate alveolar ventilation.

The increase in $\dot{V}_E$ is further supported by the significant fall in $P_{ET}CO_2$ suggesting a degree of hyperventilation. Previous reports of hyperventilation with threshold loading are mixed. It was recorded at low threshold loads in seven normal subjects, but at higher loads (>55%Pm/PI_{max}) there was an

increase in the $P_{ET}CO_2$ (Martyn 1987). Conversely, an elevated $P_{ET}CO_2$ was recorded during assessments of endurance (Nickerson 1982), and during incremental loading, where it occurred only at the higher threshold loads (Eastwood 1994). Both of these studies were performed with normal subjects. In a study from Yanos (1990), which employed sustained threshold loading at four loads in normal subjects, there was a decrease in $P_{ET}CO_2$. The fall was less profound at high loads, but was significant for loads of 20, 40 and 60% of PI_{max}. The results from the current study have demonstrated hyperventilation with ITL occurs in the presence of COPD.

Overall, the evidence to date suggests threshold loading does provoke hyperventilation in normal subjects and the effect is influenced by the relative workload. At high loads it is diminished or absent and at very high loads $P_{ET}CO_2$ may increase, suggesting alveolar hypoventilation. The present study confirms the hyperventilatory effect is preserved in COPD, up to threshold loads of 65% of PI_{max} presented for short periods of time.

The protocol adopted for the current study did not control for end-expiratory lung volume (EELV). This may have changed as a consequence of the increased ventilation and any dynamic hyperinflation would impose an extra burden (additional to the external threshold load) to the oxygen cost of the exercise. In normal subjects ITL has been shown to cause a progressive decline in EELV, which approached RV at high loads (Eastwood 1994). A decrease in EELV places the inspiratory muscles at an advantageous position on the length-tension curve for the generation of greater inspiratory pressures (Pride 1995). Conversely, it is well documented that EELV increases with increasing ventilation in COPD e.g. during progressive exercise (Pride 1995). Therefore it may be reasonable to assume the increased ventilation seen during the ITL provoked an increase in the EELV. However there was a significant increase in TV, which suggests changes in diaphragm length, as a result of any increases in EELV, were minimal and did not effect inspiratory muscle function adversely. To determine the extent of any hyperinflation and its effect on performance would have required the imposition of more complex measurements e.g. inductance pneumography.

The purpose of this study was to evaluate unconstrained performance which allowed the development of individual responses to the task. The cardio-respiratory changes therefore represent the resultant cost of the individual strategies adopted.

The relatively small increase in $\dot{V}O_2$ during ITL, in comparison to the approximate four-fold increases recorded during whole body exercise in COPD (Brown 1985), reflect the small muscle mass involved in the performance of the task. The increased $\dot{V}O_2$ at peak Pm was in response to the additional cost of the respiratory exercise over and above the requirements whilst resting in an upright, sitting position. Patients were instructed to relax, and to breathe at a comfortable rate and depth, any changes were the result of the strategy adopted to overcome the additional resistance to breathing. The magnitude of the $\dot{V}O_{2peak}$ was greater than the $\dot{V}O_{2peak}$ measured in a recent study of 7 patients with COPD who performed constant threshold loading (40% of PI_{max} for 10 minutes) (Gosselink 1995). The constant load test yielded a $\dot{V}O_{2peak}$ of 288 $ml.min^{-1}$, whilst at maximal loads a $\dot{V}O_{2peak}$ of 367 $ml.min^{-1}$ was measured in the current study. The difference between the values of $\dot{V}O_{2peak}$ from the 2 studies enforces the maximal nature of the incremental protocol.

A similar percentage increase in $\dot{V}O_2$ (55% vs 47% from the current study) was measured in normal subjects at 65% PI_{max} using the weighted plunger method and with two minute increments in load (Martyn 1987). However there are few data available concerning $\dot{V}O_2$ during ITL in COPD. The same is true for the HR response during the technique. A HR of 93 $beat.min^{-1}$ was reported by Nickerson (1982) following measurement of sustainable inspiratory pressure using the weighted plunger device. This is slightly higher than the 89 $beat.min^{-1}$ from the current data, despite a similar achievement of $\%PI_{max}$. However, the former measurement was in a group of younger subjects, therefore the % maximum HR may well be similar.

The mean maximal $\%PI_{max}$ achieved by the patients was lower than achieved by the group of healthy subjects using the solenoid valve (65 versus 90%) (Bardsley 1993). Other studies on healthy subjects using the weighted plunger method with an incremental protocol have also achieved a higher $\%PI_{max}$ (Martyn 1987, McElvaney 1989, Eastwood 1994). In an age-matched controlled study, 79% of the PI_{max} was achieved in healthy, elderly subjects compared to 48% in 8 patients with severe COPD (Morrison 1989a). A similarly reduced $\%PI_{max}$ of 41% was also reported by van't Hul (1995) in 20 patients with moderate to severe COPD.

Respiratory muscle function is compromised in COPD (Rochester 1989) and the reduced $\%PI_{max}$ was not a surprising finding of the study. Additionally, any increase in EELV, as a result of the additional external load, would act to reduce further the pressure generating capacity of the respiratory muscles. Normal subjects possess the capability to reduce EELV which would act to improve the force generating capacity of the diaphragm. However, other factors affecting both respiratory muscle strength and endurance capacity in COPD are also likely to contribute to a reduced performance. These have been discussed in chapter 2, and include nutritional influences, medication, hypoxia and hypercapnia.

The patients from the current study managed to achieve a higher $\%PI_{max}$ compared to the findings of Morrison (1989a) and van't Hul (1995) despite a similar degree of airway obstruction in the patients studied. This might be explained by the differences in protocol and loading device used. A two minute incremental protocol and a weighted plunger device were used in the previously cited studies. The weighted plunger requires the maintenance of the threshold pressure throughout inspiration to hold the plunger open, whereas this is not a requirement with the solenoid valve. As a consequence greater work ($\int Pdt$) is performed with the weighted plunger for equivalent threshold loads (Bardsley 1993). The additional work performed throughout inspiration (holding the plunger against gravity), will influence the onset of muscle fatigue and therefore the maximum pressure achieved. Additionally, a two minute incremental protocol will increase the work performed and

energy consumed, and may lead to the premature cessation of the test, prior to the achievement of a true maximal pressure.

The solenoid valve device presents a true threshold load, i.e. a load is applied only during the initial stages of inspiration, and is therefore more akin to the development of PEEPi as a result of dynamic hyperinflation in COPD e.g. during exercise. However, it may be argued a true threshold load does not entirely mimic the processes present during exercise or symptom exacerbation in COPD. In reality, patients with lung hyperinflation have to overcome a true threshold (PEEPi) as a prelude to inspiration, before the airways obstruction imposes a resistive load. In this respect the ideal device would be a combination of an initial threshold load followed by a resistive load.

The PI_{max} measured prior to the ITL test was reduced in the patient group (81% predicted) and although TLC and its subdivisions were not reported, when corrected for lung volume PI_{max} is often normal or supra-normal in patients with COPD (Rochester 1991). However, the absolute value of peak Pm achieved at the end of the threshold test was reduced in comparison to values from a healthy, elderly group described by Morrison (1989a) where a mean value of 95 cm H_20 was reported. The reduced value from the group of patients examined was an expected finding of the study. The physiological consequences of COPD on the respiratory muscles are widely described (Rochester 1979 and 1991) and discussed in detail in chapter 2 of this thesis.

The relationship between PI_{max} and peak Pm was significant, however it was only moderate (r=0.650). PI_{max} is a static measure which assesses maximum inspiratory pressure generated during a single manoeuvre, and reflects global respiratory muscle strength (Gibson 1989). Bellamere (1982) demonstrated respiratory muscle endurance was related to the force and duration of respiratory muscle contraction. The fraction of maximal force (PI_{max}) generated during each breath was shown to be an important factor in endurance capacity. Therefore, respiratory muscle strength will influence endurance and incremental dynamic performance, however the moderate relationship suggests other factors are important in the determination of peak

Pm. These may include: the development of respiratory muscle fatigue (this was possible since the critical pressure required to induce respiratory muscle fatigue was reached by some patients (60-75% $PI_{max,}$ when using alinear resistances, Roussos 1977)); perception of breathlessness; general exhaustion; nutritional (substrate) status; and generalised muscle weakness. Baseline lung function (FEV_1 and FVC) appeared to have little effect, with poor and non-significant relationships with peak Pm.

A number of studies have examined the endurance time for a particular load (T_{lim}) (McElvenay 1989) or determined the maximum load which can be tolerated for a specific time (Nickerson 1982, Martyn 1987). McElvenay (1989) reported less intra-individual variability using a two minute incremental test compared to an endurance test. Improved reproducibility and a greater maximal performance were also reported by Martyn (1987) using an incremental protocol, compared to the measurement of sustained inspiratory pressure over a 10 minute period. The purpose of the protocol adopted for the current study was to examine the response to quantifiable increases in workrate in a continuous test, and in a manner that was analogous to achieving a peak workload on a cycle ergometer or treadmill. Use of a standardised protocol with well defined end points is essential if the test is to be repeated at a later stage to assess the effects of an intervention, or to monitor progress.

An important aspect of the protocol was the avoidance of any external controls for TV, inspiratory time and flow, and fR. Previous work has shown that breathing pattern influences the measurement of T_{lim} (Clanton 1985). However, Morrison (1989b) reported it was unnecessary to fix fR during incremental loading tests, following a comparison of fixed and unfixed fR. In a comparison of naive and experienced patients with COPD, Richardson (1988) reported good repeatability between incremental tests performed on three occasions without any external constraints on breathing pattern. The effect of unfixed and fixed breathing pattern was examined by Bardsley (1993) using the solenoid valve device. Though subjects tended to reduce fR and shorten the duty cycle, there was no difference between the peak Pm, $\%PI_{max}$ and $\int Pdt$ achieved at the end of the tests. One of the main objectives

for the current study was to measure the response to increases in workload with the patient able to respond freely to the challenge and therefore mimic real life. The absence of external constraints allowed patients to develop their own strategy, thus reflecting a more natural response to the imposed task.

The repeatability obtained for peak Pm was similar to that found by Hopp (1993) in patients with COPD, using the weighted plunger. The author recommended one practice test after finding a significant difference between the first and subsequent visits. This view is supported by the current findings, the smallest differences occurred after one practice test. Other studies have reported no significant differences in peak Pm and $\%PI_{max}$ on repeat testing in normal subjects (McElvenay 1989, Morrison 1989a) and in COPD (Richardson 1988, Morrison 1989a). The significant correlation between the differences of repeat peak Pm and the mean of the measurements (figure 4.8) suggests repeatability changes with the magnitude of the measurement. At the extreme values of peak Pm (≥ 100 cmH2O) the difference between repeat tests represented 10% of the measurement. However for lower values of peak Pm, closer to group mean value, the differences between repeat tests equated to ±6%.

In contrast to the good repeatability of the peak Pm, there was wider variability in the $\dot{V}O_{2peak}$ and $\dot{V}_E$ measurements. This finding suggests the internal work performed varied between tests e.g. extent and pattern of muscle recruitment, possible changes in EELV, whilst the external work remained consistent (i.e. Pm and $\int Pdt$). This contrasts with measurements of whole body exercise in COPD, were good repeatability of $\dot{V}O_{2peak}$ and maximal work rate implies both internal and external components remain consistent (Brown 1985). Data from the preliminary evaluation studies of the gas analysis equipment revealed good repeatability of measurements (appendix 1) with a mean difference of 14 $ml.min^{-1}$ for repeat measurements of $\dot{V}O_{2peak}$ at maximal exercise work rates with limits of agreement (± 2 SD) of -148 to 121 $ml.min^{-1}$. The poor repeatability of the $\dot{V}O_{2peak}$ and $\dot{V}_E$ during ITL suggests this aspect of the test might be less useful for repeat studies.

Previous studies have shown blood lactate concentration peaks at approximately 4 minutes following whole body exercise in normal subjects (Åstrand 1986). In this study there was no significant change in lactate at 4 minutes post-loading. However a small and significant increase occurred at 2 minutes post-loading suggesting a sampling time effect. This may have been examined further by the use of serial sampling throughout the exercise period, in addition to the recovery period. Because of the relatively small muscle mass involved in the performance of the task lactate production will be small and result in a low blood concentration. Lactate is rapidly broken down by the liver, heart and the resting skeletal muscle, and any small scale production is likely to have been processed rapidly.

A number of workers have investigated several different ventilatory challenges, to provoke a lactate response, with mixed effect. Freedman (1983) found a small but significant increase in lactate (Δ 1.10 $mmol.l^{-1}$) following sustained maximum voluntary ventilation (SMVV) in normal subjects but no effect from a resistive load over a period of 200 breaths. Conversely Cooke (1983) was unable to measure any change in blood lactate following SMVV manoeuvres in 5 patients with COPD. Eldridge (1966) was able to provoke an increase in lactate in normal subjects following a period of increased ventilation induced by a large deadspace whilst breathing a reduced oxygen concentration of 15%. Again the increases were only small (Δ 0.41 $mmol.l^{-1}$). The results from the current study demonstrate an additional threshold load to breathing does provoke an increase in blood lactate concentration in COPD. In addition there was a *good, positive relationship between the peak blood lactate concentration* and the peak threshold load achieved (r=0.800). How this lactate production relates to lactic acid production during whole body exercise in COPD is examined in the second part of the study and described in chapter 5.

In summary, the results of this study have shown firstly, ITL using the solenoid valve device with standardised increments of workload can be used to evaluate respiratory muscle performance in COPD. Without imposing cumbersome and artificial external regulation, the test was

repeatable for peak Pm and ∫Pdt. It also required only one practice test. Secondly, there was a significant increase in $\dot{V}O_2$, $\dot{V}_E$ and HR during the test. The small increase in $\dot{V}O_2$ reflected the small muscle mass involved in the performance of the task. The technique also provoked a small increase in blood lactate, and there was a linear relationship with the threshold load. Although there were significant increases in the cardio-respiratory measurements there was wide variability between repeat tests. Thus serial assessment of the energetics of the task, which reflect the internal work performed during threshold loading, would be unreliable.

Decramer (1994) suggests the clinical relevance of assessing respiratory muscle performance is largely unclear. If ITL is to be used as a measure of performance to assess impairment, monitor progression and evaluate therapeutic intervention, its sensitivity to change and how it relates to other, conventional measures of functional capacity is an important consideration. The second part of this study, described in the following chapter, therefore addresses two issues: 1) how ITL relates to whole body exercise performance and 2) the effect of an inhaled bronchodilator on respiratory muscle performance.

Chapter 5

THE ROLE OF INSPIRATORY MUSCLE PERFORMANCE AND THE EFFECT OF IPRATROPIUM BROMIDE ON MAXIMAL EXERCISE CAPACITY IN COPD

5.1 INTRODUCTION

The previous chapter demonstrated ITL was a simple and reproducible indicator of respiratory muscle performance in COPD. The test was capable of eliciting an increase in blood lactate concentration and provoked a significant cardio-respiratory response. This chapter describes the second part of the study which aimed to develop further an understanding of the ITL test, its clinical relevance, sensitivity to an intervention and the nature of any association with the exercise response in COPD. The study examined how ITL related to conventional measurements of whole body exercise, and determined the effects of an inhaled bronchodilator on both the respiratory muscle and whole body exercise performance.

Several studies have investigated the relationships between static respiratory muscle function and exercise capacity in COPD (Mahler 1988, Dillard 1989, Loiseau 1989, Wijkstra 1994). In addition the effects of various training regimens on static respiratory muscle function and exercise capacity have been examined (Pardy 1981, Larson 1988, Lisboa 1994, Wanke 1994). If respiratory muscle endurance is important in the ventilatory limitation to exercise, as suggested by Decramer (1994), and ITL mimics an increase in PEEPi, the resultant threshold load from dynamic hyperinflation, then the question of how ITL relates to whole body exercise performance arises. Specifically, this study addressed whether dynamic indices of respiratory muscle performance, namely peak Pm and $\int Pdt$, were associated with the maximal exercise response in COPD.

Inhaled bronchodilators are commonly used in the treatment of COPD. The anticholinergic agent ipratropium bromide (IB) is frequently used either singly or in combination therapy with ß2-agonists. However many patients

show a variable and often poor spirometric response to bronchodilators though symptomatic relief is reported (Guyatt 1988, Chrystyn 1988). In addition, several studies which have demonstrated clinically trivial changes in lung function, report significant improvements in exercise tolerance and the subjective response to exercise (Chrystyn 1988, Hay 1992, Grove 1996). The mechanisms by which bronchodilators might improve exercise tolerance are not fully elucidated, though evidence suggests a reduction in dynamic hyperinflation and changes in airway resistance reduce the mechanical load, and lead to reduced exercise breathlessness (Belman 1996). Thus the question arisies, if bronchodilators lead to a reduction in the mechanical load is there a concurrent improvement in respiratory muscle performance detectable by ITL?

This study had the following aims:

1) To examine how ITL relates to measurements of whole body exercise performance.
2) To evaluate the sensitivity of ITL to an inhaled bronchodilator.
3) Compare changes in whole body exercise performance and ITL following an inhaled bronchodilator.

5.2 METHODS

5.2.1 Patients

The same 12 patients (mean FEV_1 1.32 l, age 62) described in chapter 4, attended for an additional 5 visits to complete this part of the study. All the patients (9 men, 3 women) had COPD as the primary diagnosis, had reported symptomatic relief from inhaled bronchodilators and had shown some improvement of spirometric indices on a previous occasion. Seven patients were using inhaled steroids, 9 an inhaled ß2-agonist, and 6 inhaled IB. Patients were requested to refrain from their inhaled bronchodilators 4 hours prior to testing. The CRDQ was administered every two weeks to assess functional stability. Patients with co-existent cardiac disease or locomotor disorders were excluded.

5.2.2 **Study Design**

On separate days, and following practice sessions for each test (performed at a previous visit), patients performed a maximal treadmill exercise test, an incremental shuttle walk test and an ITL test. The order of testing was randomised, and followed the administration of nebulised IB (250 μl), or normal saline placebo (P), in double-blind, randomised, cross-over manner. The FEV_1 and FVC were measured before and 30 minutes after the nebulised solutions. The PI_{max} was measured on the ITL test days following nebulisation. All tests were performed at the same time of day. Measurements of $\dot{V}O_2$, $\dot{V}_E$ and HR were made throughout the ITL test and the treadmill exercise tests. Lactate was measured from arterialised earlobe blood samples at rest and following each of the test conditions. Patients were asked to rate breathlessness and perceived exertion from Borg scales at the start and end of each test.

5.2.3 **Incremental Threshold Loading**

The technique and solenoid valve have been described in detail in chapter 4. Prior to the commencement of the test PI_{max} was assessed as described in chapter 4. The peak Pm achieved was taken as the highest pressure achieved for a full minute.

5.2.4 **Treadmill Test**

This was an incremental, symptom-limited test. A brisk walking pace was determined initially for each patient during a practice test. The walking pace remained constant throughout. The gradient was increased every 2 minutes by 2.0% from an initial setting of zero. The aim was to achieve a symptom limited maximum performance within 8 to 10 minutes. A single-lead ECG was monitored throughout. All the patients were encouraged to give maximum effort, and to indicate when they were unable to continue because of breathlessness, fatigue or for any other reason.

5.2.5 **Shuttle Walk Test**

The test was performed as described in chapter 3. The heart rate was monitored and the total distance walked recorded.

5.2.6 **Cardio-respiratory and Metabolic measurements**

The $\dot{V}O_2$ and $\dot{V}_E$ were measured during the treadmill exercise and the ITL test using the computerised gas analysis system (described in chapter 3). Prior to testing patients relaxed for 10 minutes with the mouthpiece in and with the noseclip on. During the last 3 to 5 minutes of the rest period the gas analysis and HR measurements were recorded. The breath by breath analysis was averaged over the last 30 seconds of each minute.

Arterialised capillary blood samples were collected from the earlobe (2 x 20 µl) at rest and 4 minutes post testing for the measurement of lactate concentration. The technique and analysis was described in chapter 3.

5.3 **RESULTS**

Three patients showed a deterioration in symptoms during the study, from the onset of common colds, (fall in CRDQ scores, and in baseline FEV_1). Testing on these patients was suspended until they returned to baseline levels. One patient was unable to tolerate the noseclip during the ITL test, but was able to complete the treadmill and the shuttle walk tests. The mean time between visits was 7.4 (5) days. The anthropometric details and baseline lung function were as shown in table 4.1 (chapter 4).

There was a minor degree of breathlessness at rest (prior to the commencement of any testing) with a mean Borg score of 1.5 (1.2) (median score 1.0) for all visits. Most patients had some improvement in spirometric measurements following IB, though the response was variable. The FEV_1 response to IB and P is shown in table 5.1. The $\dot{V}O_{2peak}$, $\dot{V}_E$ and HR at peak treadmill exercise were compared to predicted values and shown in figure 5.1.

Table 5.1 FEV_1 pre- and post-nebuliser at six different test visits

		Treadmill	Shuttle	ITL
P	pre	1.32 (0.12)	1.28 (0.09)	1.32 (0.10)
	post	1.25 (0.11)	1.28 (0.11)	1.28 (0.10)
IB	pre	1.33 (0.10)	1.32 (0.12)	1.32 (0.12)
	post	1.52 (0.14)	1.49 (0.16)	1.56 (0.14)

n=12

Mean (SD) FEV_1 (l) pre- and post-placebo (P) and ipratropium bromide (IB)

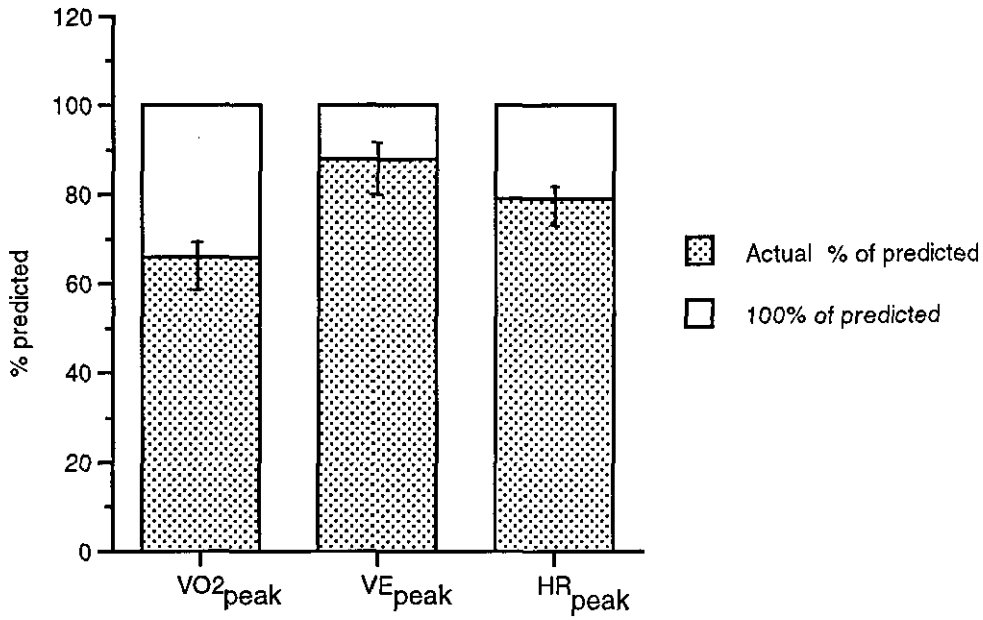


Figure 5.1 Peak treadmill achievement expressed as mean % of predicted values (±SE) (P)

5.3.1 **Effect of ipratropium bromide**

The mean ventilatory, gas exchange and heart rate responses at peak workload for each of the test conditions following both treatments are given in tables 5.2 - 5.4. With the exception of the shuttle walk test there was a tendency for higher values following IB, though the differences between treatments only reached significance for peak $\dot{V}_{Epeak}$ (ITL and the treadmill test). There were no significant treatment effects on the peak work rates achieved (treadmill time, peak Pm, $\int Pdt$, shuttle distance). The differences between treatments for the treadmill $\dot{V}O_{2peak}$ and HR_{peak} showed borderline significance (p values were 0.053 and 0.055 respectively).

The blood lactate concentrations increased significantly from resting values following the treadmill and shuttle walk tests for both treatment conditions. It reached significance during ITL following IB only (p=0.03). Following IB, treadmill exercise provoked a significantly greater change from baseline levels (Δ lactate) than the shuttle walk test. However there were no significant differences between the peak lactate concentrations following the treadmill and the shuttle walk test. A summary of the lactate analysis is given in table 5.5.

There were no treatment effects on the subjective rating of breathlessness and perceived exertion for all of the test conditions. However breathlessness was rated significantly higher following the treadmill test compared to the ITL and shuttle walk test. Perceived exertion was significantly lower following the shuttle walk test compared to the treadmill and ITL. The mean and median results for both sensations are given in table 5.6.

5.3.2 **Relationships between test variables**

The peak Pm correlated significantly with treadmill $\dot{V}_{E\ peak}$, (figure 5.2) and with treadmill $\dot{V}O_{2peak}$ following IB (table 5.7). The correlation with treadmill time and shuttle walking distance was poor (r=0.502 and r=0.529 respectively, $p>0.05$). There was a significant correlation with PI_{max} (r=0.794, $p<0.01$, and r=0.650, $p<0.05$ following IB and P respectively), but not with

Table 5.2 Peak performance and cardio-respiratory response to incremental threshold loading

	PI_{max} (cm H_2O)	Peak Pm (cm H_2O)	% PI_{max}	JPdt (cm $H_2O.s^{-1}$)	$\dot{V}O_{2peak}$ ($ml.min^{-1}.kg^{-1}$)	$\dot{V}_{Epeak}$ ($l.min^{-1}$)	HR_{peak} ($beat.min^{-1}$)
P	78.5 (7.1) 41 - 127	52 (7) 20 - 100	65.3 (6) 41 - 127	1410 (261) 400 - 2750	5.1 (0.3) 3.5 - 6.4	24.2 (1.9) 13.8 - 33.4	89 (5) 58 - 122
IB	78.1 (7.8) 42 - 126	53 (7) 30 - 109	67.8 (4) 42 - 126	1876 (337) 640 - 4240	5.6 (0.5) 3.7 - 8.9	27.3 (1.9)* 18.4 - 38.6	89 (6) 64 - 121

n=11, * $p<0.05$ for differences between treatments

Mean (SE) and range of peak performance and cardio-respiratory response to ITL following placebo (P) and ipratropium bromide (IB)

$\dot{V}O_{2peak}$ expressed as $ml.min^{-1}$: P 367(20), IB 390(30)

Table 5.3 Cardio-respiratory response to symptom-limited treadmill exercise

	Time (min)	$\dot{V}O_{2peak}$ ($ml.min^{-1}.kg^{-1}$)	$\dot{V}_{E\ peak}$ ($l.min^{-1}$)	HR_{peak} ($beat.min^{-1}$)	RER
P	9.1 (0.6) 5.5 - 12	18.4 (1.3) 12 - 27.6	42.2 (3.8) 24 - 67.1	127 (6) 87 - 170	0.90 (0.03) 0.75 - 1.05
IB	10.1 (0.8) 6 - 14	19.8 (1.6) 9.6 - 30.1	48.3 (4.7)* 27.8 - 87.7	131 (7) 87 - 175	0.92 (0.03) 0.78 - 1.06

n=12 * $p<0.05$ for differences between treatments

Mean (SE) and range of exercise time and cardio-respiratory response to peak exercise following placebo (P) and ipratropium bromide (IB).

Table 5.4 Shuttle walk test performance and heart rate response

	Distance (m)	HR_{peak} (beat.min^{-1})
P	372 (32) 190 - 540	121 (5) 86 - 148
IB	368 (27) 210 - 530	122 (5) 92 - 148

n=12

Mean (SE) and range for distance walked and peak heart rate during shuttle walk test following placebo (P) and ipratropium bromide (IB)

Table 5.5 Capillary blood lactate response to exercise

		Baseline	post exercise +4 min	Δ
Treadmill	**P**	0.45 (0.08) 0.14 - 1.05	1.81 (0.46) 0.23 - 5.77	1.36 (0.42) 0.09 - 5.09
	IB	0.46 (0.07) 0.10 - 0.84	2.12 (0.52) 0.27 - 7.01	1.67 (0.51)* 0.17 - 6.52
ITL	**P**	0.68 (0.09) 0.29 - 1.76	0.82 (0.08) 0.49 - 1.18	0.15 (0.07) 0.02 - 0.46
	IB	0.57 (0.08) 0.21 - 0.96	0.77 (0.07) 0.46 - 1.16	0.21 (0.08) 0.04 - 0.79
Shuttle	**P**	0.85 (0.12) 0.28 - 1.48	1.53 (0.20) 0.50 - 2.67	0.68 (0.18) 0.01 - 1.92
	IB	0.68 (0.09) 0.17 - 1.21	1.27 (0.16) 0.4 - 2.42	0.59 (0.13) 0.09 - 1.36

n=12 except ITL where n=11

* $p<0.05$ cf shuttle IB (satistical comparison between treadmill and shuttle)

Mean (SE) and range of blood lactate concentrations ($mmol.l^{-1}$) at baseline, 4 min post exercise and Δ (difference from baseline), following placebo (P) and ipratropium bromide (IB).

Table 5.6 Borg ratings of breathlessness (BS) and perceived exertion (RPE)

	Treadmill		ITL		Shuttle	
	BS	RPE	BS	RPE	BS	RPE
P						
mean (SE)	6.7 (0.6)	16.6 (0.4)	4.5 (0.6)	17.0 (0.7)	5.0 (0.6)	14.8 (0.9)
median	7.0	17.0	5.0	17.0	4.6	14.6
IB						
mean (SE)	7.1 (0.6)	16.5 (0.6)	5.0 (0.8)	17.0 (0.4)	4.1 (0.6)	14.4 (0.8)
median	7.0	16.5	5.0	17.0	3.6	14.2

Mean (SE) and median Borg scores rated at the end of all three test conditions following placebo (P) and ipratropium bromide (IB).

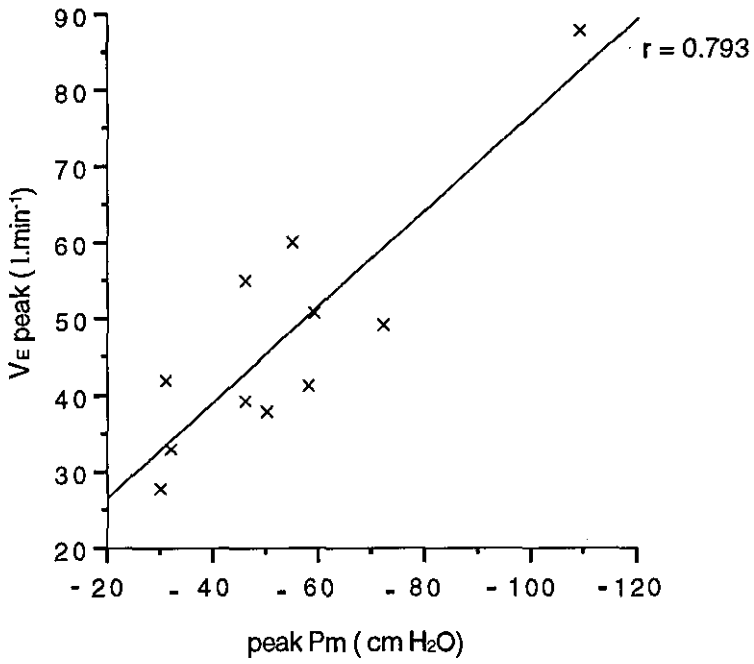


Figure 5.2 Relationship between peak Pm and peak treadmill ventilation

Table 5.7 Relationships between test variables

	$\dot{V}O_{2peak}$		$\dot{V}_{Epeak}$	
	P	IB	P	IB
peak Pm	0.498	0.671**	0.702**	0.793**
FEV_1	0.592*	0.479	0.651**	0.671**
Shuttle distance	0.678**	0.708**	0.595*	0.620*

* $p< 0.05$, ** $p< 0.025$

Correlation coefficients (r) of peak Pm, FEV_1 and shuttle walk distance with $\dot{V}O_2$ and $\dot{V}_E$ at peak treadmill exercise

FEV_1 (r=0.574, p>0.05). There were no significant relationships between ∫Pdt and treadmill $\dot{V}O_{2peak}$, treadmill $\dot{V}_{Epeak}$ or shuttle walk distance.

There was no relationship between the absolute values of $\dot{V}O_{2peak}$ attained during ITL and the treadmill test. However there was a significant relationship between the ITL $\dot{V}O_{2peak}$ expressed as a percentage of the total available $\dot{V}O_2$ i.e. treadmill $\dot{V}O_{2peak}$ (r=0.752, p<0.05, figure 5.3). The relationship remained unaltered following IB (r=0.749). The $\dot{V}_{Epeak}$ achieved during the ITL test was 60 (19)% of the $\dot{V}_{Epeak}$ achieved during maximal treadmill exercise, and the $\dot{V}O_{2peak}$ during ITL was 30 (10) % of that achieved during exercise. These values did not change substantially following IB.

There were no significant relationships between the static measure of respiratory muscle function, PI_{max}, and any of the exercise variables (treadmill time, treadmill $\dot{V}O_{2peak}$, $\dot{V}_{Epeak}$ and shuttle walk distance). Both the shuttle walking distance and the FEV_1 correlated significantly with treadmill $\dot{V}O_{2peak}$ and $\dot{V}_{Epeak}$. Generally IB tended to strengthen the relationships between variables. A summary of the correlation coefficients and the treatment effect is given in table 5.7.

There was a moderate relationship between the absolute blood lactate increases following ITL and treadmill exercise (r=0.677, p<0.05). However one outlying data point influenced the relationship. It was not significant when this was removed. However, there was a significant relationship between the ITL blood lactate response, expressed as a percentage of the total lactate response, and the whole body exercise concentration (r=0.729 (P), p<0.05) (figure 5.4). The blood lactate increase following ITL (at 2 and 4 min), expressed as a mean percentage of the increase following treadmill exercise was 41(25)%. This did not change substantially following IB.

The variables which had shown significant correlations with treadmill $\dot{V}O_{2peak}$ and $\dot{V}_{Epeak}$ were entered into a multiple linear regression analysis (computer

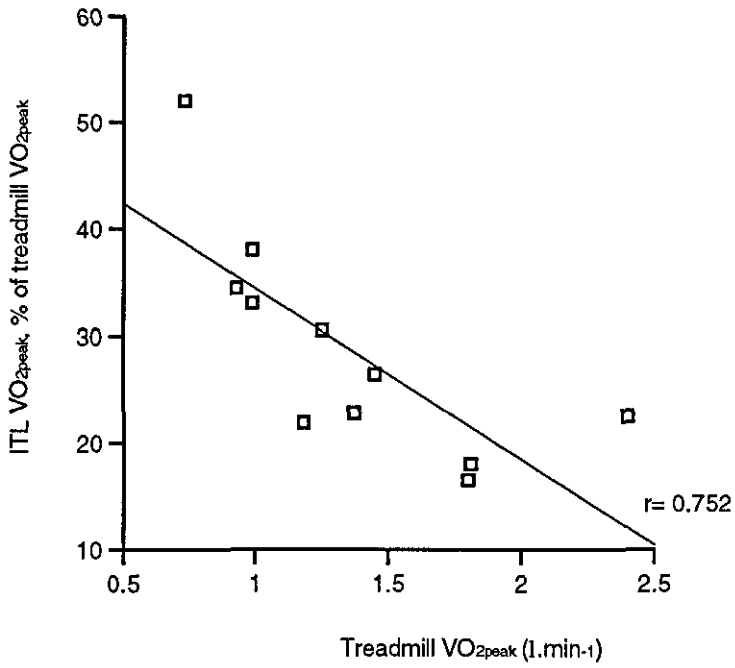


Figure 5.3 Relationship between incremental threshold loading VO_{2peak} (% of treadmill VO_{2peak}) and treadmill VO_{2peak}. (P)

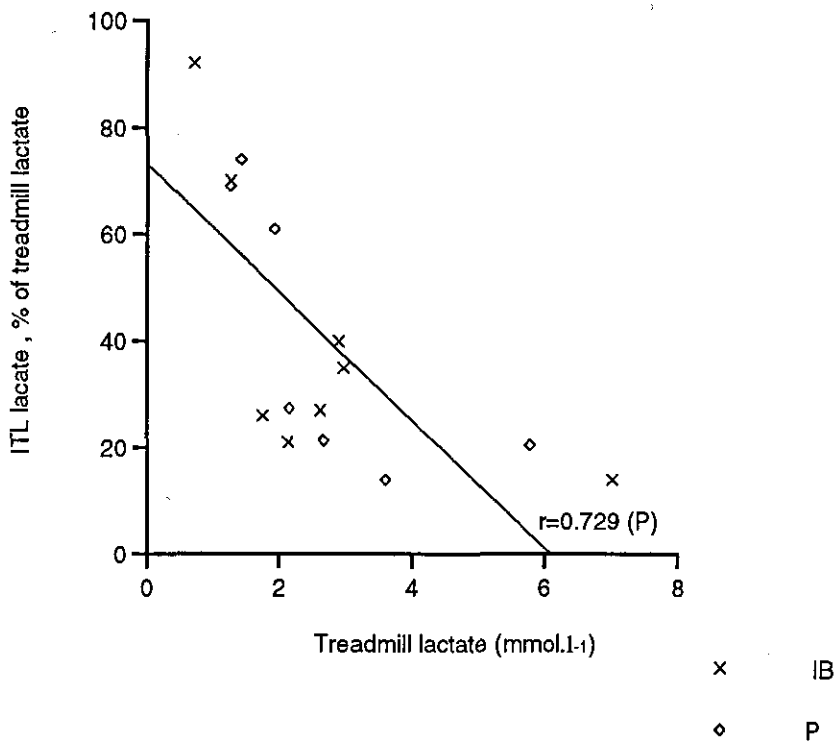


Figure 5.4 Relationship between blood lactate concentration following ITL (% of treadmill lactate) and the whole body lactate response

programme Microsoft, Statview 512). The strongest correlations occurred following IB and these were used in the analysis. The analysis revealed shuttle walking distance, peak Pm and FEV_1 together explained 63% of the variance in the treadmill $\dot{V}O_{2peak}$, with R=0.860, $p<0.025$. However only shuttle walking distance appeared as a significant, individual determinant of $\dot{V}O_{2peak}$ ($r=0.708$, $p<0.05$). The same three variables also explained 71% of the variance in treadmill $\dot{V}_{E\,peak}$, with R=0.892, $p<0.01$. None of the variables appeared as significant individual determinants of $\dot{V}_{E\,peak}$.

5.4 DISCUSSION

Exercise capacity is commonly reduced in COPD and a reduced ventilatory capacity is generally considered the main limiting factor. The exercise capacity of this group of patients was markedly reduced in terms of the $\dot{V}O_{2peak}$ achieved (66% of the predicted normal value). The predicted values for exercise ventilation were calculated from a regression equation derived from a group of patients with COPD (Spiro 1975). The attainment of 88% of the predicted value suggests a peak exercise response was achieved. There was a moderate heart rate reserve (79% of the predicted heart rate achieved at peak exercise) which suggests a ventilatory limit to exercise.

During ITL the respiratory muscles were stressed in a continuous manner with progressive increments in work load, similar to the incremental and progressive demands placed on the respiratory musculature during the whole body exercise test. As with a whole body exercise test patients were allowed to respond to the task without any external constraints on breathing rate or depth, thus developing their own natural response to the additional inspiratory load. A good relationship between the whole body exercise $\dot{V}_{Epeak}$ and peak Pm was demonstrated. This has not been examined previously, and extends the range of associations between respiratory muscle function, assessed by static and semi-static methods, and exercise performance.

Peak Pm reflects both respiratory muscle strength and endurance, and generally those patients who achieved greater inspiratory threshold pressures were able to achieve higher levels of ventilation during the whole body exercise. However multiple linear regression analysis did not select peak Pm as a significant independent determinant of $\dot{V}_{Epeak}$. Thus respiratory muscle performance alone does not explain fully the ventilatory limit to exercise. Other variables are important, and respiratory muscle performance acts in combination with these in the determination of peak exercise ventilation.

The static indices of respiratory muscle function already identified with exercise performance include PI_{max} and oesophageal pressure ($PI_{max}P_{oes}$). In a large study of 113 patients with COPD, Loiseau (1989) demonstrated a strong relationship between maximal cycle work rates and PI_{max} and respiratory impedance ($P_{0.1}$/ Vt/Ti). Wijkstra (1994) assessed a wide range of indices including inspiratory pressures, quality of life measures and Borg ratings of dyspnoea, and their relationship to exercise performance in COPD. Amongst the variables examined, transfer factor (TL_{CO}) and $PI_{max}P_{oes}$ were found to be significant determinants of the 6 minute walk test and maximal cycle work rate. However, in the current study no significant relationships were detected between the measures of respiratory muscle performance (peak Pm, PI_{max} and $\int Pdt$) and the indices of maximal exercise work rate, i.e. treadmill time and shuttle distance. Methodological differences may partly explain this finding. The choice of the treadmill protocol may have influenced the exercise time achieved by the patients (the increments were deliberately chosen to achieve a symptom limited maximum performance within 10 minutes) and this may have affected its relationship with other variables. The shuttle walk test utilises an incremental protocol in contrast to the 6 MWT test, which is more akin to a submaximal endurance test. This operational difference may explain the absence of a relationship between the respiratory muscle performance and the shuttle walk distance.

The correlation coefficient (r) of 0.702 (and 0.793 post IB) for peak Pm and treadmill $\dot{V}_{Epeak}$ was of similar magnitude to that determined by Dillard (1989) for PI_{max} and $\dot{V}_{Epeak}$ (r=0.765), in a study of 20 patients with COPD. Dillard (1989) assessed the relationships between a range of lung function variables (FEV_1, FVC, TL_{CO}), inspiratory muscle strength (PI_{max}), age and maximal exercise performance. The PI_{max} was found to constitute a significant determinant of $\dot{V}O_{2peak,}$ and this was additional to the effects of TL_{CO} and $\dot{V}_{Epeak}$ in a multiple regression analysis. In a study from Mahler (1988), which sought to determine the non-exercise variables which could be used to reliably predict $\dot{V}O_{2peak}$ in COPD, a significant correlation between PI_{max} and $\dot{V}O_{2peak}$ was demonstrated. However the author was unable to detect any predictive power.

The current study was unable to detect any relationship between the static measure of respiratory muscle function, PI_{max} and treadmill $\dot{V}O_{2peak}$ and $\dot{V}_{Epeak}$, unlike the studies cited above. One reason for the absence of a significant correlation may be the differences in study populations. There was a greater degree of airflow obstruction in the present study group compared to the two former studies, were the mean FEV_1 values were 1.72 and 1.65 litres respectively. In addition, the mean $\dot{V}O_{2peak}$ of the patient group from Dillard (1989) was greater than the measurement in the current study (23 vs 19.8 $ml.min^{-1}.kg^{-1}$), and the study from Mahler (1988) (19.9 $ml.min^{-1}.kg^{-1}$). In moderately severe airflow obstruction respiratory muscle strength will be compromised as a result of increased gas trapping and hyperinflation. In addition, dynamic hyperinflation occurs during exercise, and there is usually a marked reduction in exercise capacity and $\dot{V}O_{2peak}$. It is possible these changes, and other factors associated with more severe impairment, lead to a breakdown in the relationship between the static measures of respiratory muscle strength, PI_{max}, and the exercise performance. In contrast, peak Pm, reflecting the dynamic response of the respiratory musculature, remained associated with the whole body $\dot{V}O_{2peak}$ and $\dot{V}_{Epeak}$ despite the degree of impairment. This suggests both respiratory

muscle endurance and the whole body performance may be similarly affected by the changes associated with COPD and exercise.

The relationship between PI_{max} and peak Pm improved following IB. However in this group of patients, with moderately severe airflow obstruction, the peak Pm remained more closely associated with the incremental treadmill variables than the static measure of respiratory muscle strength, PI_{max}. This finding would support a hypothesis in which the dynamic measures of respiratory muscle performance are more closely associated with indices of whole body exercise performance than static measures of respiratory muscle function in more severe COPD.

The relationship between peak Pm and $\dot{V}_{Epeak}$ was significant and improved following inhaled IB. However the relationships between $\int Pdt$ and $\dot{V}_{Epeak,}$ and $\int Pdt$ and $\dot{V}O_{2peak,}$ were poor and non-significant. This was a surprising finding of the study since $\int Pdt$ is an index of the external work performed by the respiratory muscles during loaded breathing (Collett 1985) and may reflect the response mounted to maximal exercise stress. However there was wide variability in $\int Pdt$ between patients, reflected in the large standard deviation, which suggests a range of strategies were developed in response to the increased threshold load. The variability of the measurement will influence its relationship with other variables.

Although the spirometric response to IB was weak and variable, the bronchodilator tended to strengthen the relationships between the treadmill exercise variables and peak Pm. The absolute values of $\dot{V}_{Epeak}$ and $\dot{V}O_{2peak,}$ during both ITL and whole body exercise, also improved following IB. The relationships between variables were sensitive to the changes induced by the inhaled bronchodilator, suggesting an improved coupling between different aspects of the exercise performance e.g. the mechanical changes and respiratory muscle performance and the resultant exercise ventilation and gas exchange. This finding suggests the application of additional interventions aimed at improving functional capacity, e.g. respiratory muscle

training and general exercise training, may be capable of maximising the improved ventilatory capacity, and the associations between components of the exercise response.

Many patients with COPD fail to demonstrate spirometric improvement following inhaled bronchodilators, and some patients show only a minimal response or partial reversibility (Calverley 1995). The benefits associated with small and often variable changes are difficult to evaluate, and several studies have investigated exercise tolerance and symptom scores to examine the functional benefits from bronchodilators in COPD. However evidence for the role of inhaled bronchodilators and improvements in exercise performance in COPD is conflicting. A number of studies have measured increases in maximal work rate, or distance walked, following either ß2-agonist or anticholinergic type inhalers, or both, whilst some reports have demonstrated changes in subjective measurements only. The message is confounded by the choice of drug, dosage, acute and chronic effects and not least the type of exercise employed.

Early recommendations suggested the ß2-agonist salbutamol should be the drug of choice when improvements in exercise tolerance were sought in chronic bronchitis (Leitch 1978). It provoked a significant increase in 12 MWT where IB did not (Leitch 1978). However only a low dose of IB (40µg) was used in the study from Leitch (1978), and in a recent study Ikeda (1996) has shown higher doses of IB (≥160µg) are necessary to demonstrate improvements in exercise capacity in COPD.

Oxitropium bromide (OB), (an anticholinergic agent similar to IB), was shown to increase the 6 MWT, with significant improvements in exercise breathlessness in COPD (Spence 1993). Additionally it improved $\dot{V}_{Epeak}$ and $\dot{V}O_{2peak}$ during cycle exercise with corresponding decreases in symptom scores. Improvements in the 6 MWT following OB were unrelated to changes in spirometric indices (Hay 1992, Spence 1993). The long acting ß2-agonist salmeterol had no effect on the cardio-respiratory responses to a

progressive cycle test, or on 6 MWT, following both acute and chronic dosage, however perceived exertion was less during the walk test (Grove 1996).

In the current study the patients had a small and variable spirometric response to IB, however there were significant improvements in $\dot{V}_{Epeak,}$ and a tendency for higher $\dot{V}O_{2peak}$ values during treadmill exercise and ITL. The improvements in the ventilatory and gas exchange response did not translate to significant improvements in peak work rates i.e. treadmill exercise time, shuttle walk distance, $\int Pdt$ or peak Pm, suggesting mechanisms additional to the ventilatory impairment were contributing to the exercise limitation. There is now strong evidence the systemic musculature has a significant role in the limitation of exercise in COPD. Recently, Gosselink (1996) has demonstrated the existence and importance of peripheral muscle weakness in the limitation of exercise in COPD. This was *additional to the contribution from respiratory muscle and resting lung* function to exercise performance.

Further evidence of the effect of general deconditioning in the limitation to exercise was demonstrated by Killian (1992). In a large study of 97 patients, patients with moderate and severe COPD reported leg fatigue as frequently as control subjects, for the primary reason for exercise termination, rather than breathlessness. The results from the current study demonstrate, despite small and variable changes in the FEV_1 following IB, changes induced by the bronchodilator were amplified during exercise with significant improvements in exercise $\dot{V}_{Epeak}$. However improving the ventilatory response in isolation *did not produce significant improvements in exercise capacity. This finding* supports the evidence that additional factors have an important role in the limitation of exercise in COPD.

The subjective ratings of breathlessness and perceived exertion showed little change following IB. This contrasts with the findings of Belman (1996) from a study of 13 patients with moderate to severe COPD (FEV_1 1.20 l),

where maximal cycle exercise was performed following an inhaled ß2-agonist and following a placebo inhaler. The authors measured a reduction in dynamic hyperinflation and a concurrent reduction in the Borg breathlessness score during exercise (4.5 to 3.1) following the active inhaler. Other workers have also found reduced subjective ratings of breathlessness (Spence 1993) and perceived exertion (Grove 1996). In the current study the effects of a single treatment dose of IB were examined. The effects of a period of pre-treatment were not examined and this may have lead to additional benefit. The presence of a mouthpiece and noseclip may also have influenced the Borg ratings for the laboratory based tests, since these were higher than the ratings for the field test. Additionally, the subjective ratings for the shuttle walk test had a tendency to fall following IB, though the differences failed to reach significance. Any element of anxiety with the laboratory based tests may have acted to mask the effect of IB on the subjective sensations.

There was a minimal increase in the blood lactate concentration following ITL, and a more appreciable change following the whole body exercise tests, reflecting the greater muscle mass involved. The treadmill exercise provoked a greater increase in lactate than the shuttle walk test, and this was significant following IB. With the exception of the first two minutes, patients walked at an increasing gradient during the treadmill test compared to walking on the level throughout the shuttle test. Previous studies (Cockcroft 1985, Mathur 1995), have demonstrated exercise modality influences the magnitude of the lactate response in COPD, with cycle exercise producing a greater increase than treadmill walking. During cycling the emphasis of muscular work differs from that in walking exercise. Similarly, the muscular activity involved in walking along a gradient differs from walking on the flat. Thus differences in muscle recruitment on the inclined treadmill may explain the differences in blood lactate concentration between the two walking tests.

Levison (1968) measured an increased oxygen utilisation by the respiratory muscles during exercise in COPD. In a study which compared the oxygen

cost of volitionally increased ventilation during exercise between control subjects and patients with COPD, Levison (1968) noted a disproportionate increase in the oxygen utilisation of the respiratory muscles in COPD (9.3 $ml.l^{-1}$ vs 4.2 $ml.l^{-1}$ of ventilation). This accounted for approximately 35 - 40% of the maximum oxygen consumption. The author proposed there was likely to be significant competition between limb and respiratory muscles for the available O_2 in COPD during exercise. A point may be reached where any benefits of increasing ventilation may be offset by the additional energy cost incurred to the respiratory muscles. In the current study the oxygen cost of the ITL test equated to 30% of the $\dot{V}O_{2peak}$ measured on the treadmill. If ITL imposes similar ventilatory loads as those encountered during exercise in COPD, the oxygen cost of the respiratory musculature will amount to a substantial proportion of the $\dot{V}O_{2peak}$.

Once oxygen demand exceeds oxygen delivery anaerobic pathways are engaged, and the lactic acid load then becomes an important limiting factor of exercise (Åstrand 1986). How the increased energy cost of breathing might influence the lactic acid load during exercise in COPD was examined by Engelen (1995) in 8 patients with COPD. The patients performed an incremental exercise test (IWR) and constant work rate tests (CWR). During one of the CWR tests patients increased ventilation volitionally to levels achieved during the IWR test. Though the volitional increase in ventilation provoked an increase in blood lactate, the end exercise concentrations following the CWR tests were not significantly different (0.11 $mmol.l^{-1}$). Additionally, much larger increases were measured following the IWR test. The authors concluded the respiratory muscles were unlikely to have an important influence on the blood lactate levels achieved during maximal exercise in COPD.

The 8 patients studied by Engelin (1995) were selected on the basis of a significant blood lactate response to exercise (mean peak lactate 5.3 ± 2.8 $mmol.l^{-1}$). Many patients with more severe COPD show a reduced and less than significant increase blood lactate concentration during exercise

(Belman 1993). How respiratory muscle lactate production influences exercise tolerance in these patients is unclear. In the current study 6 patients had < 2 mmol.l^{-1} increase in blood lactate following treadmill exercise (IB). The ITL blood lactate response expressed as a proportion (%) of the individual lactate response, measured after the treadmill exercise, gave a mean value of 40 (10)% for the whole group. Thus the question of whether respiratory muscle lactic acid is more important in patients with severe impairment warrants further investigation. Engelin (1995) noted the more severely obstructed patients demonstrated higher rates of respiratory muscle lactate production per unit increase in ventilation. The author suggested further studies were required to explain why many patients with COPD experience a blood lactate response at relatively low work rates.

The mean change in the blood lactate concentration provoked by the respiratory muscle exercise during the ITL test (0.15 mmol.l^{-1}, following placebo) was similar to that reported by Engelen (1995). The change was achieved at much lower levels of ventilation (24 vs 48 l.min^{-1}). However, during ITL additional static work is required to overcome the imposed threshold load. The changes in blood lactate following IB were greater, and probably reflect the higher ventilation levels achieved. Again the changes were at lower levels of ventilation compared to the study from Engelin (1995) (27 vs 48 l.min^{-1}). This suggests the work rate imposed during the ITL test represents a similar challenge to the respiratory muscles to that imposed by a volitional increase in ventilation during exercise, as described by Engelin (1995).

There was a strong relationship between the distance walked during the shuttle walk test and the $\dot{V}O_{2peak}$. This has been shown previously in a study which validated the shuttle walk test against a symptom limited maximal incremental treadmill test (Singh 1994a). There was also a significant relationship between the distance walked and $\dot{V}_{Epeak}$. These findings support the use of the shuttle walk test as a valid measure of functional capacity which provokes an incremental and maximal performance in COPD.

In summary, this study has demonstrated: 1) a good relationship between peak Pm and whole body exercise $\dot{V}_{Epeak}$. However, unlike previous reports, there was no relationship between the static measure of respiratory muscle function, PI_{max}, and whole body exercise performance. This may be explained by the greater degree of airflow obstruction in this patient group, and suggests dynamic indices of respiratory muscle performance (peak Pm) are more closely associated with exercise ventilation in moderately severe impairment; 2) peak Pm, FEV_1 and shuttle distance explained 71% of the variance in the treadmill $\dot{V}_{Epeak}$. None of these variables were selected as independent determinants of the ventilatory response. The three variables also explained 63% of the variance in $\dot{V}O_{2peak}$, and shuttle distance was a significant individual determinant $\dot{V}O_{2peak}$; 3) There was a significant improvement in exercise ventilation following IB. Additionally, IB improved the relationships between variables. This suggested a closer coupling of the events contributing to the exercise performance e.g. respiratory muscle performance and the ventilatory response. However, the improvements in $\dot{V}_E$ and $\dot{V}O_2$ were not accompanied by improvements in work rate, which suggests the exercise limitation in COPD cannot be explained fully by the abnormal ventilatory response.

The findings from this study suggest the respiratory and systemic musculature is likely to play an additional role in the exercise limitation in COPD. This component may be reduced by exercise training. An intervention of exercise training may also maximise the improvements in the relationships between whole body exercise performance and the respiratory muscle contribution. In order to examine exercise training in this patient group appropriate and sensitive methods of assessment are necessary. This aspect is addressed in the following chapter.

Chapter 6

THE DEVELOPMENT OF A FIELD TEST OF WALKING ENDURANCE CAPACITY

6.1 INTRODUCTION

The previous experiments in this thesis demonstrated a reduced respiratory muscle performance in COPD, and a high oxygen cost of the ITL exercise. Whilst the relationship between ITL and the ventilatory response to exercise was strengthened following an inhaled bronchodilator, and peak exercise $\dot{V}_E$ and $\dot{V}O_2$ improved, there were no significant changes in the peak work rates achieved. These findings suggested improving the ventilatory capacity in isolation does not improve exercise capacity in COPD. They also support the contention that other factors, such as generalised muscle weakness and deconditioning, are important in the exercise limitation in COPD. In order to maximise the improvements achieved by conventional inhalation therapy it was suggested additional therapeutic interventions, such as exercise training, could be introduced for this patient group.

A number of studies of pulmonary rehabilitation have demonstrated substantial improvements in endurance capacity, in addition to more modest improvements in maximal exercise capacity, in COPD (Chester 1977, Ries 1987, Niederman 1991). As everyday activities rarely, if ever, engage maximal capacity, assessment of submaximal endurance capacity in this group is important, especially if training interventions aim to improve performance of everyday activities. It is unlikely the factors which produce a ventilatory limit to maximal exercise will improve following exercise training and rehabilitation. Thus the assessment of submaximal performance may prove more sensitive to training induced changes in fitness, co-ordination and strength.

Field walking tests are commonly used for the assessment of disability and as an outcome measure following rehabilitation in patients with COPD. The 12 and 6 minute walk tests are self-paced tests which measure the distance

covered in a set time (McGavin 1976, Butland 1982). The non-standardised nature of the tests contributes a degree of variability in the performance of the test (Guyatt 1984, Knox 1988). The incremental shuttle walk test (ISWT) (Singh 1992) is standardised with external pacing, and pre-determined increments in walking speed. The incremental nature of the protocol has been shown to produce a maximal response in patients with COPD (Singh 1994a). However a standardised field test of endurance capacity, using constant walking speeds, external regulation of pace and where all patients experience the same relative level of exercise intensity, does not exist for use with this patient group. For practical reasons a standardised field test of endurance capacity would be desirable for the routine assessment of patients with COPD. As external regulation of walking speed has already been achieved with the ISWT, use of a similar format in the development of a standardised, constant-paced endurance test would complement its use, enabling both endurance and maximal capacity to be assessed along the same walking course.

The purposes of this study were:

1) To develop a standardised field test with a constant walking pace, and which complemented the shuttle walk test, to assess endurance capacity in patients with COPD.

2) To assess a range of exercise intensities to ensure the test was applicable for use within the clinical and pulmonary rehabilitation environment.

6.2 METHODS

6.2.1 Patients

Ten patients (9 men) with moderate and severe COPD were recruited to examine the response to the three field endurance tests (mean FEV_1 1.01(0.36)l , age 63.7(5.5)). Six of the patients had participated in previous studies, and 4 had attended the hospital pulmonary rehabilitation course. The CRDQ (Guyatt 1984) was administered at the start and every alternate week, and the FEV_1 was measured at every visit. Height and weight were

measured at the first visit and weight was rechecked at intervals throughout the study. Nine patients were using inhaled ß2 agonists, 7 an inhaled steroid, 4 ipratropium bromide and one patient was using oral theophyllines. There were no alterations to prescribed medications although patients were instructed to use their inhaled bronchodilator within 1 hour of testing.

6.2.2 **Study Design**

The patients attended on 4 separate occasions. At the first visit two ISWT were performed (described in chapter 3). The first test was considered a practice, and the 2nd test was performed after a rest period of 45 minutes. The predicted $\dot{V}O_{2peak}$ was calculated from the greatest distance walked (Singh 1994a). The endurance shuttle walk tests (ESWT) were performed during the 3 subsequent visits, each at a different walking speed. The exercise intensities for the ESWT related to 75%, 85% and 95% of the $\dot{V}O_{2peak}$ predicted from the ISWT performance. The level of exercise intensity for each visit was randomised. All tests were performed at the same time of day. Heart rate was monitored throughout the walking tests and breathlessness and perceived exertion rated from Borg scales.

6.2.3 **Endurance shuttle walk test**

The endurance walk test had a similar format to the ISWT i.e. the same 10 m course demarcated by cones and pre-recorded bleeps from a cassette player to regulate walking speed. The test objective was to measure the duration of exercise at the set endurance walking pace. The basic requirements of the test were a constant walking speed, and the avoidance of a lengthy test duration if the test was to be applicable in the clinical environment. At the start of each endurance test there was a 2 minute warm-up period at a slower pace. This was followed immediately by the set endurance pace, externally controlled by bleeps from a cassette and which remained constant throughout the remainder of the test. The bleeps indicated when the patient should be turning around a cone at either end of the course. Patients walked up one side of the course and returned down the opposite side, turning around the cone at each end of the course. To allow

for turning the actual straight line distance between cones was 9.0 m, thus allowing 0.5 m for turning (figure 6.1). To avoid the possibility of some patients walking for very long periods, a time limit of 20 minutes was imposed. However, all the patients remained unaware of this time limit to avoid target setting.

Initially a variety of suitable endurance walking speeds were identified and a series of cassette tapes pre-recorded with a range of bleep frequencies. The choice of walking speeds was achieved in two ways: 1) identification of the maximum walking speeds, and distances, most frequently achieved during the ISWT. Results were analysed from 36 patients with COPD referred to the pulmonary rehabilitation service at the Glenfield Hospital; 2) from the construction of a graph of $\dot{V}O_{2peak}$ values predicted from the ISWT [regression equation $\dot{V}O_{2peak}$ = 4.19 + (0.025xdistance), Singh 1994a] and the corresponding shuttle walking speeds (figure 6.2). From the graph 15 endurance walking speeds were selected which covered a range of predicted $\dot{V}O_{2peak}$ values from 4.9 to 16.9 $ml.min^{-1}.kg^{-1}$. The $\dot{V}O_2$ values were deemed representative for this type of patient, following the examination of test results from 36 patients referred to the pulmonary rehabilitation service. The graph relating speed and $\dot{V}O_2$ (figure 6.2) was subsequently used to determine the endurance speeds for the patients entered into the study.

To regulate the walking speed around the 10 m shuttle course the bleep frequencies were calculated (table 6.1). The cassette tape recordings were undertaken by the Audio-Visual Service of the Loughborough University. A one minute calibration signal, and a set of standardised instructions to the patient, were also recorded at the start of each tape (appendix 7).

The 10 m course was inside the hospital on a quiet, flat corridor. The pre-recorded test instructions were played to each patient prior to their first performance of the endurance walk. Patients were instructed to walk at the constant speed (the 'endurance' speed) for as long as possible, until they were too breathless, too tired or could no longer keep up the set pace. The

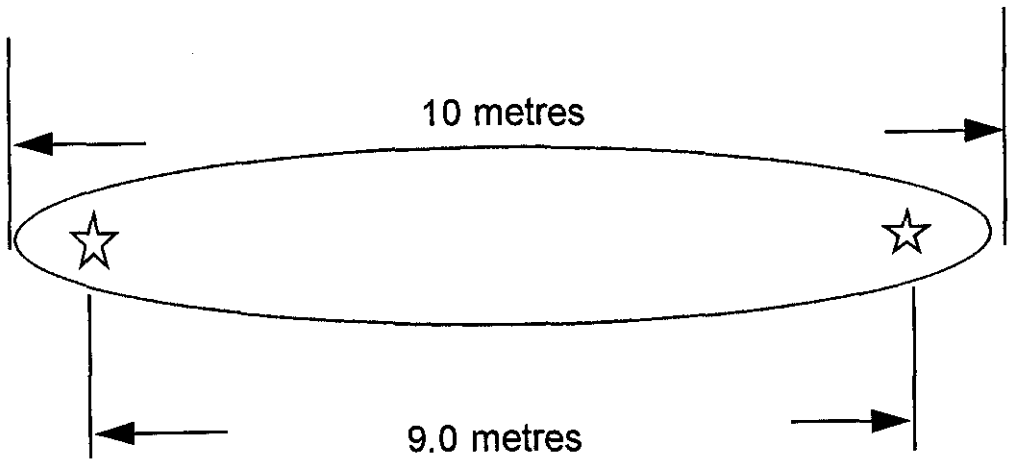


Figure 6.1 Shuttle course

Figure 6.2 Incremental shuttle walking speeds and predicted VO_{2peak}

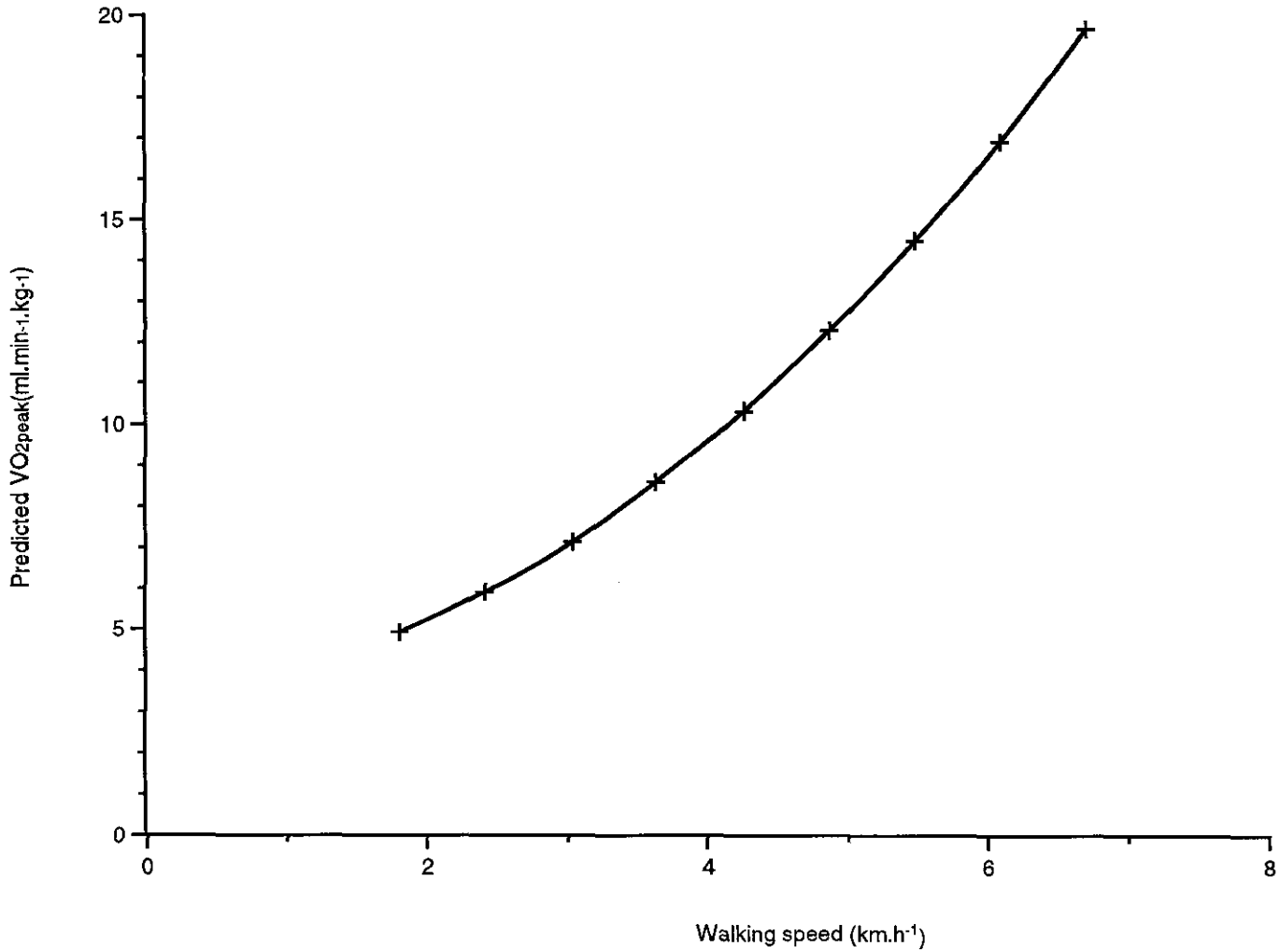


Table 6.1 Range of pre-recorded walking speeds

Level	Warm-up speed ($km.h^{-1}$)	Endurance speed ($km.h^{-1}$)	Time / 10 m shuttle (s)
1	1.44	1.80	20.00
2	1.44	2.06	17.50
3	1.44	2.40	15.00
4	1.44	2.67	13.50
5	1.44	3.00	12.00
6	1.44	3.27	11.00
7	2.40	3.60	10.0
8	2.40	3.89	9.25
9	2.40	4.24	8.50
10	2.40	4.50	8.0
11	2.40	4.80	7.50
12	2.40	5.14	7.00
13	2.40	5.33	6.75
14	2.40	5.76	6.25
15	2.40	6.00	6.00

Duration of warm-up speed 2 minutes, and 20 minutes for endurance speed

first 2 minutes of the walking signal was at a slower, warm-up pace. At the end of the warm-up period the following taped message occurred 'at the next *triple bleep increase your walking speed'. The endurance pace lasted for* twenty minutes, therefore the maximum possible exercise time was 22 minutes including the warm-up period. Throughout the operator remained silent at the edge of the course and recorded the time walked at the endurance speed. Heart rate was recorded using the telemetry device.

The test was symptom limited and terminated for the following reasons: patient request (e.g. too breathless to continue or leg fatigue); patient completed 20 minutes of the endurance pace; stopped by the operator when *the patient was unable to keep up the set pace. If the patient was 0.5 m, or* more, away from the next cone at the sound of a bleep, the patient was encouraged to catch up on the next lap. If the patient was still beyond 0.5 m from a cone at the next bleep the test was terminated.

Determination of endurance walking speeds

The $\dot{V}O_{2peak}$ was predicted for each patient from the total distance covered *during the ISWT, (Singh 1994a). Three target* $\dot{V}O_2$ *values were calculated* which related to 75%, 85% and 95% of the predicted $\dot{V}O_{2peak}$. From the graph of $\dot{V}O_2$ vs walking speed (figure 6.2) the corresponding speed for each $\dot{V}O_2$ value was determined. Tapes closest to each speed were selected from the bank of 15 pre-recorded cassettes.

6.3 **RESULTS**

All patients completed the study and the average time between visits was 10.0 (4) days. Two patients had an exacerbation of symptoms (not related to participation in the study) and testing was suspended until they returned to baseline levels. A further two patients had significant changes in 3 aspects of the CRDQ on one occasion, and one patient had changes in two aspects. The measurements of FEV_1 did not change during these periods. On direct questioning the patients were able to identify specific causes for the changes and did not recognise any general deterioration in condition. As a result they

continued in the usual manner. The lung function at the first visit, the percentage of predicted normal values and anthropometric details of the group are presented in table 6.2. Eight patients identified some breathlessness at rest at each visit, whilst 2 patients identified some breathlessness at rest on two visits. The resting Borg scores and FEV_1 values for each visit are given in table 6.3.

The peak performance during the ISWT is shown for each patient in table 6.4. All the patients identified breathlessness as the main reason for the termination of exercise. The Borg ratings for breathlessness and perceived exertion are summarised in table 6.8.

The endurance capacity was defined as the exercise duration at the set endurance speed. The endurance walking speeds for each patient were derived from their peak performance during the ISWT and are shown in table 6.5. The time achieved by each patient and the reason for terminating the endurance exercise is shown in table 6.6. Three patients completed 20 minutes during the 85% test and 4 during the 75% test. One patient completed 20 minutes during all 3 endurance tests. As a precaution this patient repeated the ISWT to ensure a peak performance had been achieved during the initial test. The results from the repeat test were identical to the results from the initial test.

A summary of the endurance times and peak heart rate responses for the group are shown in table 6.7. The individual heart rate responses to each endurance test are illustrated in figure 6.3. There was a progressive decrease in the endurance times as the exercise intensity increased, though individually some patients (n=3) achieved the maximum time (20 minutes) for both the 75% and 85% exercise intensities. Analysis of variance revealed the endurance time achieved during the 95% test was significantly different from the 85% and 75% tests ($p<0.05$). There was no significant difference between the 75% and 85% times. The 95% HR was significantly different from the 75% HR ($p<0.05$), but it was not significantly different from the 85%

Table 6.2 Summary of patient characteristics

	Mean (SD)	Range	% of predicted
FEV_1 (l)	1.01 (0.36)	0.6 - 1.65	35
FVC (l)	2.92 (0.55)	2.03 - 3.9	81
% FEV_1/FVC	34 (6)	25 - 42	-
Age (y)	63.7 (5.5)	54 - 72	-
Height (m)	1.69 (0.07)	1.56 - 1.77	-
Weight (kg)	69.7 (12.6)	55.5 - 99	-

n=10, 9 men, 1 woman

Table 6.3 FEV_1 and Borg ratings (BS) for breathlessness at rest

Visit		ISWT	75%ESWT	85%ESWT	95%ESWT
FEV_1 (l)		1.05 (0.29) 0.55 - 1.5	1.02 (0.27) 0.65 - 1.5	1.06 (0.33) 0.6 - 1.68	1.07 (0.33) 0.6 - 1.75
BS	mean	1.1(0.8) 0 - 3	1.5(1.1) 0 - 3	1.3(0.9) 0.5 - 3	1.2(0.9) 0.5 - 3
BS	median	1.0	1.2	1.2	1.0

Mean (SD), median (BS only) and range for baseline FEV_1 and Borg ratings of breathlessness at rest at each visit

Table 6.4 Incremental shuttle walk test performance

Subject	Distance (m)	HR_{peak} (beat.min^{-1})	max. walking speed (km.h^{-1})	predicted $\dot{V}O_{2peak}$ (ml.min.$^{-1}$ kg^{-1})
1	250	126	4.25	10.32
2	320	125	4.86	12.03
3	330	102	4.86	12.30
4	120	111	3.03	7.13
5	360	134	5.47	13.01
6	280	115	4.86	11.05
7	420	146	5.47	14.48
8	360	84	5.47	13.01
9	240	146	4.25	10.1
10	450	136	6.08	15.22
mean (SD)	**313 (96)**	**123 (20)**	**4.86 (0.86)**	**11.87 (2.35)**

Total distance walked, HR_{peak}, maximum shuttle walking speed attained, and $\dot{V}O_{2peak}$ predicted from the distance achieved.

Table 6.5 Individual endurance walking speeds

Subject	75% ESWT	85% ESWT	95% ESWT
1	3.27	3.60	3.89
2	3.89	4.24	4.50
3	3.89	4.24	4.50
4	2.06	2.67	3.00
5	4.24	4.50	4.80
6	3.62	3.89	4.24
7	4.50	4.80	5.33
8	4.24	4.50	4.80
9	3.27	3.60	3.89
10	4.50	5.14	5.33
Mean (SD)	**3.76 (0.72)**	**4.12 (0.71)**	**4.43 (0.71)**

Walking speeds ($km.h^{-1}$) for 3 levels of endurance intensity

Table 6.6 Individual endurance times (min) and reason for terminating exercise

Ex. level / Subject	75% min / reason	85% min / reason	95% min / reason
1	3.4 / C	2.4 / C	1.5 / C
2	14.2 / B	12.6 / B	7.5 / B
3	17.6 / LF	13.0 / LF	5.5 / B
4	7.8 / B	3.4 / B	1.2 / B
5	20 / -	20.0 / -	5.3 / B
6	5.0 / B	2.8 / B	1.8 / B
7	20.0 / -	20.0 / -	4.2 / B
8	3.4 / C	2.7 / C	3.0 / C
9	20.0 / -	20.0 / -	20.0 / -
10	20.0 / -	5.3 / C	3.4 / B

Time completed at each exercise intensity and the reason for terminating exercise.

B - breathless

LF - leg fatigue

C - combination of breathlessness and leg fatigue

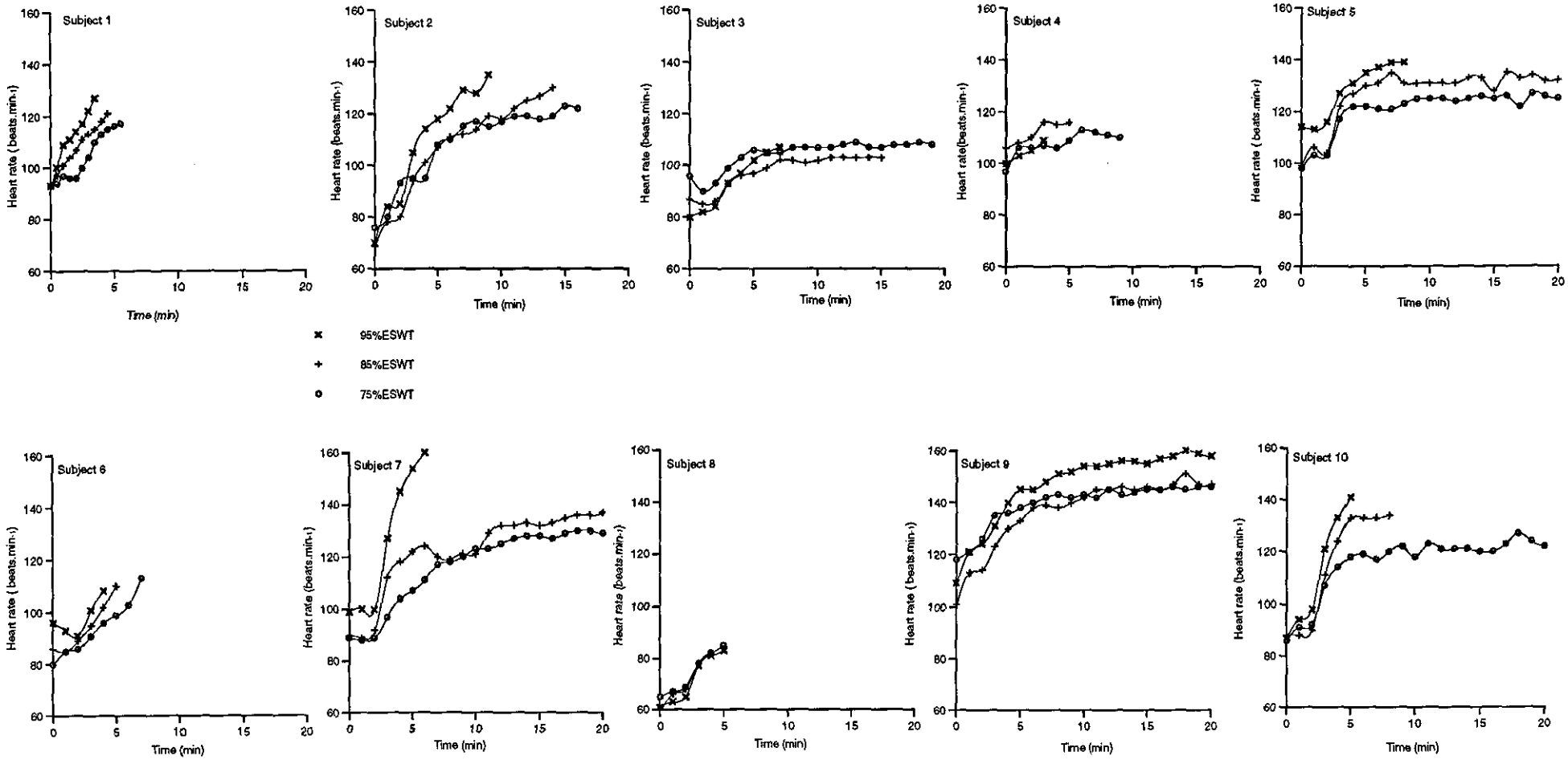
\- - completed 20 minutes of endurance walking speed

Table 6.7 Endurance shuttle walk test performance and heart rate response

	75% ESWT	85% ESWT	95% ESWT
Time (min)	13.1 (2.3) 3.4 - 20	10.2 (2.5) 2.4 - 20	5.3 (1.7) 1.1 - 20
HR_{peak} ($beat.min^{-1}$)	118 (5) 86 - 146	121 (6) 82 - 148	127 (8) 82 - 159

Mean (SE) and range for endurance time completed and peak heart rate during the three endurance tests (ESWT)

Figure 6.3 Individual heart rate response to 3 endurance shuttle walk tests (includes warm-up speed)



HR. There was no significant difference between the 75% and 85% HR_{peak}.

The Borg ratings of breathlessness and perceived exertion for both the ISWT and the ESWT are summarised in table 6.8. There was a trend for the Borg ratings of breathlessness to increase as the endurance intensity increased, however there were no significant differences between the scores. The same was true for the ratings of perceived exertion.

There was no relationship between the FEV_1 and the endurance times. There was a moderate and significant relationship between the 75% and the 85% times ($r=0.827$, $p<0.05$, figure 6.4). There was no relationship between the 95% time and the two lower intensities.

6.3.1 *Comparison of endurance and incremental field tests*

The mean time spent walking during the ISWT was 343 (75) s. There were no relationships between the ISWT and ESWT times. Seven patients achieved a higher HR following the 95% test, and 4 patients following the 85% test, compared to the HR_{peak} following the ISWT. However the differences in HR_{peak} between endurance tests and the ISWT did not reach significance. There were no significant differences between the Borg ratings for the ISWT and the ESWT. The reasons for terminating exercise differed markedly. Breathlessness was the main reason for all patients during the ISWT and for 7/10 of the patients during the 95% test. Whilst more leg fatigue, either singularly or in combination with breathlessness, occurred during the 85% and 75% tests.

6.4 DISCUSSION

Although a variety of field tests for the assessment of endurance capacity are available for healthy individuals, this is not the case within the clinical environment where there is little choice of field test, and an absence of a standardised endurance test. The adaptation of the ISWT format to provide an externally paced endurance field test has shown standardisation of walking pace is achievable, and the walking speeds may be individually

Table 6.8 Borg ratings for breathlessness and perceived exertion

		75%ESWT	85% ESWT	95%ESWT	ISWT
BS	mean (SE)	3.9 (0.4)	4.6 (0.6)	5.0 (0.5)	4.9 (0.6)
	range	2 - 7	2 - 9	4 - 9	3 - 9
	median	3.7	4.3	4.8	4.6
RPE	mean (SE)	13.5 (0.6)	13.6 (0.9)	14.3 (0.7)	13.3 (0.6)
	range	11 - 17	9 - 19	13 - 19	11 - 17
	median	13.4	13.4	14.1	13.2

Borg ratings for breathlessness (BS) and perceived exertion (RPE) rated following the ESWT and the ISWT

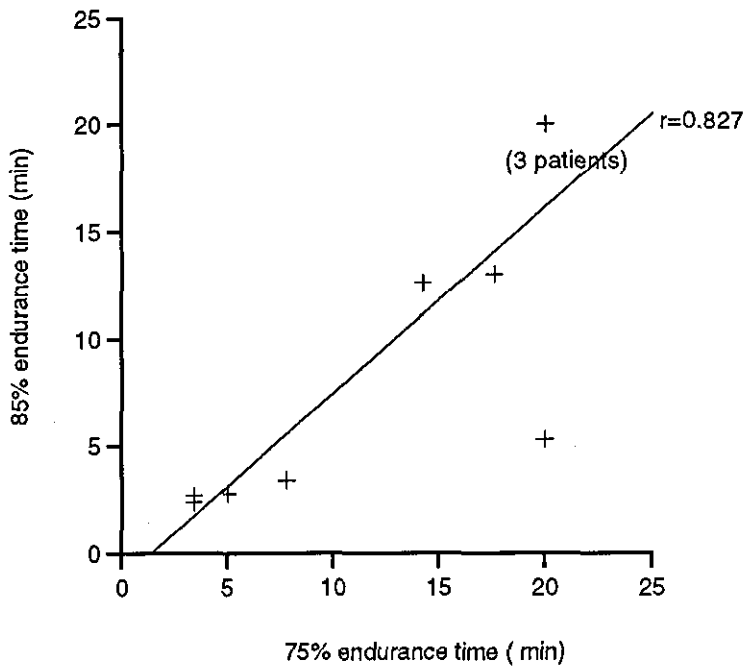


Figure 6.4 Relationship between 75% and 85% endurance times

determined from the peak performance measured during the ISWT.

The advantages of a standardised field test for the assessment of endurance capacity include ease of use and simplicity for operator and patient, and the avoidance of expensive laboratory equipment and time. Additionally the provision of a standardised walking pace improves intra- and inter-subject comparisons. The ESWT is based on a familiar activity and employs only minimal equipment. In the rehabilitation setting where there is often a large throughput of patients, a quick and simple assessment of endurance capacity, which is not confined to one area, is desirable. The determination of the walking speeds from a graph increased the complexity of the test, however this may be simplified by the production of a table or formula which related ISWT performance to suitable endurance speeds. The actual endurance speeds determined for each patient were similar to the relative percentages of maximum ISWT speed achieved. Therefore a simple percentage calculation, involving the maximum ISWT speed, may provide an alternative approach.

The range of pre-recorded endurance speeds was wide to accommodate a variety of exercise tolerances. However some of the faster speeds were *unused, whilst some of the moderate and slower speeds were used* repeatedly. A greater variety of walking speeds in the moderate range would improve selection for those patients who achieve only 1 or 2 shuttles at their final, maximum ISWT speed, i.e. a reduction in the increment size between the endurance speeds. To avoid the requirement for a large number of pre-recorded tapes the unused faster speeds might be removed without detriment to the versatility of the test in similar patients.

Any new instrument for patient assessment should be sensitive to change and possess good repeatability. A number of studies have demonstrated endurance capacity is sensitive to change following exercise training in patients with COPD (Chester 1977, Ries 1987, Niederman 1991, Singh 1996). Therefore it would be appropriate to assess the sensitivity of the

ESWT following pulmonary rehabilitation. The issue of sensitivity and repeatability is addressed in the final experimental chapter of this thesis.

The 75% and 85% endurance tests did not provoke significantly different responses in HR, time and subjective ratings. However the endurance time achieved during the 95% endurance test was significantly less than the 75% and 85% tests. A short test is desirable in terms of practical application and for the wider margin it leaves for change following an intervention. A number of patients completed the full 20 minutes of the lower intensity endurance tests therefore for these patients the 95% test may be more suitable for the demonstration of change following intervention. Alternatively, some patients achieved very short times during the 95% test, and also tended to achieve shorter times during the 75% and 85% tests. This is consistent with the findings of Singh (1996) where some patients have short endurance times, even at 50% of predicted $\dot{V}O_{2peak}$, but achieve large improvements following exercise training and rehabilitation.

There was a moderate and significant relationship between the 75% and 85% endurance times, whereas the relationship between the 95% time and the 75% and 85% times were poor and did not reach significance. There are two possible influences which may explain these findings. Firstly, a time limit of 20 minutes was imposed on the test thus artificially influencing the endurance time achieved by some patients. A large proportion of patients were stopped by the 20 minute limit during the 85% and the 75% tests (30% and 40% respectively). Secondly, the 95% test produced a maximal performance in some patients, as evidenced by the HR response, and this may have influenced the relationship with endurance time.

The lack of a relationship between the maximal performance and endurance capacity is further supported by the absence of an association between the ISWT time and the endurance times. This finding suggests endurance capacity may be related to other factors rather than the constraints which limit maximal exercise in COPD. This contention is supported by the

contrasting reasons for the termination of exercise during the incremental and endurance tests. Breathlessness was the reason identified by all patients during the ISWT and by 7/10 patients during the 95% endurance test. However leg fatigue, either singly or in combination with breathlessness, was identified more often during the 85% and 75% endurance tests, where longer exercise times were achieved at the lower intensities. This would suggest deconditioning, skeletal muscle changes and possibly depletion of local energy stores are also important factors of endurance capacity in COPD, and these are additional to the ventilatory abnormalities. The finding would support the case for endurance type training in this patient group.

In the current study the walking speed was externally paced and patients were given no indication of how long they had been walking. In addition they were not informed of the 20 minute time limit of the test. In this sense the ESWT was open ended, in contrast to the 6 or 12 MWT which are time limited and self-paced. Previous studies which have examined timed walking tests in detail have demonstrated that patients pace themselves according to the duration of the test. Bernstein (1994) examined the distances covered in each 2 minute interval of the 12 MWT. The distance in the first 2 minutes was slightly higher than the distances walked in the other 5 intervals. However there were no significant differences between distances and the correlation coefficients were highly significant. These findings were similar to those of Butland (1982) who also examined the distances covered in the 2 minute segments of a 12 MWT. Additionally 2, 6, and 12 minute tests were compared and the distances were highly correlated. However the author did not extrapolate the shorter test distances. When multiplied the 2 minute distance would be greater than the distance achieved during the 12 minute test, suggesting the pace was different for each test. Guyatt (1984) demonstrated a highly significant difference between the distance covered during a 2 minute test and the distances during the 2 minute intervals of a 6 minute test. All three studies concluded patients do pace themselves according to the duration of the test. These findings emphasise the non-

standardised nature of the timed walk test which relies on individual judgement of pace and a self imposed work rate. Any variability in work rate was avoided with the ESWT where the walking speed was externally imposed.

All the patients in the study group had moderately severe to severe airflow obstruction. They all had some breathlessness at rest and reported symptoms of breathlessness to a wide variety of daily activities e.g. dressing, washing, housework etc. All the endurance times were below 8 minutes during the 95% test with the exception of one patient, whilst there was wider variation at the 75% and 85% tests. This may reflect greater random variation, or is possibly an indication that lower intensity exercise may be a better discriminator of exercise tolerance in a fairly homogeneous group of patients. Previous studies of field test performance in patients with COPD have shown a wider spread of results with longer tests. Butland (1982) measured greater variance with a 12 MWT compared to the 6 and 2 MWT, although the differences were not large. However, in the routine clinical situation responsiveness to treatment is usually more important than the ability to discriminate between patients, hence a shorter test which is sensitive to change is likely to be more desirable.

The 95% endurance test provoked a higher mean heart rate than the ISWT, and the 85% test provoked a higher heart rate in 4 patients. There are two possibilities which may explain this finding. Firstly patients did not give maximum effort during the incremental test. All reasonable precautions were taken to minimise this possibility - patients received the standardised instructions recorded at the start of the ISWT tape, and patients were reminded to continue walking until too breathless or exhausted to continue i.e. to attain a symptom limited maximum. A practice test was always performed, and on the second test patients were encouraged to catch up with the bleeps if they slowed down. In the one patient in whom the ISWT was repeated the results were identical to the previous test which supports the correct conduct of the ISWT.

Secondly, a high intensity constant work rate test may provoke a higher heart rate in some patients than an incremental test. During the progressive test a steady state is unlikely to be attained in the shorter time available at each work rate. However when the object of the progressive exercise test is to measure $\dot{V}O_{2max}$, increases in work rate should continue until the $\dot{V}O_2$ reaches a plateau. In the clinical situation the $\dot{V}O_{2max}$ is rarely attained, and the symptom limited $\dot{V}O_{2max}$ or $\dot{V}O_{2peak}$ is measured i.e. the highest values are recorded in the absence of a plateau. The absence of a steady state during the peak work rate may lead to an underestimation of the maximum heart rate. In the current study the work rate remained constant throughout (following the slower warm-up period) and more time was available to attain a steady state at a high work rate. This is supported by the graphs of individual heart rate response where a plateau occurred during the higher work rates in some patients. As a consequence higher heart rates were recorded than during the ISWT.

A number of studies have shown a similar peak effect with the use of constant high work rate and steady state tests. Matthews (1989) recorded higher heart rates in both a control group, and in patients with moderate COPD, during a constant workload test at 75% of maximum workload. Whilst Cotes (1969) measured higher heart rates at equivalent work rates during a steady state test compared to progressive exercise, in both healthy subjects and, in a subsequent study, subjects with asbestos-related lung disease (King 1987).

The 95% test provoked a peak response in some patients whilst the 75% and 85% tests demonstrated patients with COPD can sustain relatively high work rates. This is consistent with previous studies which have found patients are able to exercise at relatively high work rates approaching, or in some cases exceeding, maximal performance (Ries 1987, Punzal 1991). An additional use of the ESWT may be as a training aid within the hospital rehabilitation setting. The rehabilitation programme at the Glenfield Hospital includes brisk walking as part of the exercise training, thus periodic use of

the tapes and the 10 metre course with individual patients may provide the opportunity to reinforce the prescribed training intensity.

There are a number of outcomes from this initial developmental study and several issues which require further investigation. External pacing of a field test for endurance capacity is achievable and the test can be relatively short which is both practical for the operator and not to onerous for the patient. Walking speed and hence the exercise intensity can be determined from the peak performance achieved during the ISWT. The lower intensity tests elicited longer exercise times and a greater incidence of leg fatigue. This finding supports deconditioning as an important limiting factor during endurance exercise in COPD.

The endurance shuttle walking test has the potential to be used as a quick and simple field test to assess disability, monitor progression and evaluate the outcome of therapeutic interventions. However to become a reliable method of assessment it is necessary to examine its relationship with the laboratory assessment of endurance exercise, and this issue is addressed in the following chapter. The repeatability of the test also requires investigation. Finally the test will only be worthwhile if it is sensitive to change. This would be most suitably assessed following an intervention of pulmonary rehabilitation with exercise training. These aspects are examined in the final experimental chapter of the thesis.

Chapter 7

THE CARDIO-RESPIRATORY AND METABOLIC RESPONSE TO ENDURANCE EXERCISE IN COPD

7.1 INTRODUCTION

The previous chapter described the development of a standardised field test of walking endurance and examined three levels of exercise intensity in 10 patients with COPD. However to be accepted as a reliable method of assessment the shuttle endurance walking test has to be both valid and repeatable.

Conventional laboratory based tests, using a treadmill or cycle ergometer, enable the assessment of the cardio-respiratory and metabolic responses to standardised work rates. A number of studies have related field and laboratory exercise performance. McGavin (1976) compared the 12 MWT test with maximal cycle performance and demonstrated a significant, though moderate relationship, with $\dot{V}O_{2peak}$ (r=0.52). Bernstein (1994) examined the correlation between $\dot{V}O_{2peak}$ and the distance walked during each 2 minute interval of a 12 MWT test. The highest correlation (r=0.71) occurred with the distance walked during the 6 to 8 minute interval. Singh (1994a) demonstrated a strong relationship between incremental shuttle walk test distance and $\dot{V}O_{2peak}$ (r=0.88). The cardio-respiratory response to constant work rate exercise in COPD has been examined previously in terms of the ventilatory and gas exchange kinetics and the establishment of steady state (Nery 1982). Other studies have compared the cardio-respiratory responses to both high and low intensity steady state cycle exercise in COPD and normal control subjects (Matthews 1989).

The aims of this study were as follows:-

1) To examine the relationship between the shuttle endurance walk test performance and endurance performance on a treadmill at the same relative levels of exercise intensity i.e. 75%, 85% and 95% of $\dot{V}O_{2peak}$.

2) To describe the cardio-respiratory and metabolic response to endurance exercise in COPD.

7.2 METHODS

7.2.1 Patients

The same ten patients (9 men, 1 woman), who had participated in the field test study, attended for an additional 6 visits. The demographic details, administration of the CRDQ, baseline lung function measurements and instructions regarding medications were the same as described in chapter 6.

7.2.2 Study Design

Patients performed six treadmill exercise tests during separate visits. All visits were repeated at the same time of day. The first test was a practice incremental test to familiarise patients with the equipment and walking on the treadmill. The second test was a symptom limited incremental test to measure $\dot{V}O_{2peak}$. The third test was a steady state test to determine the relationship between $\dot{V}O_2$ and walking speed. A regression equation was derived relating the steady state walking speeds and the corresponding $\dot{V}O_2$. From the equation 3 endurance speeds were calculated which related to 75%, 85% and 95% of the $\dot{V}O_{2peak}$. For the endurance tests patients walked at each of the calculated speeds on separate occasions and in randomised order.

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
practice	incremental	steady state	endurance	endurance	endurance

Visit 4-6, level of exertion randomised

7.2.3 Incremental and Steady State Exercise Tests

The incremental test was performed to determine the $\dot{V}O_{2peak}$. A brisk walking pace was determined for each patient from performance during the practice test. The treadmill gradient was increased by 2.0% every two minutes from an initial setting of zero. Patients were instructed to indicate when they could no longer continue because of breathlessness, fatigue or any other reason. They were encouraged to give maximum effort. The test

was symptom limited and performed according to the safety criteria described in chapter 3.

The steady state test was performed to determine the relationship between walking speed and $\dot{V}O_2$ for each patient. Patients walked for four minutes at three different speeds, with a period of recovery between each speed. Low, medium and medium high speeds were determined from the peak performance during the incremental test. The average $\dot{V}O_2$ during the final minute of each walk was plotted against the walking speed, and a linear regression line fitted by a computer graphics programme (Microsoft, Cricket Graph III, version 1.5). The derived equation was used to calculate the endurance walking speeds corresponding to 75%, 85% and 95% of the $\dot{V}O_{2peak}$ measured during the incremental test.

7.2.4 **Endurance Tests**

The endurance walking speeds were presented in randomised order over three visits. Patients walked for two minutes at a slower warm-up pace followed immediately by the endurance pace. Patients were instructed to walk until they felt too breathless or tired to continue. They were not informed of any time limit, and discouraged from asking or estimating how long they had been walking. All clocks were turned out of sight from the patient. A time limit of 20 minutes was imposed where there was an absence of symptoms and where there were indications the patient would continue comfortably for some time (i.e. low Borg ratings, subjective confirmation of state, visual assessment of patient by operator, appearance of steady state $\dot{V}O_2$ and HR on the exercise computer screen). Otherwise the test was conducted according to the safety criteria described in chapter 3.

7.2.5 **Measurements**

The FEV_1 was measured prior to exercise, and breathlessness rated from Borg scales whilst seated and resting. The following measurements were made during a 5 minute rest period and throughout the exercise periods:- $\dot{V}O_2$ and $\dot{V}_E$ measured using the Oxycon system, a single lead ECG for HR

and oxygen saturation (%SpO_2) using an earlobe probe pulse oximeter (Ohmeda Biox 3700e). At the end of exercise patients rated specifically how breathless they felt, and rated the difficulty of the exercise, from separate Borg scales. Exercise time was recorded throughout and the reasons for exercise termination noted. Earlobe capillary blood samples were collected for the measurement of blood gases, pH and lactate concentration. Blood gases and pH were measured at rest and during the final minute of the incremental test and the 85% endurance test. Blood lactate concentration was also measured at rest and 4 minutes post exercise during the incremental and the 85% endurance test.

7.3 RESULTS

All patients completed the study, the mean time between visits was 9.8 (4.8) days. The lung function at the inital visit, the percentage of predicted normal values and anthropometric details were presented in table 6.2, chapter 6. Nine patients identified some breathlessness at rest at each visit, and one patient reported breathlessness on rest on 4 occasions. The breathlessness scores at rest and FEV_1 measurement at each visit are given in table 7.1.

7.3.1 Incremental exercise to measure $\dot{V}O_{2peak}$

The mean exercise time was 8.3 (2.4) minutes. The reasons for exercise termination were breathlessness in 3 patients, leg fatigue (2 patients) and a combination of both symptoms (5 patients). The mean ventilatory, gas exchange, HR response and Borg ratings of perceived exertion and breathlessness at peak exercise are presented in table 7.2. Figure 7.1 illustrates the percentage of predicted values for $\dot{V}O_{2peak}$, $\dot{V}_E$ and HR.

Nine patients had a fall in %SpO_2 during exercise. In 6 patients the fall was $\geq$ 4 percentage points (p.p.), and in 2 patients it was only 1 p.p. The mean (SD) %SpO_2 at rest was 95.4 (1.5)% and at peak exercise was 91.5 (2.4)%. The mean fall was 3.9 (2.6)%. There was a corresponding fall in PaO_2 and a slight fall in pH. Four patients had a slight increase in $PaCO_2$ though it remained within normal limits for all cases. Only 2 patients had an absolute

Table 7.1 Borg ratings for breathlessness at rest and mean baseline FEV_1 values for all visits

Visit	Inc. test	S S	75%	85%	95%
FEV_1 (l)	1.01(0.36)	1.00 (0.29)	1.02 (0.32)	0.98 (0.29)	1.00 (0.45)
BS					
mean(SD)	1.7 (1.0)	1.6 (1.0)	1.6 (1.3)	1.6 (1.1)	1.4 (0.9)
range	0.5 - 3	0.5 - 3	0 - 4	0 - 3	0.5 - 3

Inc. Test - incremental test visit
S S - steady state test visit
75%, 85%, 95% - endurance test visits

Table 7.2 Cardio-respiratory measurements and Borg ratings during symptom limited incremental exercise

	$\dot{V}O_{2peak}$ ($ml.min^{-1}.kg^{-1}$)	$\dot{V}_{Epeak}$ ($l.min^{-1}$)	HR_{peak} ($bt.min^{-1}$)	Vt (ml)	fR ($breath.min^{-1}$)	RER	BS	RPE
mean (SD)	15.5 (3.9)	42.1 (12.8)	120 (20.1)	1614 (499)	28.2 (5.6)	0.91 (0.06)	5.5 (1.5)	15.4 (2.0)
range	9.7 - 21.2	25.9 - 64	86 - 151	897 - 2484	20.4 - 37	0.84 - 1.01	4 - 9	13 - 19

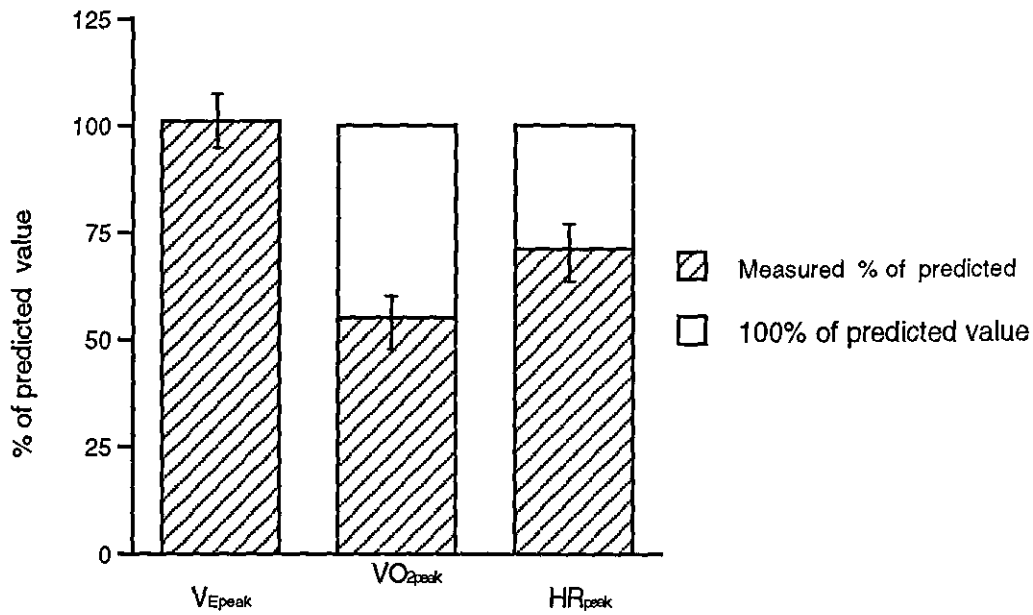


Figure 7.1 Peak incremental treadmill achievement expressed as mean (SE) % of predicted values

increase in lactate concentration exceeding 2 mmol.l $^{-1}$, and one of these had a concentration > 4 mmol.l $^{-1}$. A summary of the capillary blood gas, pH and lactate measurements is presented in table 7.3. An anaerobic threshold (AT) was detected in 5 patients using the V-slope method (Sue 1988) (figure 7.2). Only one of these had a lactate response > 2 mmol.l $^{-1}$, whilst the remaining 4 patients had minor increases in blood lactate concentration of 0.35, 0.52, 0.38 and 0.28 mmol.l $^{-1}$.

There was no relationship between the incremental $\dot{V}O_{2peak}$ and baseline lung function (FEV_1), treadmill time, the end exercise $\%SpO_2$ or the fall in $\%SpO_2$. There was no relationship between the incremental treadmill time, the FEV_1 and fall in $\%SpO_2$.

7.3.2 **Steady State Exercise**

A graph of the three steady state walking speeds and the corresponding $\dot{V}O_2$ was plotted for each patient and the regression lines fitted. The mean regression coefficient (r^2) was 0.965 (range 0.906 to 1.000). The regression equations were used to calculate the endurance walking speeds which related to 75%, 85% and 95% of the $\dot{V}O_{2peak}$ for each patient. The derived walking speeds are given in table 7.4.

7.3.3 **Endurance Exercise**

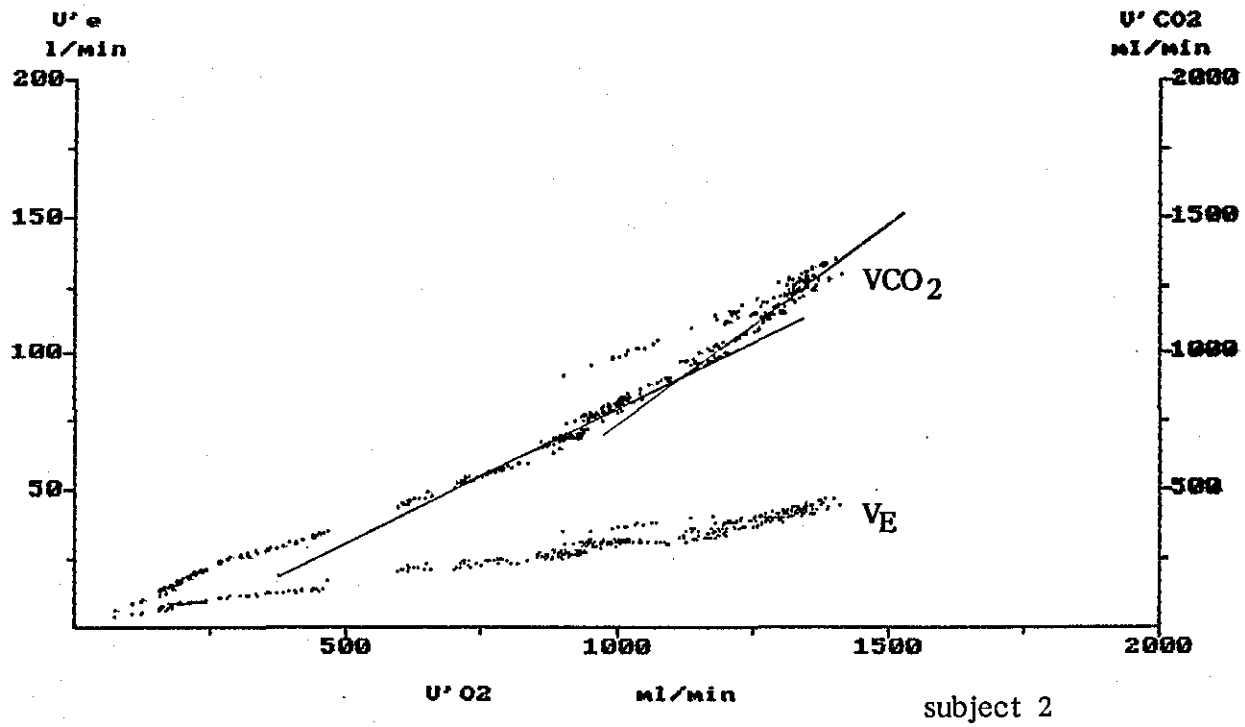
The endurance capacity was defined as the duration of exercise at the set endurance walking pace. The mean times for the three tests of endurance were 16.2 (6.6), 12.3 (7.2) and 8.1(6.8) minutes for the 75%, 85% and 95% tests respectively. The exercise times for each patient and the reasons for the termination of exercise are given in table 7.5. The Borg ratings for breathlessness and perceived exertion increased progressively as the level of exertion increased. The differences reached significance between the 95% and 75% tests for perceived exertion only. Table 7.6 summarises the Borg ratings for breathlessness and perceived exertion.

Table 7.3 Blood gases and lactate concentrations following incremental and endurance exercise

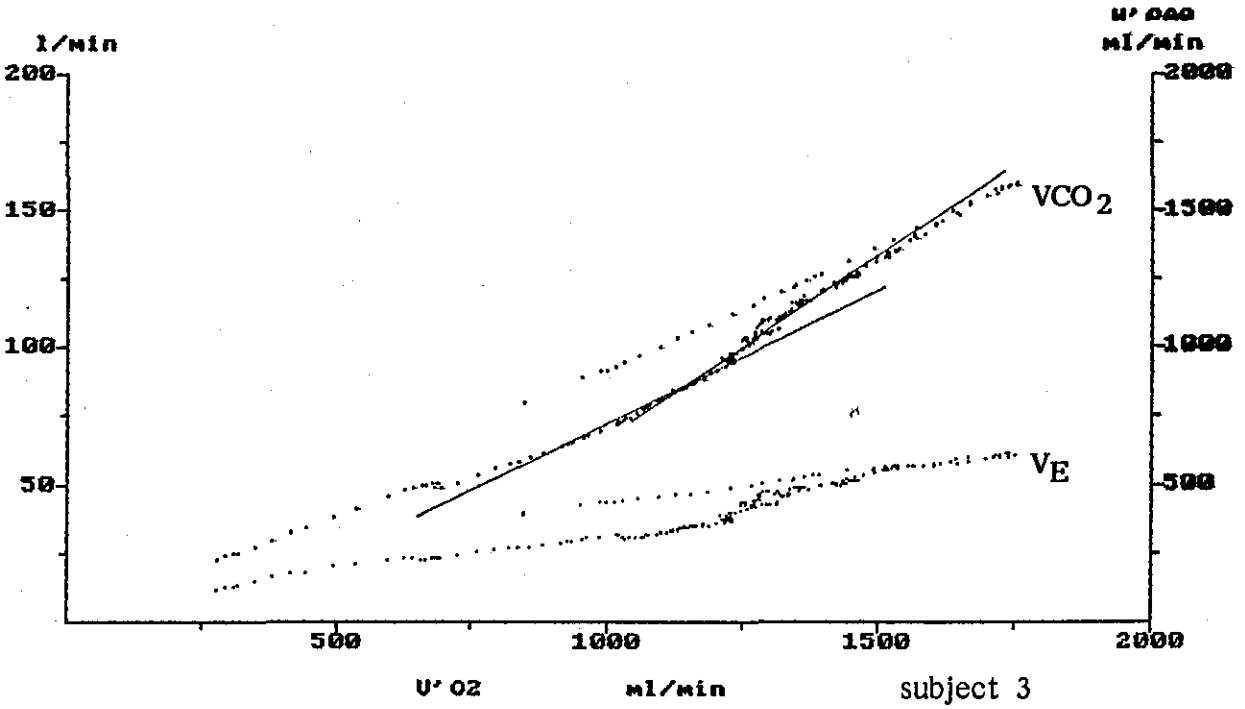
		PaO_2 (kPa)	$PaCO_2$ (kPa)	pH	lactate (mmol.l $^{-1}$)
Inc	Base	9.88 (0.32) 7.94 - 11.24	4.84 (0.06) 4.51 - 5.23	7.423 (0.007) 7.393-7.455	0.39 (0.14) 0.04 - 1.21
	peak	8.03 (0.24) 6.88 - 9.17	4.87 (0.18) 4.10 - 5.62	7.391 (0.012) 7.349-7.484	1.22 (0.52) 0.21 - 4.88
85%	Base	10.42 (0.44) 7.6 - 11.95	4.74 (0.10) 4.16 - 5.16	7.426 (0.007) 7.387 - 7.460	0.41 (0.12) 0.11 - 1.18
	peak	8.50 (0.42) 6.76 - 10.95	4.92 (0.13) 4.14 - 5.51	7.386 (0.009) 7.345-7.432	1.34 (0.56) 0.12 - 4.67

Mean (SE) and ranges for capillary blood gases, pH and blood lactate concentrations during incremental exercise (inc) and during the 85% endurance test. Values are for baseline (base) and peak exercise, except for blood lactate concentration which was at 4 mins post exercise.

Figure 7.2 Incremental exercise

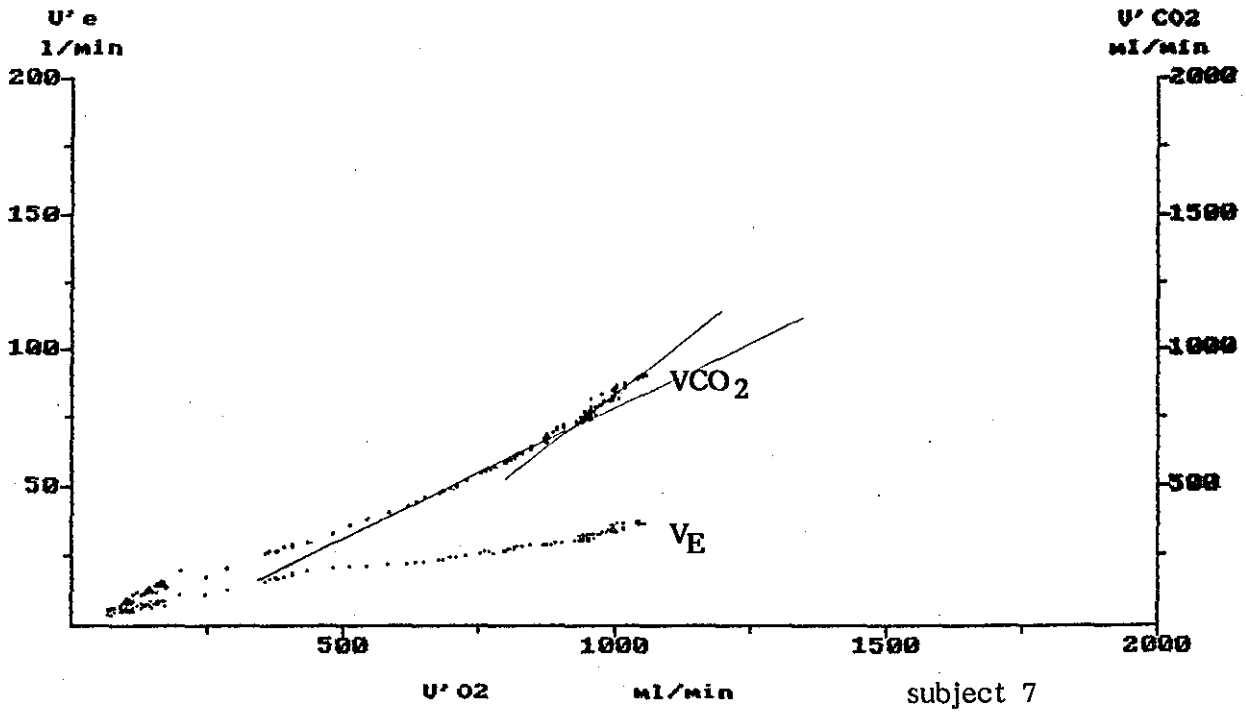


subject 2

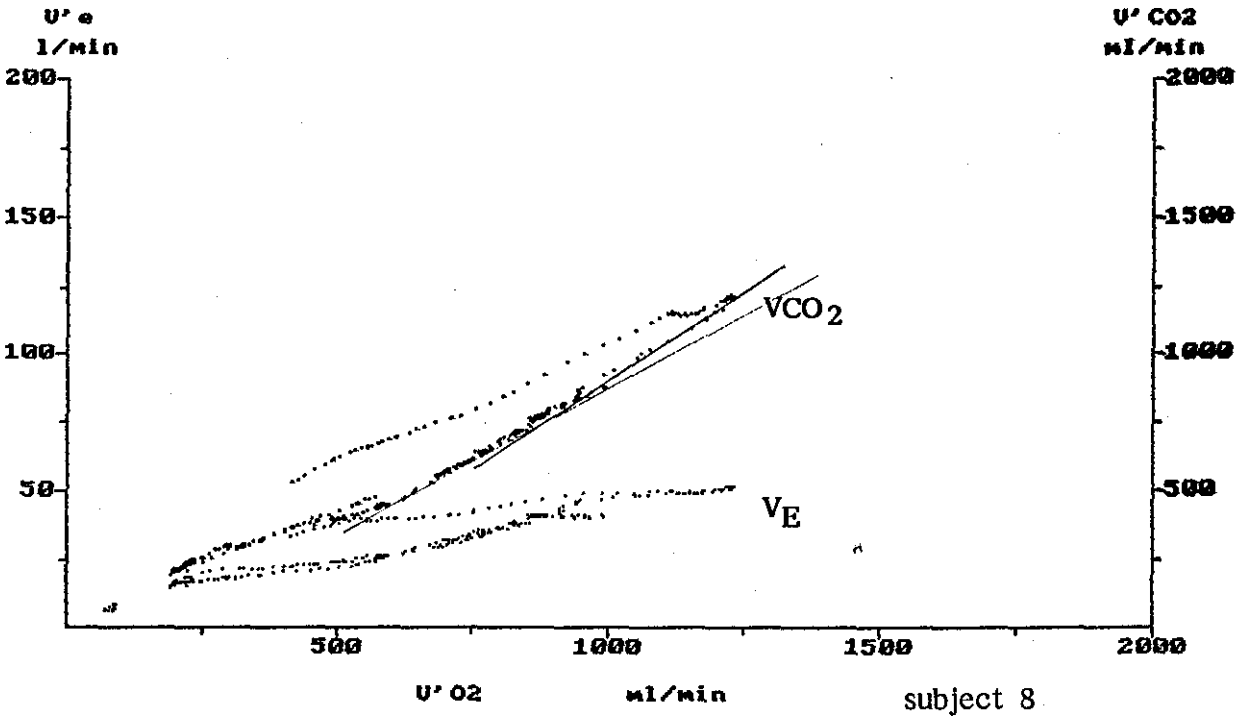


subject 3

Figure 7.2 (continued)

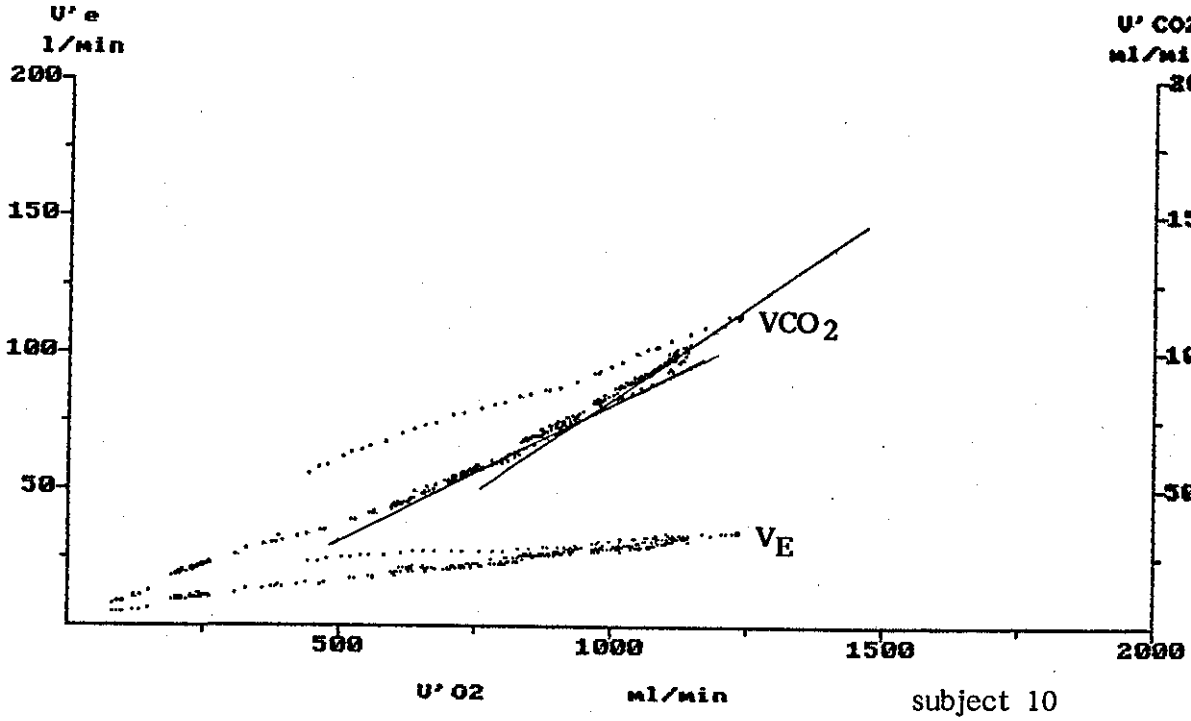


subject 7



subject 8

Figure 7.2 (continued)



subject 10

Table 7.4 Walking speeds for treadmill endurance tests

Subject	75%	85%	95%
1	1.4	1.8	2.3
2	3.9	4.4	4.9
3	4.5	5.3	6.1
4	2.7	3.5	4.4
5	4.4	5.4	6.3
6	2.5	3.2	3.9
7	3.5	4.1	4.7
8	4.1	4.8	5.5
9	2.6	3.2	3.9
10	4.0	4.7	5.4
mean (SD)	**3.36 (1.0)**	**4.04 (1.1)**	**4.70 (1.2)**

Walking speeds ($km.h^{-1}$) for 3 intensities of endurance exercise.

Table 7.5 Endurance times and reasons for termination of exercise

Test Subject	75% min / reason	85% min / reason	95% min / reason
1	13.8 / LF	12.3 / GF	9.8 / LF
2	20 / -	20 / -	17.2 / B
3	20 / -	9.0 / C	2.9 / C
4	4.7 / B	2.3 / B	2.0 / B
5	20 / -	20 / -	3.6 / C
6	20 / -	8.3 / B	4.5 / B
7	20 / -	20 / -	20 / -
8	3.9 / C	3.1 / C	2.1 / C
9	20 / -	8.2 / C	4.7 / GF
10	20 / -	20 / -	14.5 / LF
mean (SE)	**16.2 (2.1)**	**12.3 (2.3)**	**8.1 (2.2)**

Time completed for each test and reason for the termination of exercise.

B - breathless
LF - leg fatigue
GF - general fatigue
C - combination of leg fatigue and breathlessness
\- - completed 20 minutes of endurance walking speed

Table 7.6 Borg ratings for breathlessness and perceived exertion

	Endurance test	75%	85%	95%
BS	mean (SE)	4.1 (0.7)	4.5 (0.5)	5.9 (0.7)*
	range	1 - 9	3 - 7	3 - 10
RPE	mean (SE)	13.2 (0.9)	14.3 (0.8)	15.3 (0.7)*
	range	10 - 19	11 - 17	13 - 18

* significantly different from 75% test only ($p<0.05$)

Breathlessness (BS) and perceived exertion (RPE) rated at the end of each bout of endurance exercise.

The end of test mean values for $\dot{V}O_2$, $\dot{V}_E$ and HR showed a progressive increase at each level of exercise intensity (table 7.7). However there was wide variability in the pattern of the $\dot{V}O_2$ response to the endurance exercise. Four patients attained a steady state in $\dot{V}O_2$ during the 75% test ($\Delta\dot{V}O_2$, (terminal - 3 min) equal to zero, or negative (Wasserman 1994)), and 2 patients had a peak response at this level (final $\dot{V}O_2 \geq \dot{V}O_{2peak}$). Five patients had a peak response during the 95% test. The pattern of the $\dot{V}O_2$ response during the endurance exercise is illustrated in figure 7.3. Examples of the steady state response and the peak response of $\dot{V}O_2$, $\dot{V}_E$ and HR are illustrated in figure 7.4. The percentage of $\dot{V}O_{2peak}$ attained during the third and the final minute of exercise at each level of exertion is illustrated in figure 7.5. The mean (SD) % of $\dot{V}O_{2peaK}$ achieved at the end of each endurance test was 97 (11)%, 88 (13)%, and 84 (16)% for the 95%, 85% and 75% tests respectively.

The 95% test provoked a peak response in $\dot{V}O_2$ in some patients (n=5), therefore the gas analyses for these tests were also examined for evidence of an AT. An AT (V-slope) was detected in 3 of the patients. Two of these also demonstrated an AT during the peak incremental test. An AT (V-slope) was not detected during any of the 85% and 75% endurance tests. The presence of a gas exchange AT during the incremental and 95% endurance tests is summarised in table 7.8.

Analysis of variance, and post-hoc Scheffe test, revealed the 95% endurance test provoked significantly greater levels of $\dot{V}O_2$, $\dot{V}_E$ and Vt compared to the 75% test. The HR during the 95% test was also significantly higher than the HR during the 85% and 75% tests. There were no significant differences between the fR at the end of each bout of endurance exercise. Thus differences in the ventilatory response were achieved primarily by changing Vt.

Table 7.7 Cardio-respiratory measurements at the end of endurance exercise

Endurance test	$\dot{V}O_{2peak}$ ($ml.min^{-1}.kg^{-1}$)	$\dot{V}_E$ ($l.min^{-1}$)	HR ($bt.min^{-1}$)	Vt (ml)	fR ($breath.min^{-1}$)	RER
75%	11.8 (0.4) 9.4 - 14.0	33.4 (3.1) 22.4 - 51.3	112 (7) 80 - 157	1287 (104) 981 - 1792	26.6 (2.1) 12.5 - 33	0.87 (0.01) 0.82 - 0.96
85%	13.5 (0.9) 9.4 - 19.9	37.2 (4.2) 23.7 - 65	113 (6) 82 - 153	1394 (126) 900 - 2211	26.8 (1.7) 16.5 - 33	0.90 (0.02) 0.78 - 0.99
95%	15.0 (1.0)* 11.1 - 21.2	40.5 (3.4)* 27.0 - 58.9	122 (7)+ 83 - 157	1444 (103)* 906 - 2045	28.5 (2.1) 20 - 40.8	0.92 (0.02) 0.82 - 1.01

* significantly different from 75% and 85% tests ($p<0.05$) + significantly different from 75% test only ($p<0.05$)

Mean (SE) and range for cardio-respiratory measurements during the final minute of each endurance test

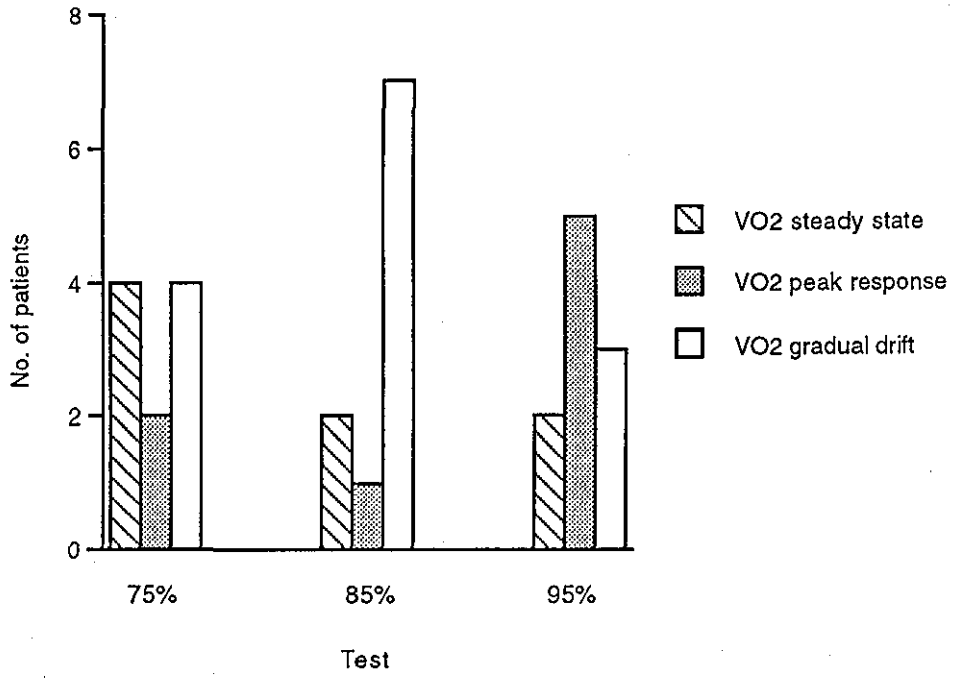
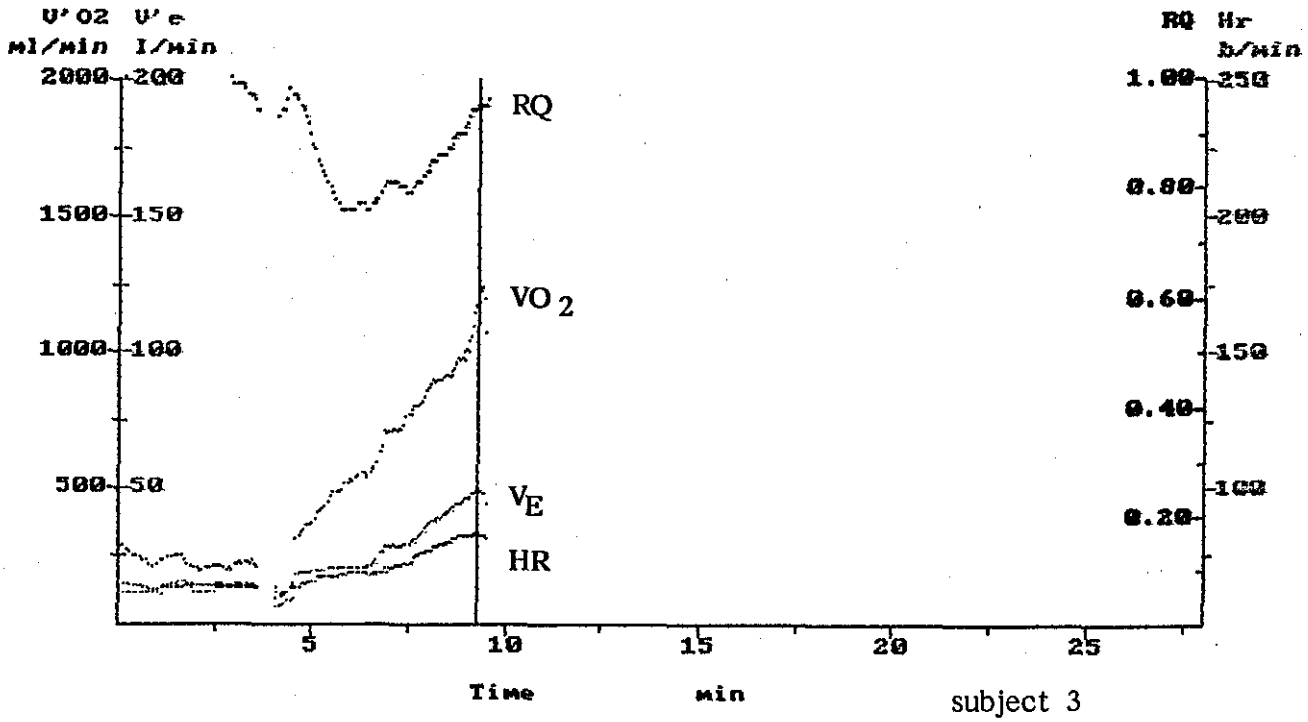


Figure 7.3: Number of patients who attained a steady state, gradual drift or peak response in VO_2 during endurance exercise

Figure 7.4 Examples of VO2 peak response and steady state during 85% endurance test.



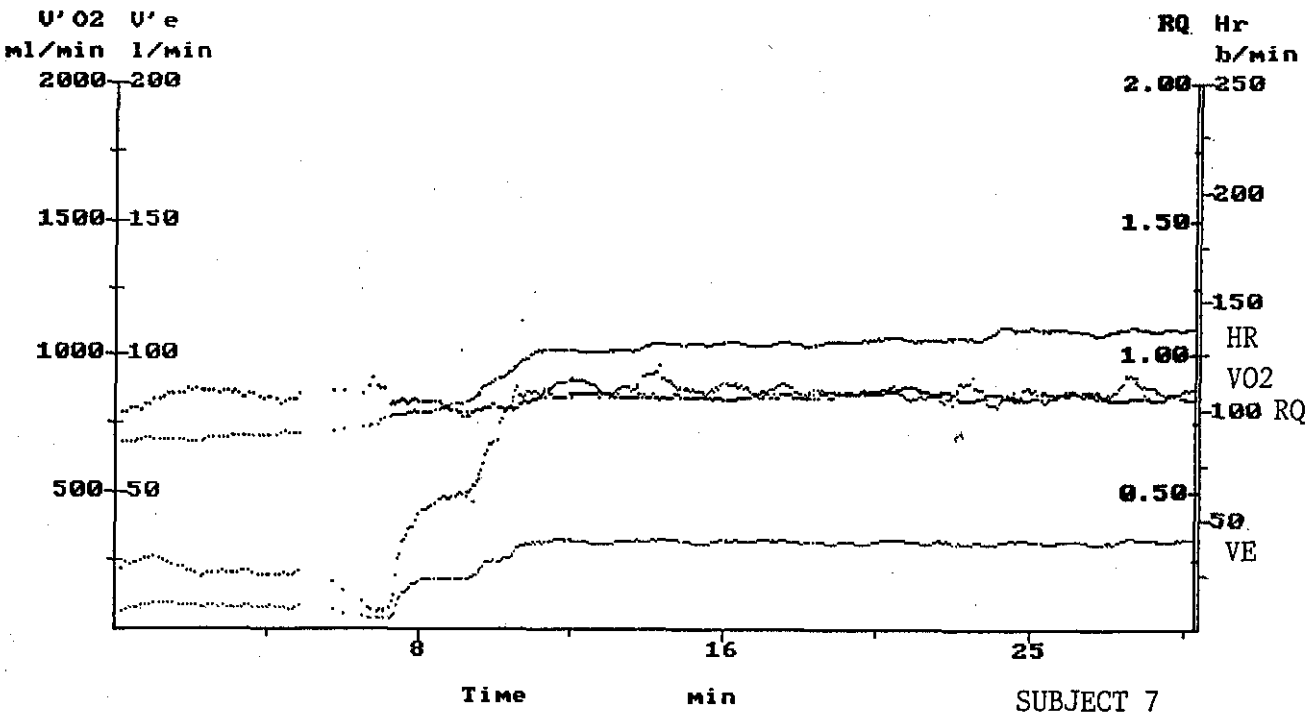


Figure 7.5 Percentage of VO_{2peak} attained at the start and end of the 3 treadmill endurance tests

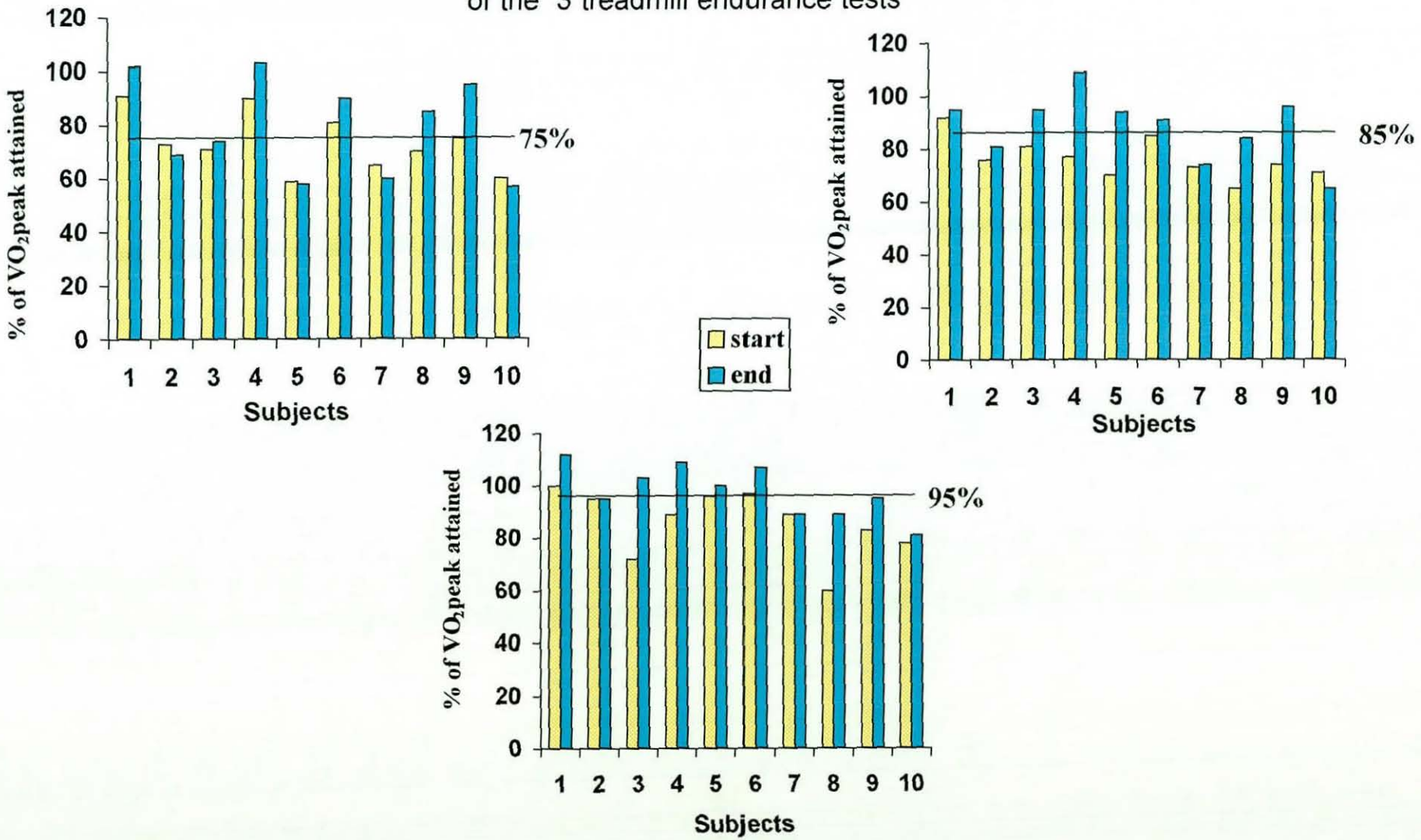


Table 7.8 Anaerobic threshold (AT) during incremental and endurance exercise

Subject	AT V-slope method	
	Incremental Exercise ($l.min^{-1}$) (%)	95% Endurance Exercise ($l.min^{-1}$)
1	NF	NF
2	1.26 (93)	NF
3	1.12 (68)	1.30
4	NF	NF
5	NF	1.25
6	NF	NF
7	0.83 (83)	NF
8	0.92 (72)	0.90
9	NF	NF
10	0.93 (80)	NF

Anaerobic threshold* detected by the V-slope method during incremental and 95% endurance exercise. (NF - not found)

* Expressed as $l.min^{-1}$ and percentage ( ) of $\dot{V}O_{2peak}$ measured during incremental exercise

NB The AT was not detected during the 85% or 75% tests

There was a fall in the mean value of $\%SpO_2$ at all levels of exertion with the greatest fall occurring during the 95% test (figure 7.6). The PaO_2 and the pH fell during the 85% test (table 7.3) (blood samples were not collected during any other endurance test). Two patients had an increase in lactate concentration > 2 $mmol.l^{-1}$ from baseline values. The blood gas and lactate analyses are summarised in table 7.3.

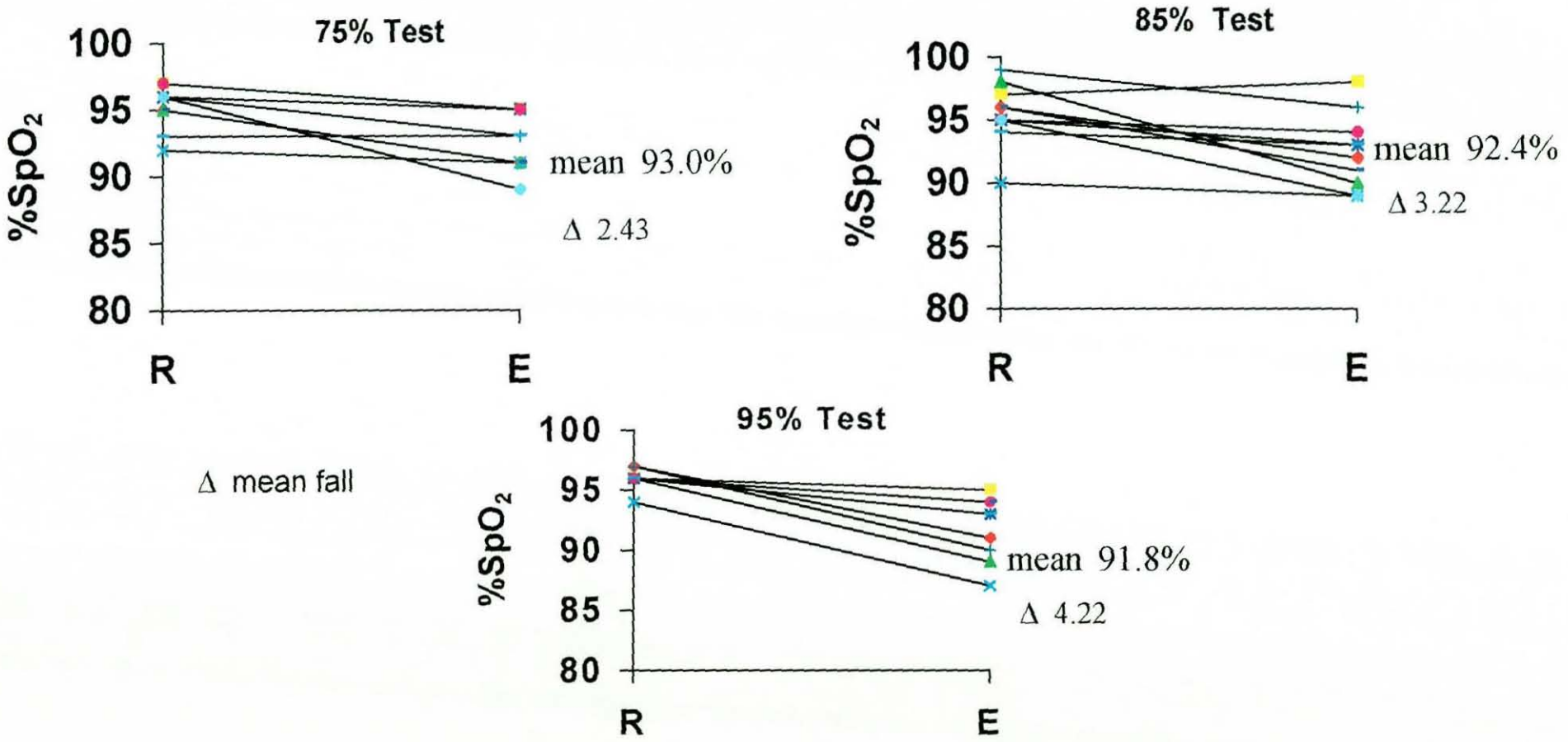
There was no relationship between the baseline FEV_1 measurements and endurance times, or between the FEV_1 and the $\dot{V}O_2$ at the end of each endurance test. However there was a significant relationship between the fall (Δ) in $\%SpO_2$ and the 85% endurance time (r value 0.717, $p<0.025$), (figure 7.7). The relationship with the 75% endurance time showed borderline significance ($r = 0.620$, $p=0.056$).

7.3.4 **Comparison of incremental and endurance exercise**

Analysis of variance revealed there were no significant differences between the peak incremental response and the end of test responses during the 95% and 85% tests for $\dot{V}O_2$, $\dot{V}_E$, HR, (illustrated in figure 7.8), and for RER, Vt and fR. Additionally the peak incremental HR, R, Vt and fR were not significantly different from the 75% endurance response. There were no significant differences between the end of test values of $\%SpO_2$ and no differences between $\Delta\%SpO_2$. There were no significant differences between the incremental and endurance tests for the Borg ratings of breathlessness. Similarly Borg ratings of perceived exertion were not significantly different with the exception of the 75% test. The exercise times achieved for the 95% test and the incremental test were not significantly different. The incremental test time was significantly less than the 85% and 75% endurance times (figure 7.9).

There was a significant but moderate relationship between the incremental test $\dot{V}O_{2peak}$ and the 85% treadmill endurance time ($r=0.663$, $p<0.05$). There was no relationship between the incremental $\dot{V}O_{2peak}$ and the 95% and 75% endurance times.

Figure 7.6 Oxygen saturation at rest (R) and at the end (E) of the 3 treadmill endurance tests



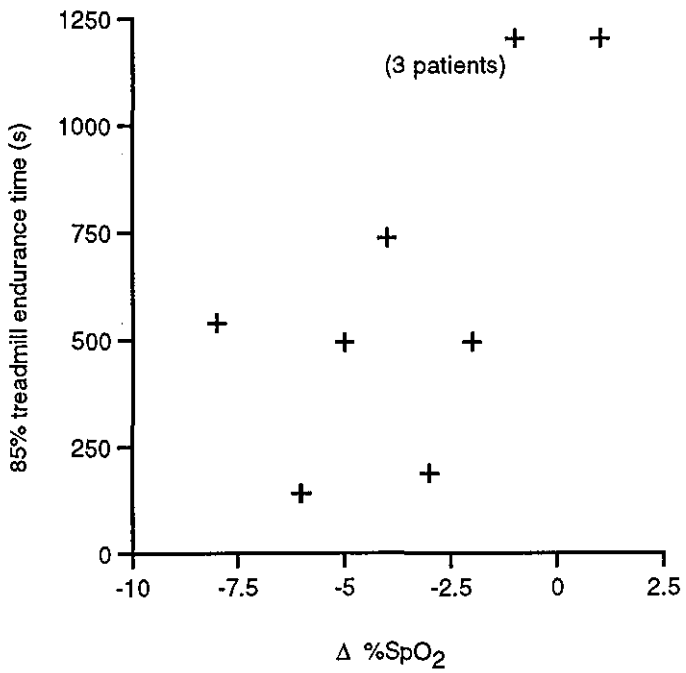


Figure 7.7 Change in %SpO2 (Δ) and time completed during the 85% endurance test

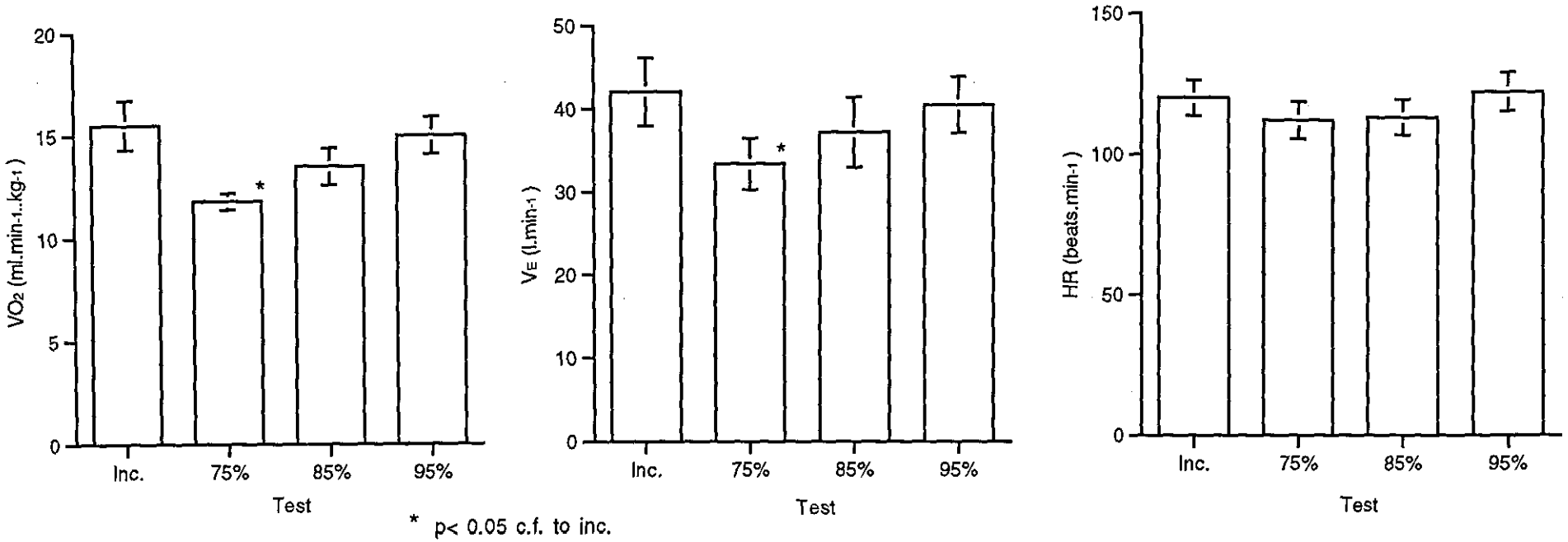


Figure 7.8: Cardio-respiratory responses (mean(SE)) to incremental and endurance treadmill exercise

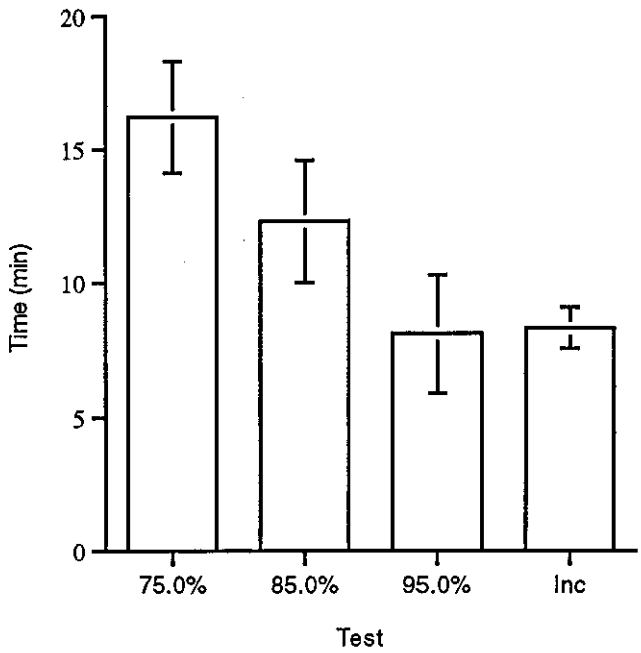


Figure 7.9 Mean (SE) exercise time achieved for the incremental and endurance treadmill tests

7.3.5 **Comparison of the field and treadmill endurance responses**

Although patients tended to walk for longer on the treadmill than around the shuttle course at all exercise intensities, there were no significant differences between the endurance times (figure 7.10). However there were wide differences in some patients and subsequently there were no significant relationships between the treadmill and field test times except for the 75% level ($r=0.681$, $p<0.05$). However this was strongly influenced by the number of patients who attained the 20 minute ceiling during both tests.

There were no significant differences between the end of test heart rate responses, or between the Borg scores for breathlessness and perceived exertion at comparative field and treadmill endurance levels. The reasons for terminating exercise on the treadmill and during the field test matched for 6 patients at both the 75% and 85% levels, and for 5 patients at the 95% level. More patients identified breathlessness as the reason for terminating exercise during the 95% ESWT (n=7) than for the 95% treadmill test (n=3).

There were significant relationships between the end of test field and treadmill heart rates (r values 0.901, 0.761 and 0.731, $p<0.025$, respectively for 95%, 85% and 75% endurance levels), figure 7.11.

There was a significant relationship between the $\dot{V}O_{2peak}$ predicted from the incremental shuttle walk test and the $\dot{V}O_{2peak}$ measured during the incremental treadmill test ($r=0.751$, $p<0.025$). However the predicted $\dot{V}O_{2peak}$ tended to underestimate the measured value. There was a significant relationship between the $\dot{V}O_{2peak}$ measured during the incremental treadmill test and the 75% field endurance time ($r=0.742$, $p<0.05$), but no significant relationship with the 85% and 95% field endurance times.

7.4 **DISCUSSION**

The aim of this experiment was to describe the cardio-respiratory and metabolic response to endurance exercise in COPD, and to examine the relationship between the field and treadmill endurance performances. To

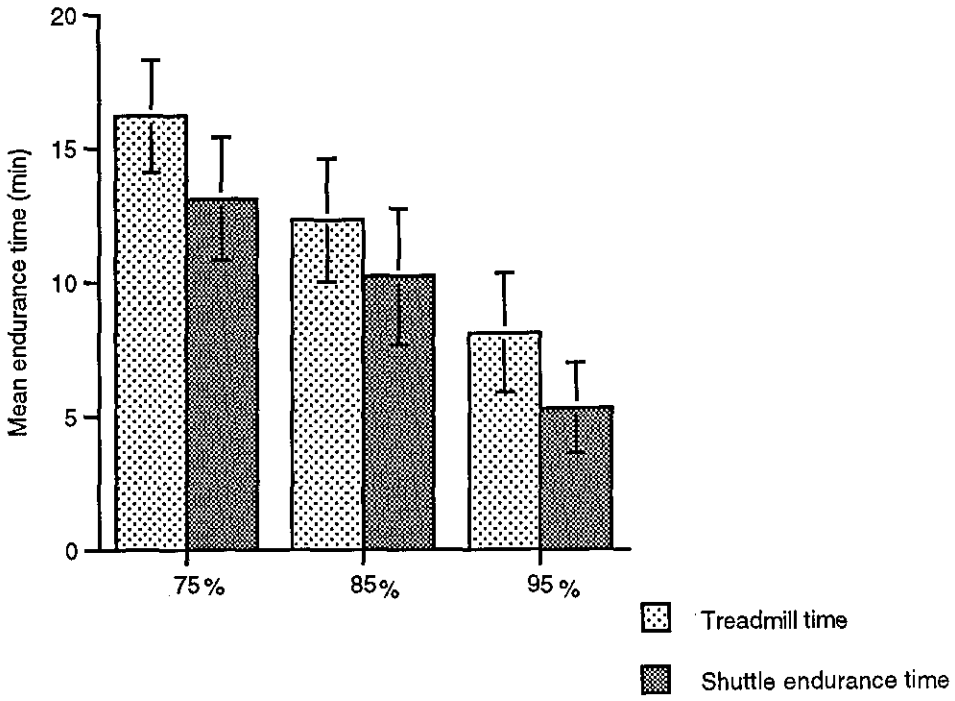


Figure 7.10 Mean (SE) treadmill and field endurance times

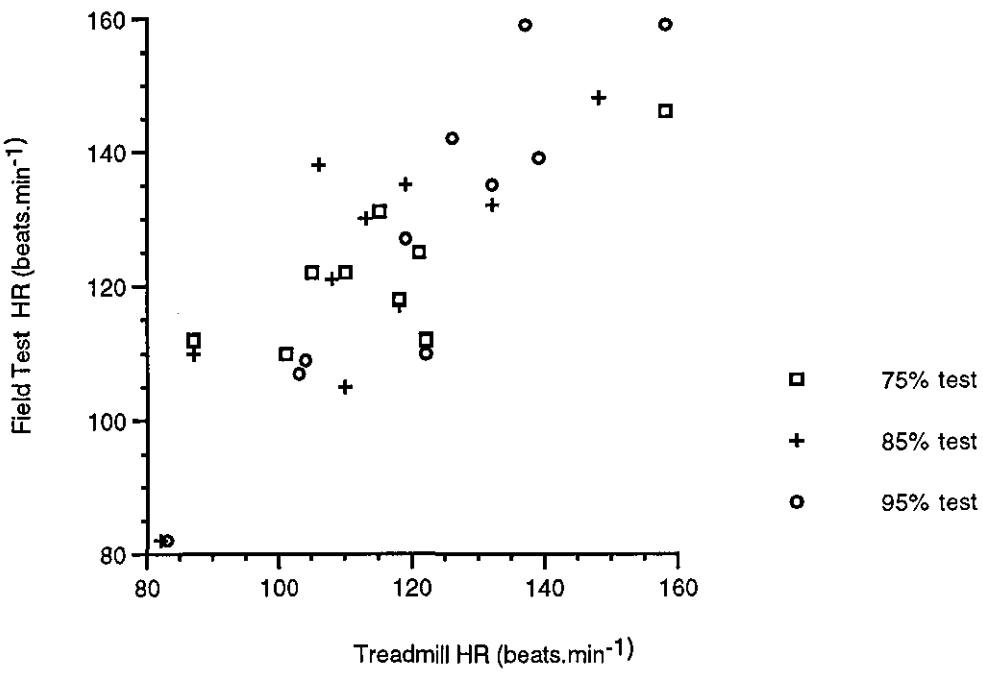


Figure 7.11 Heart rate (HR) response to field and treadmill endurance tests

produce the same relative level of stress in all patients (% of $\dot{V}O_{2peak}$) the walking speeds for each endurance test were calculated from the individual maximal performances and steady state exercise responses. The rationale for choosing the high work rates was based on three precepts: 1) the evidence that patients with COPD are able to sustain exercise at relatively high work rates; 2) endurance capacity measured at high work rates in COPD is sensitive to an intervention of exercise training (Ries 1988, Punzal 1991); 3) the necessity to develop a field test which is practical and avoids lengthy testing periods.

The group demonstrated a reduced exercise capacity. The $\dot{V}O_{2peak}$ achieved during the symptom-limited incremental test was only 55% of the value predicted for a normal population. There was also a moderate heart rate reserve at peak exercise which is consistent with a ventilatory limit to exercise. The equation to calculate the predicted $\dot{V}_{Epeak}$ at maximal exercise was derived from a group of patients with COPD (Spiro, 1975). The high percentage of the predicted value supports the attainment of maximal exercise capacity in this group of patients.

One of the aims of this study was to examine the cardio-respiratory and metabolic response to endurance exercise in COPD. Leidy (1994) described functional capacity as an individuals maximum potential to perform activities, and equated it to the measurement of $\dot{V}O_{2max}$ in the laboratory. Functional performance describes the corporeal activities of normal daily living, and functional capacity utilisation as the extent to which capacity is called upon in the selected level of performance. Thus, although performance is ultimately constrained by functional capacity, everyday fitness may relate more accurately to endurance capacity, or the ability to sustain exercise, rather than to the maximum exercise capacity. In this study endurance capacity was defined as the duration of exercise at the set intensity ($\%\dot{V}O_{2peak}$). The endurance capacity varied depending on the intensity of exercise, whilst there was a wide range of endurance times within the COPD group studied.

The range of endurance times were not significantly correlated with lung function or maximum exercise capacity ($\dot{V}O_{2peak}$). A lack of correlation between these two variables and endurance capacity has been demonstrated in patients with cystic fibrosis (Freeman 1993). This finding supports the results from the field test study (chapter 6) where there was no relationship between the time walked during the ISWT and the times completed during the endurance tests. In the current study there was a moderate relationship between incremental treadmill $\dot{V}O_{2peak}$ and the 85% treadmill endurance time (r=0.663), and between the incremental treadmill $\dot{V}O_{2peak}$ and the 75% field endurance time (r=0.742). However there were no relationships between the $\dot{V}O_{2peak}$ and any of the other endurance times (field or treadmill). This finding suggests endurance capacity may be related to other factors rather than the constraints which limit $\dot{V}O_{2peak}$. Åstrand (1986) states, for healthy subjects, the $\dot{V}O_{2max}$ is important for strenuous activity lasting approximately 5 - 30 minutes, whilst for prolonged energy demanding activities the maximal aerobic power is less important for performance. Peripheral factors, including muscle glycogen stores and muscle blood flow, and the level of pre-training are important for endurance performance.

A sub-optimal nutritional status is likely to affect both stored muscle glycogen and exogenous glucose levels. Although nutritional status was not evaluated, and there was no evidence of low body weights in the present study, previous work has demonstrated elevated resting energy expenditure in both normally nourished and malnourished patients with COPD (Lanigan 1990, Donohoe 1989), and this is likely to effect energy stores. Other studies have found changes in peripheral muscle strength and endurance (Newell 1989, Gosselink 1996b) and differences in muscle fibre types (Jakobsson 1990). Gosselink (1996b) examined quadriceps and handgrip force in a group of younger patients (mean age 58), and with slightly better lung function than the current study (FEV_1 % of predicted was 43%). Reduced peripheral strength was demonstrated in addition to reduced respiratory muscle strength.

In the study from Jakobsson (1990) skeletal muscle metabolites and fibre types were compared in two groups of patients with severe COPD, one group had respiratory failure. Both groups had a reduced percentage of type 1 fibre types (high oxidative capacity, low glycogenolytic capacity) (17% and 22%) compared to a control group (% not given). The respiratory failure group also had significantly reduced concentrations of glycogen and creatine phosphate. The authors found a significant correlation between the arterial PaO_2 and muscle glycogen, and between PaO_2 and the type 1 fibres, for both groups. There were some abnormalities in PaO_2 in the present study group. How this, and other abnormalities associated with the chronic condition, influenced muscle strength, energy stores, enzyme systems and the measured endurance capacity cannot be confirmed. However changes in peripheral muscle strength and energy stores, and their subsequent influence on endurance capacity, cannot be ruled out in this patient group.

In the current study there was no evidence of hypercapnia, however there was a significant correlation between the 85% endurance time and the fall in $\%SpO_2$ (r=0.717), and a weaker relationship with the 75% endurance time (r=0.620, p=0.056). There was no relationship between the fall in $\%SpO_2$ and the incremental exercise time. Two studies which examined the effects of oxygen supplementation on exercise performance in COPD (Bye 1985) and in interstitial lung disease (ILD) (Bye 1982) found endurance capacity was substantially improved (113% and 263% respectively) with O_2. However there was no effect on the incremental exercise performance (measured in the patients with ILD). The author suggested a mechanism of improved O_2 delivery and utilisation of O_2 by the tissues and limb muscles. Additionally, there was a delay in the onset of EMG evidence of diaphragm fatigue in the COPD patients, which suggested there were improvements in the respiratory muscle performance.

In a recent study which examined the effect of O_2 supplementation on the O_2 deficit and $\dot{V}O_2$ kinetics during exercise in COPD, Palange (1995) measured improved phase two $\dot{V}O_2$ time-constants, reduced O_2 deficit and steady state

ventilation during constant work rates in hypoxaemic patients. The author concluded O_2 supplementation accelerated $\dot{V}O_2$ kinetics, and enhanced aerobic metabolism, in the skeletal muscles in COPD. Although the results from the current study do not demonstrate a causal effect, they support a *relationship between the fall in* $\%SpO_2$ *and endurance exercise capacity.* They do suggest further investigations for the role of $\%SpO_2$, and the influence of ambulatory oxygen and endurance exercise.

Since everyday activity is more likely to relate to endurance capacity, levels of habitual activity, deconditioning, and motivation are likely to influence tests of endurance capacity. All the patients in the current study were retired from regular work, and though not quantified, qualification of daily activities revealed a wide range of levels. Resting lung function did not explain the wide range in endurance times. In the field test study (chapter 6) there was a marked contrast between the reasons for exercise termination during the ISWT *and the* 95% ESWT, *(main reason - breathlessness), and the reasons* indentified for the lower intensity endurance tests (leg fatigue and combination of symptoms). This suggested deconditioning was an important determinant of endurance capacity, whilst breathlessness remained the principal symptom limiting the shorter 95% and the incremental test (ISWT).

The reasons for exercise termination in the current treadmill study differed slightly from those identified during the field exercise. A greater incidence of leg fatigue was identified during the incremental and the 95% treadmill tests than for the corresponding field tests. The incremental treadmill test may have provoked more peripheral muscle fatigue than the incremental field test, since patients walked up an increasing gradient. Additionally, patients tended to walk for longer during the 95% treadmill endurance test, with greater incidence of leg fatigue, than during the comparative field test. The incidence of leg fatigue suggests there may have been deconditioning in some patients. Whether deconditioning was an important factor in the exercise limitation of this patient group requires further investigation.

It has been suggested the respiratory muscles may contribute importantly to the exercise limitation in COPD (Dodd 1984), and ventilatory muscle training has been shown to increase submaximal exercise performance in some studies (Pardy 1981, Larson 1988). This was discussed in some detail in the previous chapters. Gallagher (1994) suggests inspiratory muscle function influences endurance exercise time in some patients, since unloading the respiratory muscles with the use of continuous positive airway pressure led to significant improvements in endurance capacity in some patients (O'Donnell 1988).

The purpose of the steady state exercise tests (3 x 4 minute stages at different walking speeds) was to establish the relationship between walking speed on the treadmill and $\dot{V}O_2$ for each patient. This allowed individual walking speeds to be determined for the endurance tests, to provoke a given percentage of the $\dot{V}O_{2peak}$. This model was largely successful for the 95% and the 85% tests, however there was a wide scatter in the $\%\dot{V}O_{2peak}$ achieved, indicated by the large standard deviations. The $\dot{V}O_2$ achieved at the end of the 75% test was much higher (mean value 84%) than the target level. This latter finding is consistent with a study from Matthew (1989) where the application of a cycle ergometer work rate, equivalent to 75% of the maximal work rate, provoked a maximal $\dot{V}O_2$ response in both a COPD group and an age-matched control group.

The finding of a high $\dot{V}O_2$ at the lower exercise level (75%) raises a number of issues. The relatively slower walking speeds on the treadmill provoke a high $\dot{V}O_2$ in this patient group. The maximal exercise capacity may be so reduced that lower intensity exercise will engender a higher proportion of the maximal capacity, and even minimum exertion will elicit a relatively high energy expenditure. However 75% of $\dot{V}O_{2peak}$ is a relatively high level of exercise, even if in absolute terms the walking speeds might be considered slow or moderate. The energy requirement for walking on the level at 2 mph is between 2 - 4 $kcal.min^{-1}$, or less than 1 $l.min^{-1}$ of O_2 (Åstrand 1986). This

oxygen consumption is close to the $\dot{V}O_{2peak}$ measured in most of patients in this study. However, despite the high $\dot{V}O_2$ there was a graduated response in endurance times and the endurance capacity (length of time walked at each level) varied according to the imposed exercise intensity. The ability of patients to exercise at relatively high intensities supports the findings of others (Toshima 1990, Punzal 1991), where high intensity exercise training and testing regimens have been used as part of a rehabilitation programme.

At the 95% level of exertion 4 patients exceeded their $\dot{V}O_{2peak}$ and 6 patients exceeded their HR_{peak}. Submaximal exercise $\dot{V}O_2$ and HR values which exceed peak values in patients with moderate and severe COPD has been shown elsewhere (Matthews 1989, Punzal 1991). This finding suggests the incremental test may not always be the best method to obtain the highest value of $\dot{V}O_2$ for some patients. A similar response for HR was found during the field test study and was discussed in chapter 6. It is likely the shorter work stages during the incremental test did not allow the physiological variables sufficient time to stabilise. Thus peak values were not achieved prior to the termination of exercise. During the 95% endurance test the work intensity was high and persisted long enough for peak values to occur. A study which compared the ventilatory and gas exchange time constants between patients with COPD, and an age-matched control group, demonstrated patients had significantly longer phase 2 time-constants prior to the attainment of a steady state (Nery 1982). Additionally Wasserman (1994) reports considerably delayed steady state time with exercise above the AT.

The 95% endurance test provoked a peak response in 4/10 patients, and a gas exchange AT in 3 patients. The lactate response following the 85% test was not significantly different from the incremental response. One of the patients with a gas exchange AT during the 95% endurance test did not demonstrate an AT during the incremental test. These findings further support the usefulness of a high intensity constant work rate test to provoke a maximal response in some patients. At present there is no consensus

regarding the most appropriate exercise test for patients with respiratory disease. A test duration of 8 - 12 minutes for the measurement of $\dot{V}O_{2peak}$ has been recommended. The work rate increments should be tailored to the individual, taking into account habitual activity, clinical details and the results of any prior respiratory function tests (Wasserman 1994). The results from the present study indicate the use of a constant work rate, of high intensity, may provoke a higher $\dot{V}O_{2peak}$ compared to an incremental test in some patients.

The increases in $\dot{V}O_2$ between 3 and 6 minutes ($\Delta\dot{V}O_2$ (6-3)) of a constant work rate test were related to changes in lactate concentration in both normal subjects, and patients with heart failure (Wasserman 1994). The author suggested where the work rate was above the AT, the $\dot{V}O_2$ will continue to rise, and only when the work rate was below the AT will the $\dot{V}O_2$ assume a steady state. Using the same criteria in the current study, the 95% and 85% endurance tests were below the AT for the 2 patients who achieved a $\dot{V}O_2$ steady state, and the 75% level was below the AT for 4 patients. However, due to the variable lactate response, and the absence of serial measurements, the relationship between changes in $\dot{V}O_2$ and the blood lactate concentration cannot be confirmed in this group.

There was wide variation in the pattern of the $\dot{V}O_2$ response at the same relative levels of exercise (% of $\dot{V}O_{2peak}$). Some patients achieved a steady state $\dot{V}O_2$ at 2, or more, exercise intensities, whilst others had a rapid rise in $\dot{V}O_2$ and attained or exceeded their $\dot{V}O_{2peak}$. Finally some patients had a gradual increase in the $\dot{V}O_2$ throughout the endurance exercise. Roston (1987) suggested a continual slow increase in $\dot{V}O_2$ was associated with increased blood lactate concentration. The occurrence of a steady state $\dot{V}O_2$ in the current study could not be explained by the baseline lung function (FEV_1).

The results of the treadmill endurance tests from the present study substantiate the field test findings, that this group of patients with moderately severe COPD can tolerate exercise at relatively high work rates. The findings are consistent with previous studies which have examined patients prior to exercise training programmes and have demonstrated exercise of a relatively high intensity can be sustained. Punzal (1991) found patients who did not reach an AT were able to train at a higher percentage of maximum exercise capacity than patients who had reached an AT. Casaburi (1991) compared high and low intensity training in patients with moderate COPD, pre-selected on the basis of a detectable metabolic acidosis, and found patients were able to sustain and improve endurance exercise at 90% of the work rate associated with an AT. The present study has demonstrated both types of patients (with and without evidence of an AT), are able to exercise at high levels of $\dot{V}O_2$.

The group achieved longer endurance times walking on the treadmill with slightly lower heart rates compared to walking around the shuttle test course. The shuttle and corresponding treadmill speeds were different for some patients, however there are additional reasons which may explain this finding: 1) lower energy expenditure on the treadmill as a result of the belt assisting the backward movement of the foot before advancing to the next step; 2) differences in shoe to ground friction and step impact; 3) higher rate of energy expenditure as a result of turning the corners of the shuttle course compared to walking in a straight line on the treadmill. The heart rate responses provoked by the field test were comparable to those achieved on the treadmill, with significant relationships between the same levels of endurance. This finding supports the use of the field test to provoke similar cardiac responses to those provoked on the treadmill.

There was a strong correlation between the $\dot{V}O_{2peak}$ predicted from the ISWT and the $\dot{V}O_{2peak}$ measured during the incremental treadmill test. The ISWT tended to underestimate the actual $\dot{V}O_{2peak}$, however the endurance walking speeds derived from the predicted $\dot{V}O_{2peak}$ provoked similar HR responses,

and similar Borg ratings to those achieved on the treadmill. The shuttle endurance speeds were different from the treadmill walking speeds, and this reflects the differences between treadmill walking and walking around the shuttle circuit, and the differences between the predicted and the measured $\dot{V}O_{2peak}$. However the similarities between the treadmill and field test responses validates the use of the ISWT to determine suitable endurance speeds for the field test.

The gas exchange response to the incremental exercise revealed 5 patients with an AT determined by the modified V-slope method (Sue 1988). The absence of a gas exchange AT, or a metabolic acidosis, in patients with moderately severe to severe COPD is not uncommon. Sue (1988) was unable to detect an AT in 8 of 22 patients studied using the gas exchange method, and in 7 of the patients using the standard bicarbonate method i.e. fall in plasma standard bicarbonate at onset of metabolic acidosis. Belman (1992) detected only 7 patients from 29 with a metabolic acidosis (fall in bicarbonate > 2 meq.l^{-1}) during incremental exercise, whilst Wanke (1993) was unable to detect an AT in 12 of 30 patients with COPD using the same method.

In the present study patients who demonstrated a gas exchange AT (n=5) tended to have higher FEV_1 and $\dot{V}O_{2peak}$ values (mean values, 1.25 vs 0.79 l, and 17.2 vs 13.8 ml.min^{-1}.kg^{-1} respectively). This is consistent with previous reports where differences between study populations has led a number of workers to suggest disease severity may influence the appearance or absence of an AT. In the study from Sue (1988), which described the use of the V-slope gas exchange method in patients with COPD, the subjects who developed metabolic acidosis had milder airways obstruction compared to those who did not. Wanke (1993) found significantly higher airways resistance (R_{aw}) in patients who did not develop an AT, and Punzal (1991) found higher FEV_1 values in patients who developed an AT (FEV_1 1.96 vs 1.07 l). Spiro (1975) documented mean lactate concentrations of 3.63 and 2.56 mmol.l^{-1} following maximal exercise in moderate (mean FEV_1 1.45 l)

and severe COPD respectively (mean FEV_1 0.62 l). However the findings from Sue (1988) and Wanke (1993) led both authors to conclude that resting pulmonary function alone is a poor predictor of individual patients who do or do not develop metabolic acidosis during exercise. In the current study the small number of patients that displayed an AT make firm conclusions difficult. However since the application of exercise training may, in some pulmonary rehabilitation centres, rely on the development of an AT, the relationship between disease severity and the development of an AT is worthy of further investigation.

The patients who demonstrated the gas exchange AT had a longer mean incremental exercise time compared to the rest of the group (mean (SD) exercise time 9.3 (3.3) vs 7.7 (1.6) min). A reduced exercise capacity, which precluded the development of metabolic acidosis, may additionally explain the absence of an AT response in some patients. Previously it had been contended most patients with moderate and severe COPD did not develop an AT as a result of premature peak exercise levels (Belman 1986). However more recent work indicates a lactic acidosis can occur at low work rates in some patients, and the peak response is reduced in comparison with normal control subjects (Sue 1988, Casaburi 1991). Singh (1994b) demonstrated a markedly reduced blood lactate response in 10 patients with COPD (only 2 patients had an increase >2mmol.l^{-1}), and detected an AT by the gas exchange method in 6 patients. A gas exchange AT and significantly higher lactate concentrations were detected in 10 age-matched control subjects. The control group achieved longer exercise times (9.5 minutes) compared to the patient group (7.6 minutes). In the current study the small number of patients in the AT and non-AT groups make it difficult to draw reliable conclusions concerning the influence of exercise time. However it is likely a reduced exercise capacity, and termination of exercise prior to any significant increase in blood lactate concentration may explain the absence of an AT in some of the patients.

There was only one patient with a gas exchange AT and an increase in blood lactate concentration > 2.0 mmol.l^{-1}. The remaining patients with a gas exchange AT (n=4) had minor increases (< 1 mmol.l^{-1}). The proposed linking mechanism between the rise in blood lactate concentration and the sharp increase in CO_2 production, relative to $\dot{V}O_2$, is the release of additional CO_2 from the dissociation of carbonic acid. Hydrogen ions, released from the dissociation of lactic acid, are buffered by bicarbonate ions, forming carbonic acid which subsequently dissociates to form CO_2 and water ($Na^+ + HCO_3^- + H^+ + La^- \leftrightarrow Na^+ + La^- + H_2CO_3 (\leftrightarrow H_2O + CO_2)$ (Åstrand 1986)). Both CO_2 and increases in the hydrogen ion concentration stimulate the respiratory centre via the carotid bodies (Wasserman 1993).

The absence of a blood lactate increase, despite the presence of a gas exchange AT, in 4 of the patients suggests two possible mechanisms: 1) the ventilatory response in some patients may be triggered by very small increases in the H^+ ion, or CO_2 concentration, and this is possible since some patients are extremely intolerant of small fluctuations in $PaCO_2$ (Wasserman 1993); 2) the ventilatory and metabolic anaerobic thresholds may only be coincidentally and not causally linked. This hypothesis was argued by Loat (1993) in a review article which examined the relationships between the ventilatory, gas exchange and the lactate thresholds during exercise. The authors argued several points for a coincidental relationship and these included: i) patients with McArdles disease (deficiency of muscle phosphylase) demonstrate a normal hyperventilatory response to exercise despite the failure to produce lactic acid; ii) studies involving the comparison of the ventilatory and lactate thresholds during exercise in the normal and in glycogen depleted states demonstrated the two thresholds could be manipulated independently; iii) studies have shown the two thresholds respond differently to a training stimulus.

The findings from the current study cannot confirm the mechanisms for the gas exchange AT response to exercise. However they demonstrate that some patients may not manifest a conventional blood lactate response to

exercise (i.e. > 2mmol.l^{-1} increase or an absolute value > 4 mmol.l^{-1}) in the presence of a gas exchange AT. Additionally, the results would support a contention that the blood lactate increase following maximal exercise in COPD is reduced in comparison to a healthy population. There are a number of possible mechanisms for this finding, including reduced exercise times, or work rates, the premature termination of exercise due to symptoms, and reduced muscle bulk

A number of studies have shown the mode of exercise can influence the lactate response in patients with COPD. In a comparison of cycling and treadmill exercise in 8 patients with severe COPD, Mathur (1995) found cycling provoked the greatest increase in post exercise lactate concentration (mean increase for cycle ergometer 1.44 vs 0.41 mmol.l^{-1} for treadmill exercise). Cockcroft (1985) reported considerably higher lactate and ventilatory responses in 9 patients with COPD during cycling exercise compared to treadmill exercise at equivalent levels of $\dot{V}O_2$. The author suggested the smaller muscle mass involved with cycling exercise may account for the differences, since the mean metabolic rate per unit of contracting muscle is greater than for the equivalent treadmill work and thus is likely to engage anaerobiosis at a lower level of $\dot{V}O_2$. Similar findings have also been demonstrated in healthy individuals (Koyal 1976, Hermansen 1969). The use of treadmill (walking) exercise in the present study may have additionally influenced the size of the blood lactate response in this group of patients.

One patient without evidence of a gas exchange AT had the largest increase in lactate concentration of the group (post exercise value 4.88, and Δ 3.67 mmol.l^{-1}). This is consistent with the study from Sue (1988) which concluded the modified V-slope method was satisfactory for 'most individual exercise studies'. In a study which examined the reliability of the non-invasive methods of detecting an AT in COPD, Belman (1992) detected a gas exchange AT (using the V-slope method) in only 4/7 patients who had demonstrated a change in standard bicarbonate > 2 mmol.l^{-1}. The authors

describe wide inter- and intra-observer variability with the V-slope method in moderate and severe COPD. A study presented in abstract form only (Maltais 1993) has questioned the utility of the V-slope method in detecting an AT in severe COPD. A gas exchange AT was detected in only 2 patients whilst significant increases in lactate were measured in the whole group (n=15).

The results of the blood lactate analysis and the detection of a gas exchange AT during the incremental test were consistent with a number of previous reports, and, in summary, the findings were: 1) the more severely affected patients (lower FEV_1 and exercise capacity) appear not to produce a conventional increase in blood lactate (increase > 2, or absolute value of > 4 $mmol.l^{-1}$) upon maximal exercise; 2) there are inconsistencies between the occurrence of the gas exchange AT and the metabolic response. The reliability of detecting a gas exchange AT in moderate to severe COPD has been questioned, whilst changes in the blood lactate concentration may be minimal.

To summarise the findings of this study: 1) the heart rate response recorded from the treadmill endurance tests was similar to that measured during the field endurance tests described in chapter 6. There were also no significant differences between the Borg ratings from the field and treadmill tests. These findings support the use of the ISWT to derive suitable walking speeds for the field endurance test; 2) the treadmill endurance tests provoked a wide range of variation in the pattern of the $\dot{V}O_2$ response, ranging from a steady state to a peak response and this could not be predicted from the baseline lung function tests; 3) there were no substantial relationships between the peak incremental response and the endurance times for both the treadmill and the field tests (ESWT). This finding suggests endurance capacity in COPD may be related to additional factors rather than the constraints which limit $\dot{V}O_{2peak}$. The more frequent occurrence of leg fatigue during the longer tests suggested the possibility of deconditioning in some patients.

The results from the current study show patients with moderate and severe COPD are able to tolerate exercise at high levels of $\dot{V}O_2$ and this supports the use of relatively high work rates in a clinical field test. The 95% test provoked a peak response in some patients, whilst half of the patient group completed 20 minutes of the 75% test. Thus the performance of an endurance test at 85% of maximum intensity is likely to be practical i.e. not too onerous for the patient, or time consuming for the operator, and it would possess a suitable margin for improvement following an intervention. However, the sensitivity and repeatability of a high intensity endurance test is as important as the practicality of the test. These two issues are addressed in the next chapter.

Chapter 8

THE RESPONSE OF THE ENDURANCE SHUTTLE WALK TEST TO AN INTERVENTION OF PULMONARY REHABILITATION

8.1 INTRODUCTION

In order to become a reliable method of exercise evaluation the ESWT must possess both sensitivity, and repeatability. The studies reported in chapters 6 and 7 suggested an endurance test at 85% of $\dot{V}O_{2peak}$ was well tolerated by the patients examined and would provide a practicable test in terms of duration and opportunity for improvement. In this study the repeatability of the ESWT was assessed and the sensitivity of the test was examined following an intervention of pulmonary rehabilitation.

The number of practice walks recommended for the timed walk field tests varies from one to five (McGavin 1976, Knox 1988). An examination of the repeatability of the ISWT demonstrated the test required only one practice walk (Singh 1992). The 12 and 6 MWT have been shown to improve significantly following a period of pulmonary rehabilitation in patients with COPD (McGavin 1977, Cockcroft 1981, Niederman 1991). However Guyatt (1984) suggested the magnitude of change reported in some studies may represent test-retest variability and poor conduct of the test. Additionally a number of studies have failed to incorporate a control group or period, an important factor recommended by Knox (1988) where a timed walk test is used as an outcome measure.

The aims of this study were formulated as follows:

1) To assess the between day repeatability of the ESWT.
2) To assess the sensitivity of the ESWT to an intervention of comprehensive pulmonary rehabilitation following a control period of similar duration.

8.2 METHODS

8.2.1 Patients

Thirty-three patients were entered into the study (16 women, 17 men). All the patients had been referred to the Hospital pulmonary rehabilitation service following routine attendance to the out-patient respiratory clinics. All the patients had COPD as a primary diagnosis, though some patients had additional clinical problems. These were not considered contra-indications to regular exercise and were stable at the time of referral. The additional ailments were renal impairment (1), cardiac valve disease (1), old myocardial infarction (1), gastric ulcer (2), hypertension (4). Patients were contacted by letter after they had received an appointment for their initial rehabilitation assessment. In the majority of cases there was a delay of 6 to 8 weeks between referral and commencement of rehabilitation and this acted as the control period for the study. Height and weight were measured at the start, and weight was re-checked at intervals throughout the study. FEV_1 was measured at every visit, and the degree of breathlessness at rest assessed from a Borg scale. There were no alterations to any medications, although patients were instructed to use their inhaled bronchodilator within one hour of their appointment time in order to ensure maximum bronchodilation prior to exercise.

8.2.2 Study Design

Patients attended on four separate occasions. At the first visit, two ISWT and one practice ESWT were performed. The endurance walking speed was related to 85% of the $\dot{V}O_{2peak}$ predicted from the ISWT, and was calculated as described in chapter 6. The ESWT was performed during all the subsequent visits. The second visit occurred within 7 days of the initial visit, and was considered the start of the control period (no change in treatment). The third and final visits occurred at the start and end of the 7 week pulmonary rehabilitation course. In addition to the ESWT, patients also performed an ISWT at the start and end of the rehabilitation course. In order to examine the repeatability of the ESWT, 11 patients performed an additional endurance test at the start of the control period (visit 2a).

					Rehabilitation	
Visit	**1**	**2**	**2 a** (repeat study)	**Control period** 5 - 7 weeks	**3** Start	**4** End
Test	ISWT ESWT	ESWT	ESWT		ISWT ESWT	ISWT ESWT

8.2.3 **Endurance Shuttle Walk Test**

A number of modifications to improve the ESWT, and the recorded cassette tapes, were identified. These were: the inclusion of an additional moderate speed (table 8.1); alterations to the taped message at the start of the tapes; recording the complete test onto a smaller number of tapes. Four endurance walking speeds were recorded onto one 90 minute tape i.e. 2 x 20 minute tests on each side. Previous experience with the ESWT tapes during the developmental study (chapter 6), had suggested the standardised instructions recorded at the start of the tape were superfluous. All patients listened to the standardised instructions at the start of ISWT, and the instructions for the ESWT were very similar. There were two minor differences i.e. instructions concerning the 2 minute warm-up period, and the constant walking pace. Thus the instructions at the start of the ESWT tapes were removed. The one minute calibration signal remained, in addition to the following taped message at the start of each test:-

'walking test level_. The walking speed for the first 2 minutes is fairly slow, so don't go too fast. The test will start in 10 seconds, so get ready at the start now. The test starts with a triple bleep after a 4 second count-down.'

A short piece of music was also recorded at the end of each endurance test to make it immediately obvious to the operator when the full 20 minutes of the endurance bleeps had finished. In addition it also acted as an audio marker for the end of one test and the start of the next test, recorded on the same side of the tape.

The ESWT was performed as described in chapter 6. The walking speed was determined in the manner described in chapter 6, and related to 85% of the $\dot{V}O_{2peak}$, predicted from the ISWT. The heart rate was recorded throughout using the telemetry device. Breathlessness and perceived exertion were rated from Borg scales and the reason for the termination of

Table 8.1 Modified Endurance Walking Speeds

Level	Warm-up speed ($km.h^{-1}$)	Endurance speed ($km.h^{-1}$)	Time/10 m shuttle (s)
1	1.44	1.78	20.25
2	1.44	2.09	17.25
3	1.44	2.44	14.75
4	1.44	2.72	13.25
5	1.44	3.00	12
6	2.40	3.27	11
7	2.40	3.60	10
8	2.40	3.79	9.5
9	2.40	4.11	8.75
10	2.40	4.36	8.25
11	2.40	4.65	7.75
12	2.40	4.97	7.25
13	2.40	5.14	7.0
14	2.40	5.54	6.5
15	2.40	5.76	6.25
16	2.40	6.00	6.0

Duration of warm-up speed 2 minutes, and 20 minutes for the endurance speed

exercise was recorded.

8.2.4 **Incremental Shuttle Walk**

The ISWT was performed according to the description in chapter 3. Oxygen saturation was checked at rest and at the end of the test using the finger pulse oximeter. Where there was a fall in $\%SpO_2$ to <86% patients performed all subsequent walk tests with ambulatory oxygen (flow: 2 $l.min^{-1}$). The oxygen was administered via nasal cannulae, and the portable cylinder was carried by the test operator (SMR) walking behind the patient. Care was taken to walk some distance behind the patient to avoid influencing performance of the tests.

8.2.5 **Pulmonary Rehabilitation Course**

During the 7 week out-patient course patients attended the Hospital Physiotherapy Department for 2 hour classes, twice weekly. The course had educational and exercise components. The educational component consisted of inter-active talks covering a variety of topics e.g. effective cough, relaxation, control of breathing, drugs, doses and devices, pathology of COPD and current therapies, nutrition, energy saving devices, keeping well, benefits agency and lung function measurements. Patients received a folder containing notes of the talks for future reference.

The exercise training programme consisted of a circuit of flexibility and strength type exercises in the physiotherapy gym, and a home walking programme. The prescribed walking intensity related to 50% of the $\dot{V}O_{2peak}$ predicted from an ISWT performed during the initial rehabilitation assessment. The prescribed time of continuous walking was determined individually from performance during a treadmill endurance test, at the derived speed. Patients were instructed to walk every day if possible and to gradually increase the length of continuous walking at the prescribed speed. They were given a diary sheet to record the minutes of continuous walking completed and a Borg scale to rate breathlessness. Patients who

demonstrated oxygen desaturation < 86% during the initial assessment performed the exercise training with portable oxygen.

The pulmonary rehabilitation course was conducted by other dedicated Hospital personnel and has been in operation for a number of years. There were no alterations to the standard course. Although the investigator (SMR) tutored some exercise classes, the main part of the rehabilitation intervention was performed by other staff.

8.3 RESULTS

The mean (SD) duration of the control period was 5 (1.5) weeks. The study was conducted during late autumn and winter, and coincided with very low ambient temperatures and the usual increased prevalence of winter viral infections. As a result a number of patients had chest infections during the control periods, and during the rehabilitation course. Additionally several patients failed to complete the rehabilitation course due to severe exacerbation of symptoms, and for other reasons.

Four patients had exacerbation of symptoms and chest infections during the control period and were treated with antibiotics. In addition one of the patients received a short course of oral prednisolone. Two of the patients recovered in time for the start of the rehabilitation, and two of the patients had the start deferred for 2 - 3 weeks. Three patients were treated with antibiotics for chest infections during the rehabilitation course and had a break from the course for 1 - 2 weeks. One patient suffered from cystitis and did not attend for 3 weeks. Ten patients failed to complete the rehabilitation course for a variety of reasons. These were: severe exacerbation of COPD and chest infection (3); Baker's cyst on the left knee (1); exacerbation of cardiac valve disease (1); exacerbation of renal impairment (1); minor stroke (1); motivational problems (2); sciatica (1).

The data for 19 patients are presented. Three patients had not completed the course at the time of writing. An additional patient, not referred to the

rehabilitation course, was recruited for the repeatability section of the study. The measurements from this patient are included in the repeatability section only.

All patients were on regular inhaled bronchodilator and steroid treatment. Two patients were receiving low dose oral steroids (prednisolone). Eleven patients were on diuretic therapy. Two patients were receiving domiciliary O_2 therapy for at least 15 hours per day, and 6 patients were using O_2 for symptomatic relief only.

The anthropometric details of the group, baseline and predicted lung function at the time of the initial visit are shown in table 8.2. The mean FEV_1 and resting Borg breathlessness values at each visit are shown in table 8.3. Three patients had a fall in oxygen saturation to <86% during the initial ISWT and received ambulatory oxygen for all subsequent tests. In addition these patients also received ambulatory oxygen during the exercise training component of the rehabilitation programme. The mean resting $\%SpO_2$ for the whole group was 94.5 (1.5)%. At the end of the initial ISWT the $\%SpO_2$ was 90.7 (3.9) and the mean fall was 3.8 (3.0). Individual values are illustrated in figure 8.1.

The endurance walking speeds were determined from the peak ISWT performance and calculated by the graphical method described in chapter 6 (fig. 6.2). The individual endurance walking speeds are shown in table 8.4.

The endurance capacity was defined as the exercise duration at the set endurance speed of the ESWT. To enable comparison with the ISWT, the distance walked during the endurance test was also calculated, and included where appropriate. There was no significant change in the ESWT over the control period, the mean difference (SE) in time spent walking was 4.1 (9.9) s, and for distance walked was 4.7 (8.1) m, $p>0.05$. Similarly there was no significant change in the ISWT (mean difference 2.6 (9.2) m).

Table 8.2 Summary of patient characteristics at initial visit

	Mean (SD)	Range	% of predicted
FEV_1 (l)	0.80 (0.19)	0.50 - 1.20	35 (8)
FVC (l)	2.06 (0.90)	0.95 - 3.7	68 (20)
FEV_1/FVC (%)	45 (17)	15 - 78	-
Age (y)	69 (6.6)	56 - 77	-
Height (m)	1.64 (0.07)	1.53 - 1.79	-
Weight (kg)	70.8 (15.1)	53 - 106	-

n=19; 9 men, 10 women

Table 8.3 Borg rating for breathlessness at rest, and baseline FEV_1 at each visit.

Visit	1 practice	2 start control	3 start rehab.	4 end rehab.
FEV_1 (l)	0.80 (0.19)	0.82 (0.19)	0.84 (0.23)	0.85 (0.21)
BS				
mean (SD)	1.3 (1.0)	1.9 (1.0)	2.3 (1.3)	2.0 (1.3)
range	0 - 3	0 - 3	0 - 4	0 - 4
median	1.4	1.8	2.1	1.9

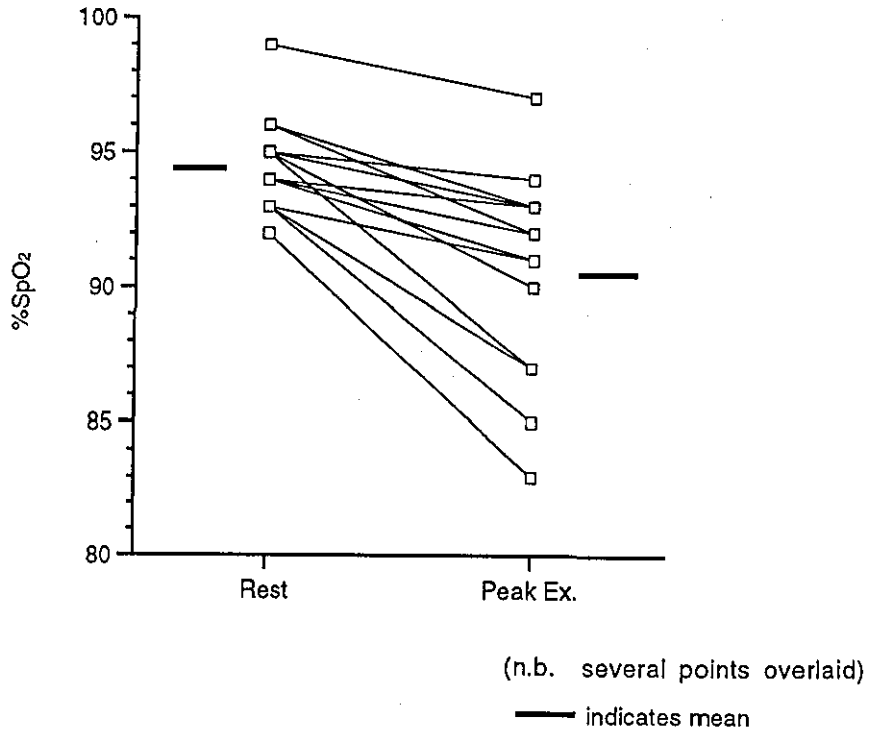


Figure 8.1 Pulse oximetry (%SpO_2) at rest and at peak exercise (n=19)

Table 8.4 Individual endurance walking speeds

Patient	85% Endurance speed ($km.hr^{-1}$)
1	3.00
2	2.72
3	4.11
4	3.60
5	2.09
6	3.79
7	2.72
8	3.00
9	4.36
10	3.60
11	3.00
12	3.00
13	2.44
14	1.78
15	3.00
16	2.09
17	4.36
18	3.00
19	3.00

All the patients, with the exception of one (patient 10), had an improvement in the ESWT at the end of the rehabilitation course. Prior to rehabilitation the maximum time achieved by any single patient during the ESWT was 709 s (11 min 49 s). Following rehabilitation 3 patients completed 1200 s (20 minutes), and 4 patients achieved > 17 minutes. The response to the ISWT was more variable, 9 patients had an improvement of ≥ 30 m (i.e. greater than the test-retest variability (Singh 1992)) and 10 patients attained the same distance or less than at the start of rehabilitation. Analysis of variance revealed there were significant improvements in both the ESWT and ISWT for the whole group. The mean percentage improvement in endurance capacity was 160%, and for the ISWT was 32%. A summary of the walking test results for both the ESWT and ISWT pre- and post- rehabilitation are shown in tables 8.5 and 8.6 (and fig. 8.2). The individual values are illustrated in figure 8.3.

The mean differences and 95% confidence intervals for the changes in both tests are shown in table 8.7. One patient died suddenly 3 weeks after completing the rehabilitation course (patient 10). This was the only patient without an improvement in the ESWT. A slight decrease in the endurance capacity was measured (start rehabilitation 436 s, end 399 s). To eliminate the possibility of a spurious result the post-rehabilitation ESWT was repeated at a separate visit. The results were within 4 seconds (399 and 395 s). Additionally there was only minimal improvement in the ISWT.

There were significant improvements in the Borg ratings for breathlessness and perceived exertion following rehabilitation for both the ESWT and the ISWT. The improvements occurred in addition to the significantly longer exercise times measured during the ESWT. Tables 8.5 and 8.6 summarise the Borg ratings for both tests.

The reasons for the termination of endurance exercise did not change appreciably during the control period. Following the ESWT most patients identified breathlessness, and a combination of breathlessness and leg

Table 8.5 Endurance shuttle walk test performance

	Start control	Start rehab.	End rehab.
Time (s)	283 (36) 81 - 681	287 (33) 100 - 564	706 (162) 200 - 1200
Distance (m)	247 (32) 40 - 548	252 (33) 49 - 582	601 (82) 116 - 1455
HR_{peak} (beat.min^{-1})	113 (4) 78 - 145	112 (4) 78 - 136	116 (4) 81 - 146
BS	4.4 (0.3) [4.1] 2 - 7	4.2 (0.3) [4.1] 3 - 7	3.6 (0.3) [3.5] 2 - 7
RPE	12.7 (0.4) [12.6] 9 - 16	12.2 (0.3) [12.1] 11 - 15	11.5 (0.4) [11.4] 7 - 15

n = 19

Mean (SE) and range for endurance time and distance, HR_{peak}, Borg ratings for breathlessness (BS) and perceived exertion (RPE) at the start of the control period and the start and end of the rehabilitation course.
[ ] indicates the median scores for the BS and RPE.

Table 8.6 Incremental shuttle test performance

	Start control	Start rehab.	End rehab.
Distance (m)	182 (18) 60 - 330	184 (22) 40 - 340	223 (22) 70 - 400
HR_{peak} (beats.min^{-1})	111 (4) 79 - 143	106 (3) 77 - 123	109 (3) 77 - 130
BS	5.1 (0.4) [4.9] 3 - 9	4.4 (0.3) [4.1] 2 - 7	3.7 (0.3) [3.5] 2 - 7
RPE	12.6 (0.3) [12.5] 11 - 17	13.8 (0.5) [13.6] 11 - 18	12.1 (0.4) [12.0] 7 - 14

Mean (SE) and range for ISWT distance, HR_{peak}, Borg ratings for breathlessness (BS) and perceived exertion (RPE) at the start of the control period and the start and end of the rehabilitation course.
[ ] indicates the median scores for the BS and RPE.

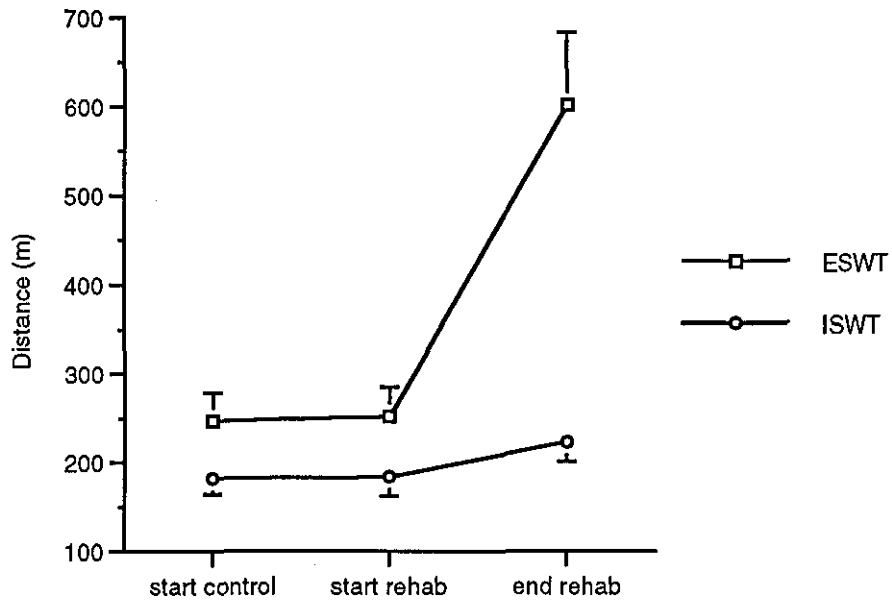


Figure 8.2 Mean (SE) distance walked during the endurance and the incremental shuttle tests

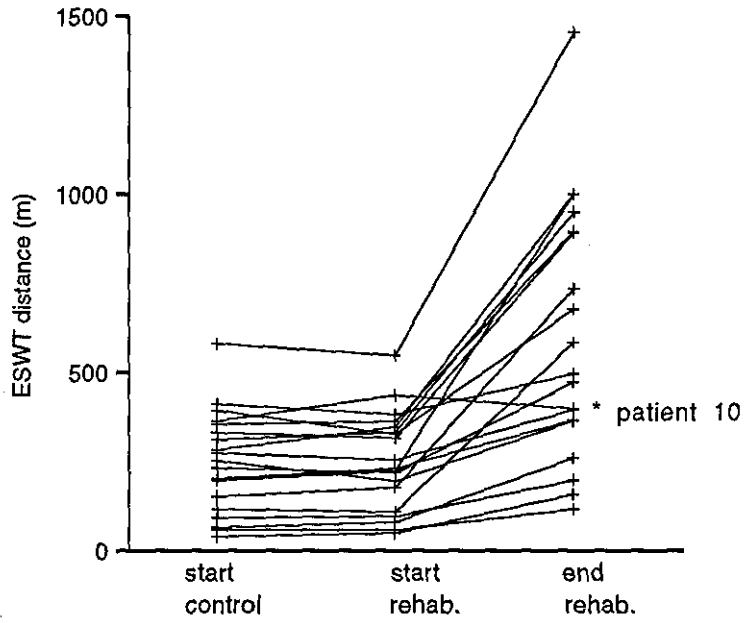


Figure 8.3a Individual endurance distance

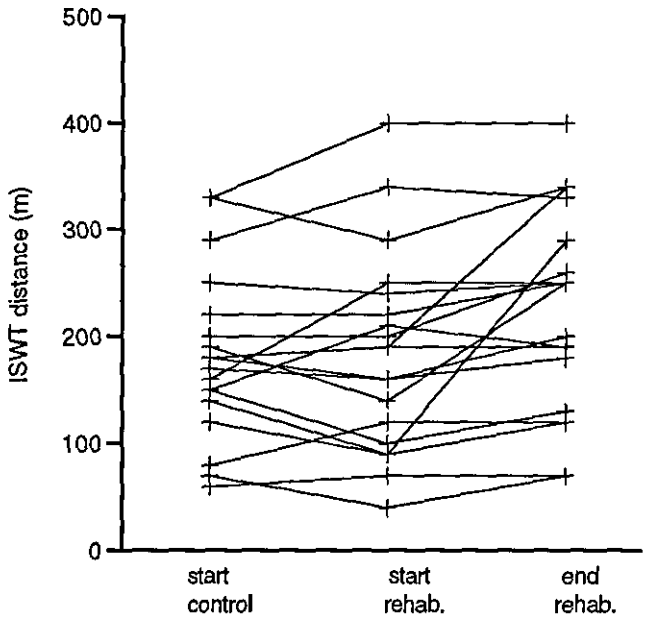


Figure 8.3b Individual incremental shuttle distance

Table 8.7 Mean differences between walking test performances

	Control visit 4 - 2	Rehabilitation visit 5 - 4	% change visit 5 - 4
ESWT time (s)	4.1 (9.9) -16.8 - 24.9	419 (70.7) 271 - 568	160 (26) 106 - 214
ESWT distance (m)	4.7 (8.1) -12.3 - 21.8	349 (62) 218 - 480	160 (26) 106 - 214
ISWT distance (m)	2.6 (9.7) -17.8 - 23.1	38.4 (13.1) 10.8 - 66.0	32.0 (12.4) 6.0 - 58.0

n=19

Mean (SE) and 95% confidence intervals for the differences between the start and end of the control period (visit 4 - 2), and the start and end of rehabilitation (visit 5 - 4).

fatigue, as the main reasons for exercise termination during the control period. Following rehabilitation breathlessness was identified less often and more patients identified tiredness as the main symptom following the ESWT. The test was terminated by the operator for 3 patients who completed 20 minutes of the test. The frequency of the different reasons for exercise termination are illustrated in figure 8.4. The main reason for termination of the ISWT was breathlessness. This remained unchanged following rehabilitation.

There were no significant changes in the peak heart rate response following both the ESWT and the ISWT during the control period, and following rehabilitation. The mean (SE) heart rate response at equivalent endurance times pre- and post-rehabilitation were 111 (4.0) and 111 (3.9) respectively. The heart rate data is summarised in table 8.5 and 8.6.

8.3.1 **Relationships between variables**

There was evidence that patient 10 was different from the rest of the group. The sudden death shortly after completing the course suggested there were additional, active medical problems, and these possibly acted to negate any effect of the rehabilitation. Therefore, it was considered reasonable to exclude the data set of this patient from an examination of the relationships between variables.

There was a significant relationship between the FEV_1 and the absolute increase in ESWT. The relationship was strongest for the baseline FEV_1 measured at the start of rehabilitation ($r=0.662$, $p=0.0028$) (figure 8.5). There was also a significant relationship between the FEV_1 and the ESWT post-rehabilitation ($r=0.685$, $p=0.006$) (figure 8.6). There was no relationship between the FEV_1 and the control (pre-rehabilitation) ESWT, or between the FEV_1 and the percentage increase in ESWT following rehabilitation. There was a significant, positive relationship between the pre-rehabilitation ESWT and the absolute increase in the ESWT post-rehabilitation ($r=0.570$, $p=0.014$) (figure 8.7).

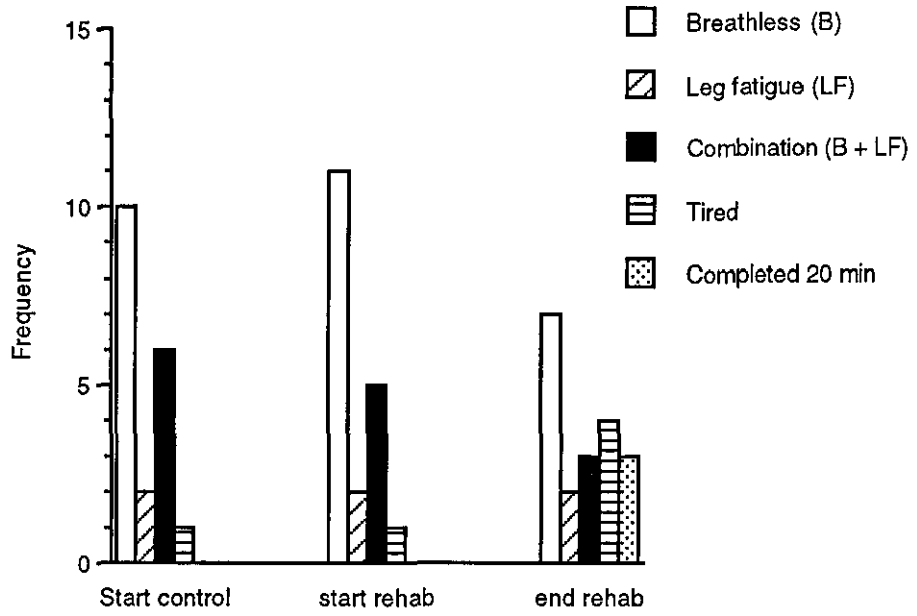


Figure 8.4 Frequency of occurance of symptoms at the termination of endurance exercise

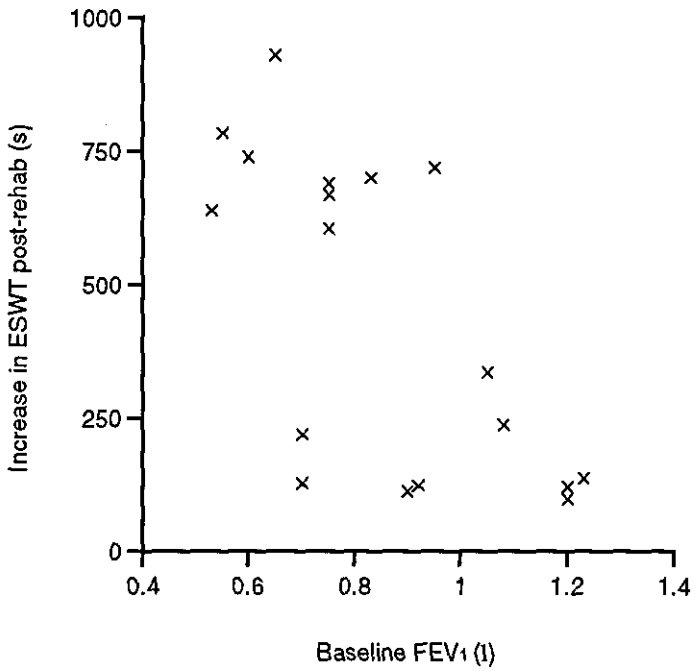


Figure 8.5 Relationship between the absolute increase in ESWT time and baseline FEV_1 (n=18)

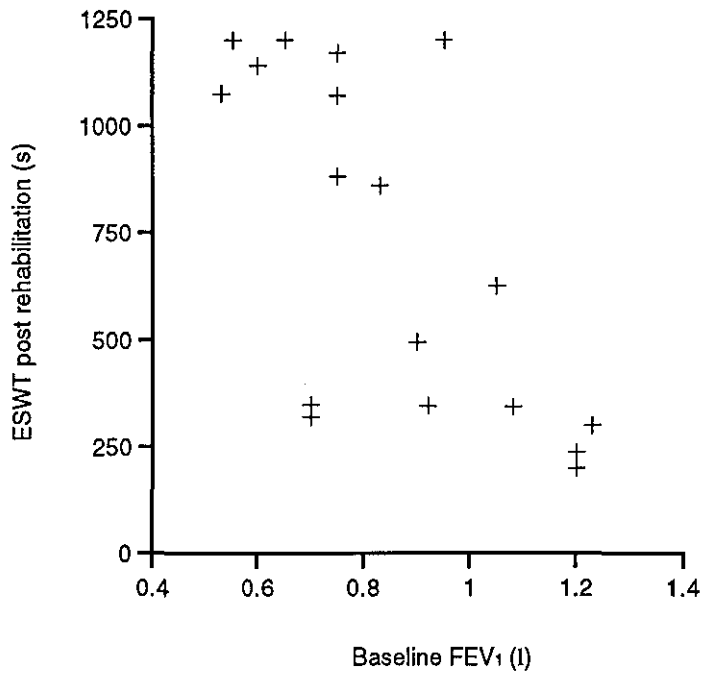


Figure 8.6 Relationship between post-rehabilitation ESWT time and baseline FEV_1 (n=18)

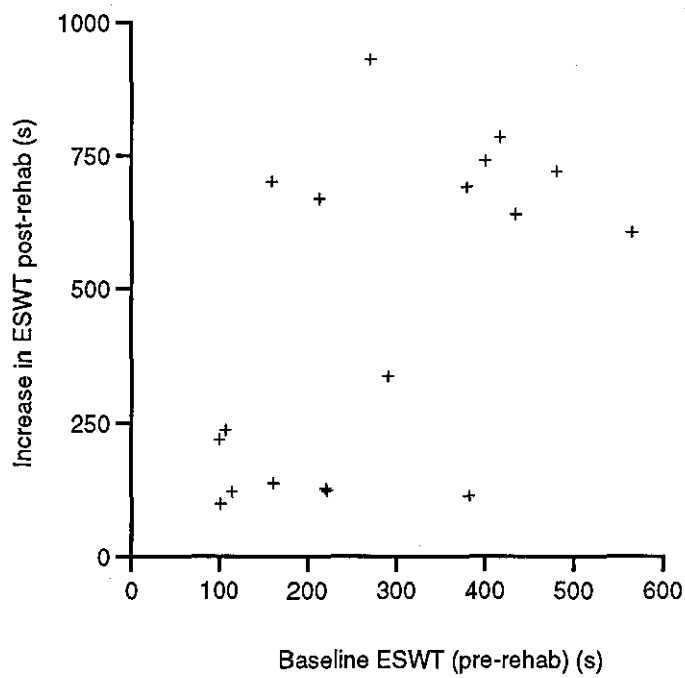


Figure 8.7 Relationship between pre-rehabilitation ESWT time and the absolute increase post-rehabilitation (n=18)

There was no relationship between the Borg breathlessness scores (actual score, and the change in score (Δ)) and the increase in ESWT post-rehabilitation (absolute and percentage increase). There was no relationship between the $\%SpO_2$ at peak incremental exercise (ISWT) and the post-rehabilitation ESWT, or with the increases in ESWT. There were no relationships between the fall (Δ) in $\%SpO_2$ and the post-rehabilitation ESWT.

8.3.2 **Repeatability of the ESWT**

A summary of the ESWT results for the 11 patients entered into the repeatability leg of the study is presented in table 8.8a. The 3 ESWT were completed within 15 days for all the patients. All patients showed an improvement in the ESWT performance after one test and 8 patients had an improvement after 2 tests. The was a strong relationship between tests 2 and 3, (r=0.995, figure 8.8). ANOVA revealed there were no significant differences between tests 2 and 3. The mean differences and 95% confidence intervals are shown in table 8.8b. The differences between tests 2 and 3 are illustrated in figure 8.9.

8.4 **DISCUSSION**

The key findings of this study were: the ESWT was sensitive to an intervention of pulmonary rehabilitation for patients with COPD; following one practice walk the test possessed good repeatability The magnitude of improvement in the ESWT following the intervention was far greater than the improvement in the ISWT. This supports previous studies which have demonstrated endurance capacity possesses greater sensitivity to change than maximum capacity in patients with COPD (Holle 1988, Niederman 1991, Singh 1996).

The current study incorporated a control period were there was no change in overall clinical management of the patients. During this period there was no significant change in functional capacity. Thus the patients acted as their own control. The study design may be criticised for not recruiting a separate

Table 8.8a Test- retest for the endurance shuttle walk (n=11)

Visit	1	2	3
FEV_1 (l)	0.75 (0.21)	0.79 (0.19)	0.82 (.24)
ESWT Time (s)	251 (120)	310 (171)	325 (158)
ESWT Distance (m)	214 (101)	262 (137)	274 (130)
HR_{peak} (beat.min^{-1})	108 (17)	107 (16)	103 (16)
BS	4.6 (2.0) [4.3]	4.4 (1.6) [4.1]	4.5 (1.7) [4.2]
RPE	12.7 (1.9) [12.6]	12.6 (2.1) [12.4]	12.9 (2.7) [12.7]

Mean (SD) for FEV_1, time, distance, HR_{peak}, Borg breathlessnes rating and perceived exertion for 3 ESWT repeated over an 15 day period.
[ ] indicates the median ratings for BS and PE.

Table 8.8b Differences in endurance time and distance between tests

TIME	Mean difference (SE)	95% CI
Test 2 vs 1 (s)	59.5 (22.4)*	9.7 - 109.2
Test 3 vs 1 (s)	74.3 (18.8)*	32.5 - 116.1
Test 3 vs 2 (s)	14.8 (6.3)	0.6 - 28.9
DISTANCE		
Test 2 vs 1 (m)	47.5 (18.4)*	6.6 - 18.4
Test 3 vs 1 (m)	60.3 (16.2)*	24.1 - 96.5
Test 3 vs 2 (m)	12.8 (4.9)	1.9 - 23.6

* $p < 0.05$

Mean differences (SE) and 95% confidence intervals between tests

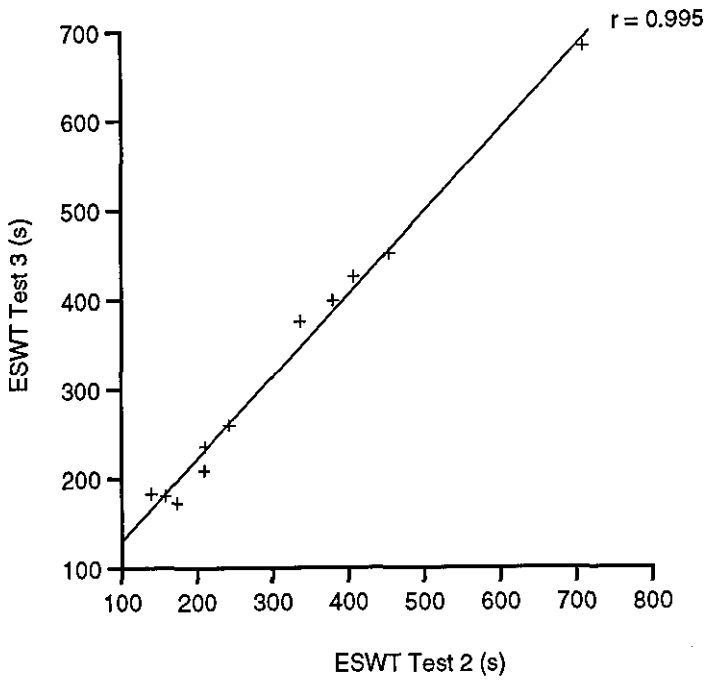


Figure 8.8 Relationship between the time walked during the ESWT tests 2 and 3.

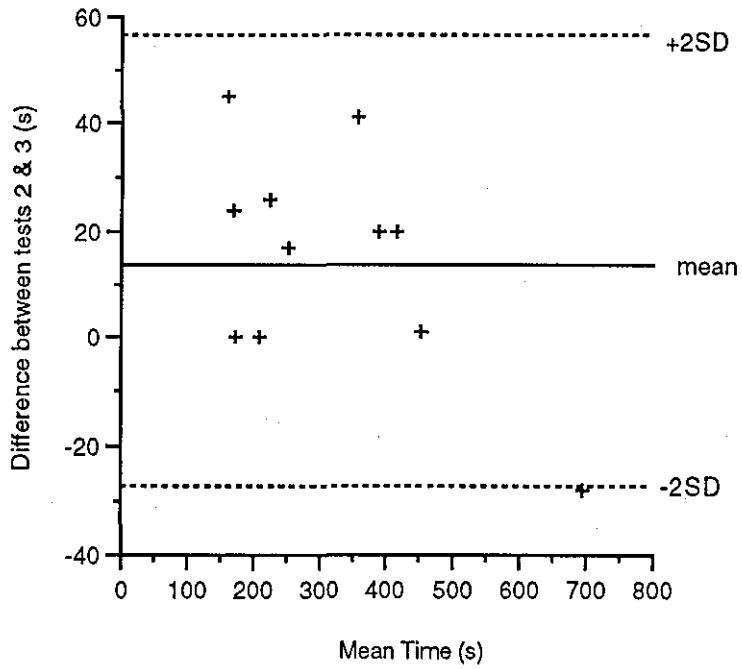


Figure 8.9 Differences in endurance time between tests 2 and 3 (n=11)

control group, and conducting a randomised, cross-over designed study. A number of rehabilitation studies with such a design have been reported (Cockcroft 1981, Weiner 1992, Wijkstra 1994), and have shown significantly greater improvement in exercise tolerance in the active groups.

One of the aims of the current study was to examine the short term repeatability of the ESWT. Use of the control period additionally provided the opportunity to examine the medium term stability of the ESWT. Although the control period was not tightly regulated, since its purpose was to act as a control for the intervention, the ESWT showed good repeatability over this timescale (mean duration 5 (1.5) weeks). The mean difference between tests at the start and end of the control period was 4 s, which contrasted favourably with the short term repeatability of 15 s. However, there was greater individual variability over the medium term, reflected in the wider confidence intervals (42 vs 28) and the wider limits of agreement for the range of differences between repeat tests (-82 to 90 seconds vs -27 to 57 seconds).

The short term repeatability demonstrated a positive improvement in ESWT with each successive performance of the test, and suggested a diminishing learning effect in the test performance. The third test improved the ESWT duration by an average of only 15 s, compared to an increase of 60 s following the first test. Thus the results suggested one practice walk was sufficient to establish good test repeatability. The greater variability in the medium term repeatability suggested the learning effect on test performance was lost after several weeks. The difficulties in conducting this study over a long period of time, in patients with severe, chronic respiratory disease, and during the winter months, have been highlighted by the incidence of disease exacerbations and the susceptibility to other ailments. If the situation encountered during the current study was a fair representation of patients with severe impairment, it may be argued the unregulated control period was reasonable for the examination of the medium term test repeatability in this patient group. However, further examination of the stability of the test over

longer periods may be warranted. The purpose of the control period was to examine functional capacity over a similar time span to the rehabilitation intervention. However the control period was shorter than the average length of time spent at rehabilitation (5 vs 7 weeks). The failure to adhere to similar time periods was the result of the difficulties experienced with patient illness, recruitment and retention.

The main exercise training component of the rehabilitation programme comprised of a home walking programme. The target for each patient was to increase continuous walking at a pace which related to approximately 50% of the $\dot{V}O_{2peak,}$ predicted from the ISWT. Both Jones (1988) and Casaburi (1993) state it is important to assess the effects of exercise training utilising a similar mode of exercise. This argument supports the ESWT as an appropriate testing mode for the current rehabilitation programme. The intensity of the ESWT (85% of the predicted $\dot{V}O_{2peak}$) was in excess of the intensity of the training prescription. However, the majority of patients achieved large improvements in endurance capacity at this higher intensity. This finding raises two important issues: firstly a low intensity training programme improves overall endurance capacity in this patient group; secondly, would re-calibration of the training intensity result in additional improvements ?

A number of studies have demonstrated benefits from high intensity exercise training in both mildly affected patients (Casaburi 1991) and patients with more severe impairment (Ries 1987, Carter 1988, Punzal 1991, O'Donnell 1995). Recently Maltais (1997) has demonstrated most patients do not achieve higher levels of exercise training. The study assessed training intensity accurately over a 12 week period, in patients with severe impairment (n=42, FEV_1 38% of predicted). The patients were prescribed high intensity training, with 30 minutes at 80% of the maximal cycle work rate as the target intensity. Few patients achieved this level, and though the training intensity gradually increased, at the end of the programme the mean intensity achieved was 60% of the W_{max}, some 20% lower than the

prescribed level. However, there were significant improvements in exercise tolerance and evidence of a physiological adaptation to training (increased $\dot{V}O_{2peak}$ and reductions in $\dot{V}_E$ and lactic acid concentration for a given work rate). The study from Maltais (1997), the current study and others (Niederman 1991, Clark 1996), would suggest useful improvements can be achieved with more moderate training intensities, and lower intensity training is successful in patients with moderate to severe COPD.

A number of reports suggest gradually increasing the training intensity (Belman 1986, Ries 1990). Whether further gains would be made by re-calibrating the training intensity in the current rehabilitation programme may warrant further investigation. Although the prescribed exercise intensity was at 50% of the predicted $\dot{V}O_{2peak}$, regular checks on walking speed were not undertaken. However the duration of walking was monitored closely with new targets for continuous walking set weekly. The results reported in chapter 7 suggested slow to moderate walking constituted a high percentage of the $\dot{V}O_{2peak}$ in this patient group, where $\dot{V}O_{2peak}$ is often severely reduced. As patients improved during the programme walking speed may have increased insidiously, though this cannot be confirmed. Informal, qualitative assessment by observation suggested the training pace adopted by patients was less than the intensity of the ESWT pace at which they were assessed. Additionally, all the patients confirmed the ESWT pace was faster than they would normally walk. The incorporation of increasingly higher intensities of exercise into the programme may be disadvantageous where it brings discomfort by way of extreme breathlessness, and the possibility of muscle and joint pain, and even injury. In such situations compliance with the training programme may be reduced.

The improvements in the ESWT demonstrated the changes in endurance capacity were not confined to the training level of exercise intensity. This pattern of response was demonstrated in a study which compared training above and below the lactate threshold in a group of healthy, elderly subjects. A constant-paced high intensity treadmill test (>75% $\dot{V}O_{2peak}$) was used to

assess both low (53% of $\dot{V}O_{2peak}$) and high intensity training (82% of $\dot{V}O_{2peak}$) (Belman 1991b). Both programmes produced similar changes, with significant reductions in HR, $\dot{V}_E$ and $\dot{V}CO_2$ during the treadmill assessment. The author suggested low intensity walking was an adequate aerobic stimulus for producing modest gains in aerobic power, in previously sedentary, elderly subjects. In the current study there was a significant improvement in the ISWT which suggested an increase in the maximal capacity and $\dot{V}O_{2peak}$ for some patients. However, there were substantially greater gains in the submaximal exercise performance, despite assessment at the higher intensity. Thus the training was more effective at improving overall endurance capacity in this patient group, where the pathophysiology of COPD is likely to limit improvements in the maximal capacity.

Following rehabilitation, three of the patients attained the 20 minute limit of the endurance test, and 4 patients achieved more than 17 minutes. Only 3 of these patients had significant improvements in the post-rehabilitation ISWT. This finding reinforces the arguments for a limit to the improvements which may be gained in maximal capacity, and for the sensitivity of endurance capacity to training. Whether post-training assessments should be conducted at pre-training intensities is an important question, and forms a natural adjunct of further research to the current study. In the case of patients achieving the 20 minute limit, simply re-assessing at the next endurance walking speed on the ESWT tape requires further investigation.

The mechanisms which contribute to endurance capacity in this patient group have been discussed in some detail in the previous chapter. However it is worthwhile considering the possible mechanisms of improvement following pulmonary rehabilitation. A number of factors are likely to contribute to the improvement in exercise tolerance and several workers have suggested one or a combination of the following: improved aerobic capacity and muscle strength, mechanical efficiency and enhanced skeletal muscle enzyme activity; increased motivation and confidence; desensitisation to the sensation of breathlessness; improved ventilatory

muscle function; improved co-ordination and technique of performance; reduced ventilatory requirement; improved tolerance to the physical and sensory requirements of exercise; (Holle 1988, Casaburi 1995, Belman 1993, O'Donnell 1995, Maltais 1997).

The results from the current study support a hypothesis of desensitisation and/or reduced breathlessness, and improved subjective tolerance of exercise, as important components of the training-induced improvements. There were significant improvements in the Borg ratings for breathlessness and perceived exertion following the assessment of endurance and maximal capacity. The majority of patients achieved substantial improvements in walking duration with similar, or reduced, ratings of breathlessness and perceived exertion, compared to the pre-training levels. This was substantiated further by the change in the reasons for the termination of endurance exercise. The symptom of breathlessness was identified less often following rehabilitation, whilst there was an increase in 'tiredness' reported from those patients who were walking for much longer periods of time.

The results from the current study cannot differentiate whether there was desensitisation to breathlessness, or a genuine reduction in breathlessness, as a result of a lower ventilatory requirement and improved respiratory muscle performance. A simple, qualitative assessment by observation, revealed signs of breathlessness were reduced during, and following, the test for some patients. Whilst for others, there appeared to be less breathlessness during the test, whereas the end-test levels appeared to be similar to pre-training levels. These observations would suggest the mechanism may vary amongst patients, and in some cases there may be a combination of desensitisation and a reduced ventilatory requirement.

A possible mechanism of a reduced ventilatory requirement was described by Casaburi (1995), following a study which identified a reduced blood lactate concentration during exercise, as a result of high intensity training in

patients with mild to moderate COPD. The consequence of a reduced lactate concentration is a lower H^+ ion load, leading to a reduced ventilatory requirement for the maintenance of pH. Recently, some evidence has emerged of a similar mechanism of improvement in patients with severe impairment. In a study involving 11 patients with severe COPD (mean FEV_1 36% of predicted), post-training skeletal muscle biopsy samples revealed increased activity in two oxidative enzymes and reduced blood lactate concentration during exercise (Maltais 1996b). These changes were accompanied by improvements in $\dot{V}O_{2peak}$ and peak cycle work rate, and reduced ventilatory and heart rate response at equivalent pre-training work rates. The training schedule consisted of high intensity cycle exercise, upper extremity exercises and self-paced walking.

The evidence of metabolic improvements in the study from Maltais (1996b) contrasts the findings of Belman (1981). In a group of 15 patients with severe COPD, Belman (1981) found no changes post-training in muscle enzyme activity, despite increases in endurance capacity. Additionally, there was no evidence of a cardiovascular training response. There was no data concerning the blood lactate concentrations in the study. The training intensity was lower in the study from Belman (1981), and Maltais (1996b) cites large inter-individual variability in the skeletal muscle adaptation to training. The variability in the blood lactate response in patients with severe COPD has been discussed in previous chapters, and is supported by data presented in this thesis. Thus, the available evidence concerning a reduction in the ventilatory requirement, as a result of blood lactate changes in severe impairment, is scarce, and does not explain adequately the changes in breathlessness and improved exercise tolerance for all patients with severe COPD.

An improved mechanical efficiency has been proposed by O'Donnell (1995), and by Holle (1988), as the mechanism of improvement following rehabilitation. In a study which incorporated a non-intervention control group, O'Donnell (1995) utilised a 6 week training programme in 30 patients

(FEV_1 42% of predicted), and related the relief of breathlessness to a fall in the ventilatory demand, as a result of enhanced mechanical efficiency (reduced $\dot{V}O_2$/work rate and $\dot{V}CO_2$/work rate slopes). Additionally, significant improvements in resting inspiratory capacity suggested a decrease in EELV, and therefore a possibility of improved inspiratory muscle function as a result of decreased elastic loading. Holle (1988) measured improved peak work rates and endurance capacity in 44 patients with severe COPD. The author proposed an enhanced mechanical efficiency as the mechanism of improvement, rather than an improved aerobic capacity, or a cardiovascular training effect, since there was no change in the HR_{max} or $\dot{V}_{Epeak}$, and only a small improvement in $\dot{V}O_{2peak}$. In the current study a change in HR pre- and post-training was not observed which suggests the absence of a cardiac training effect. However the large improvements in endurance capacity, and lowered sense of perceived exertion, would support a hypothesis of enhanced mechanical efficiency.

Further evidence of an enhanced mechanical efficiency was suggested by the variable changes in the maximal capacity. Overall there was a 32% improvement in the ISWT, which suggested there was an increase in the aerobic capacity post-training for some patients. However, without direct measurement of the $\dot{V}O_{2peak}$ this cannot be confirmed. Additionally some patients did not show an improvement in the ISWT. These findings would suggest changes in the maximal aerobic capacity were only one possible contributing factor to the improvements in some patients. Improved skill of performance and co-ordination will lead to improved efficiency and have a sparing effect on oxygen consumption. Such a mechanism would suggest more efficient use of existing capacity, and may partly explain why many of the patients in the current study showed increased endurance capacity without concurrent improvement in the maximal capacity. Belman (1993) states improved skill of performance has been found in a number of studies and cites a study from Paez (1967), which demonstrated treadmill walking improved with repeated attempts. Casaburi (1995) has suggested improved efficiency in the breathing pattern in severe COPD, with the adoption of a

slower and deeper respiratory pattern following training. This strategy would have a deflationary effect on the lungs, and lead to O_2 sparing.

An improvement in the skill of walking (and therefore mechanical efficiency) was suggested by the changes in the short and long term repeatability of the ESWT. As discussed previously there was an indication of a learning effect when the ESWT was repeated over a short period of term. However this was lost over the longer, non-intervention period. If this effect transfers to walking in general, a training effect in the skill of walking may have occurred during the rehabilitation period.

There was only one patient who did not demonstrate an improvement in endurance capacity (patient 10) following the rehabilitation. A fall in the ESWT was recorded at the end of the rehabilitation period (Δ 37 s). As indicated in the results section, the patient died within a few weeks of completing the course. Details of the sudden death indicate there was no evidence of a chest infection or deterioration in respiratory (emphysema) problems. The circumstances of the death were unusual for patients with uncomplicated emphysema and suggested other, unidentified clinical problems. The clinical notes indicated there were no other significant health problems. The lack of improvement from the rehabilitation contrasted with the other participants in the study, therefore a repeat test was performed to eliminate the possibility of a erroneous result. The difference between repeat tests was only 4 seconds, thus confirming the absence of an improvement. The lack of improvement suggests other, covert clinical problems e.g. cardiac disease, which may have acted to negate any therapeutic effects. If the ESWT is able to identify those patients who fail to improve following rehabilitation it might be used to indicate additional investigations, such as cardiac screening. There were consistent improvements in endurance capacity for the other participants, whilst the ESWT was sensitive to the lack of improvement, and also detected a slight deterioration in endurance capacity in patient 10. This finding contrasts with the situation for the ISWT, where there was a variety of responses post-rehabilitation, and therefore the

absence of a change in the ISWT would be unlikely to signal additional problems.

The influence of the disease severity (FEV_1) on the response to the rehabilitation is revealed in figures 8.5 and 8.6. Patients with the lower values of FEV_1 tended to gain the most benefit from the exercise training and had the greatest absolute change in endurance capacity (fig 8.5). The relationship between FEV_1 and endurance capacity changed following the pulmonary rehabilitation. Prior to rehabilitation there was no relationship between FEV_1 and endurance capacity. Following rehabilitation there was a moderate (negative) and significant relationship between the two variables ($r=0.685$, $p<0.01$, figure 8.6). This relationship demonstrates patients with more severe airways disease (lower FEV_1) achieve greater levels of endurance, post rehabilitation, than patients with slightly less severe airways obstruction.

The changes in endurance capacity and the relationship with disease severity raises a number of issues for clinical practice: how can the patients who are likely to be most responsive to rehabilitation be identified, when is the best time to introduce rehabilitation, and what is the most effective mode of management for those patients who are less responsive? The lack of a relationship between FEV_1 and the baseline (pre-rehabilitation) endurance capacity, emphases FEV_1 as a poor indicator of functional capacity prior to exercise training. Additionally, there was a wide range in the absolute change in ESWT, some patients had a small absolute change in endurance capacity, however this represented a large percentage improvement. Finally, patients with a higher baseline endurance capacity tended to achieve the greatest absolute increase post training (figure 8.7), however this did not necessarily represent the greatest percentage improvement in all patients.

In summary the ESWT was sensitive to an intervention of rehabilitation, which included both educational and exercise training components. The test

possessed good short and medium term repeatability. It was easy to administer for both the operator and patients. All the patients remained unaware of the 20 minute limit to the test, including those who were stopped by the operator during the post-rehabilitation assessment. Endurance times were only revealed to patients at the end of the study. There was evidence the test may identify additional, covert clinical problems which might act to override any therapeutic benefits of rehabilitation. The issue of re-calibrating the test intensity for patients who achieve the maximum 20 minute limit was not addressed, and this might form a natural extension to future evaluations of the test. In addition, the long term stability of the test is worthy of further consideration.

Chapter 9

GENERAL DISCUSSION

The studies presented in this thesis were designed to examine two relatively unexplored aspects of the exercise response in patients with COPD, namely respiratory muscle performance and whole body endurance capacity. Exercise, and the exertion required to perform routine daily activities, becomes increasingly limited as a result of the extent and severity of the pathophysiological changes associated with COPD. Breathlessness, especially on exercise, is the major symptom whilst regular chest infections and cardio-vascular complications increase in prevalence during the later stages of the disease. The predominant pathological changes associated with COPD are increased resistance to airflow and hyperinflation of the lungs, with symptoms of cough and sputum production. RV and FRC are typically elevated and may occupy as much as 70 - 85% of the TLC. Such hyperinflation causes the inspiratory muscles, especially the diaphragm, to be shortened before they contract, and thus operate at a distinct mechanical disadvantage (Rochester 1991). The total work, and energy cost of breathing in COPD is greatly elevated as a result of the increased resistive and threshold loads, and the requirement to maintain normal levels of $PaCO_2$ in the face of gas exchange and perfusion abnormalities (Rochester 1991).

The response of the respiratory muscles to the increased ventilatory demands of physical exertion will constitute an important component of the whole body exercise response in COPD. The participants in the series of studies presented in this thesis had moderate to severe COPD, with reduced exercise tolerance, and reported breathlessness to a wide range of daily activities. Although the $\dot{V}O_{2peak}$ was not measured directly in all the patients, the direct and indirect measurements indicated most had a reduced $\dot{V}O_{2peak}$ of less than 1.5 $l.min^{-1}$. In healthy individuals the oxygen cost of increasing ventilation is unlikely to constitute a limiting factor to exercise, however a number of workers propose it may be an important factor in COPD (Levison 1968, Rochester 1979, Bye 1983).

In the first experimental study incremental threshold loading was evaluated as a simple indicator of performance for the respiratory muscles. The imposition of the incremental threshold load, from the electronic solenoid valve, was likened to the increases in PEEPi which result from increased dynamic hyperinflation during exercise in patients with COPD (Pride 1995). The cardio-respiratory and metabolic demands of the ITL were measured and related to the whole body exercise performance. The O_2 cost of the exercise was 367 ml.min^{-1}, and this equated to 30% of the $\dot{V}O_{2peak}$ measured during peak treadmill exercise. If ITL reflects the magnitude of energy expenditure required to increase ventilation during whole body exercise, this high energy cost of the respiratory musculature would form a substantial drain from the total oxygen available for the non-respiratory exercising muscles. In one of the first published studies which evaluated the oxygen cost of increasing ventilation during exercise in COPD, Levison and Cherniack (1968) measured a high cost of ventilation during steady state exercise in COPD. These workers found the respiratory musculature was responsible for an oxygen consumption of 35 - 40% of the total, even at low levels of exercise, therefore only 60 - 65% was available for the exercising non-respiratory muscles. In comparison, the same experiment with healthy individuals revealed an oxygen cost of exercise ventilation of 10 - 15% of the total available oxygen.

There was no relationship between the absolute values of $\dot{V}O_2$ measured during ITL and the VO_2 measured during the treadmill exercise. However there was a significant relationship between ITL $\dot{V}O_{2peak}$, as a proportion of the absolute value of the treadmill $\dot{V}O_{2peak}$. Figure 5.3 illustrated those patients with the lowest whole body $\dot{V}O_{2peak}$ used a large proportion of the total $\dot{V}O_2$ available to perform the ITL exercise. The figure revealed patients with a whole body $\dot{V}O_{2peak}$ < 1.5 l.min^{-1} utilised > 20% of their available $\dot{V}O_2$ to perform the ITL test, and those patients with a $\dot{V}O_{2peak}$ of ≤1.0 l.min^{-1} utilised ≥30%.

If the O_2 utilisation during the ITL test was a reasonable reflection of the O_2 cost of ventilation during whole body exercise it is likely the most severely affected patients, with substantially reduced exercise capacities, incur a large oxygen debt during exercise, as a result of the reduced oxygen availability. However, there was inconclusive evidence of blood lactate accumulation following the ITL test, and low concentrations following whole body exercise. Figure 4.8 revealed a strong relationship between peak Pm and the blood lactate concentrations suggesting ITL was a sufficient challenge to induce a blood lactate response. Further investigations of the effect of respiratory muscle lactate production, and its importance in the response to whole body exercise in COPD, was suggested in chapter 4, and especially in patients with severe exercise limitation. This proposition was supported by figure 5.4 which revealed those patients with the lowest whole body exercise blood lactate response had the highest proportional concentrations following ITL. Any future studies would benefit from serial blood lactate measurements throughout the ITL test, since there was evidence of a sample time effect, and the possibility of rapid clearance of the metabolite. Thus the initial study, which examined the performance and the metabolic effects, identified ITL as a useful method for inducing a blood lactate response, and the technique benefits from the use of standardised increments in respiratory muscle work rate.

To investigate further the clinical relevance and application of ITL, the test was examined following a single dose of inhaled ipratropium bromide, and was also related to the whole body exercise response. The oxygen cost of the task did not change significantly following the bronchodilator and it continued to constitute a similar proportion of the total $\dot{V}O_2$. This finding would suggest any bronchodilator induced deflationary effects in the lung did not lead to measurable improvements in respiratory muscle efficiency. Measurement following a period of bronchodilator pre-treatment, as opposed to a single dose, may have had a greater effect, and this is a valid criticism of the study. However the majority of patients were already using

regular inhaled bronchodilators, and thus benefiting from maintenance inhalation therapy.

The lack of improvement in respiratory muscle efficiency following the bronchodilator therapy suggested additional interventions to improve respiratory muscle performance, especially during exercise, may be of benefit to patients with a reduced exercise capacity. This is an outstanding issue, and the use of ITL following an intervention of whole body exercise training, or respiratory muscle training was not pursued. There was wide variability in the cardio-respiratory response during ITL, which would make the application of these measurements less reliable for serial assessment. However ITL, as a measure of respiratory muscle performance, was reproducible and simple for the patients and operator, and therefore a useful instrument for the evaluation for respiratory muscle performance.

In the time since the ITL study was performed data concerning the reliability of a small and inexpensive threshold training device, which patients could use at home, has been published (Gosselink 1996a, Johnson 1996). However definitive evidence of the beneficial effects of respiratory muscle training in patients with COPD remains elusive. In a meta-analysis performed on 17 randomised, controlled trials of inspiratory muscle training there was little evidence of a clinically important benefit or improvements in functional capacity in patients with COPD (Smith 1992). The meta-analysis only considered respiratory muscle training in isolation. A number of studies have examined the effect of combined inspiratory and general exercise training (Weiner 1992, Wanke 1994), and demonstrated greater improvements in those patients who received the combined training.

In an editorial, Gosselink (1994) suggested the strongest indication for inspiratory muscle training lies in its combination with general exercise training. However further conflicting evidence has recently emerged. In a randomised controlled trial, Berry (1996) did not find additional improvements in functional capacity when patients received combined

training compared to a general training only group. Alternatively, in an examination of the effects of inspiratory muscle training alone, Lisboa (1997) found significant improvements in the 6 minute walk test and improved efficiency during cycle exercise, with reductions in the ventilatory and oxygen cost of equivalent pre-training work rates. The study incorporated a control group using a 15% training load. The author concluded a 30% inspiratory muscle training load was able to produce significant transfer effects to whole body functional capacity.

There is evidence of generalised muscle weakness, and deconditioning, as significant limiting factors of exercise in COPD, additional to the ventilatory limit. This proposal is supported by the findings from the second experimental study, where improvements in exercise ventilation, following the bronchodilator, were not accompanied by significant improvements in peak exercise work rates (ITL, treadmill or shuttle test). Thus improving the ventilatory capacity in isolation did not improve exercise capacity. Additional to this finding was the improvement in the relationships between respiratory muscle performance (peak Pm), exercise ventilation and gas exchange, following the bronchodilator. This suggested an improved coupling between the mechanical events of respiratory muscle performance, and the resultant exercise ventilation and gas exchange. The two aforementioned factors, in addition to the lack of improvement in respiratory muscle efficiency following the bronchodilator, and the high oxygen cost of the ITL test (suggestive of a high cost of exercise ventilation), led to a proposal for the introduction of exercise training in order to maximise the bronchodilator changes, and address the issue of deconditioning.

In order to progress the investigation into the effects of deconditioning and exercise training in this patient group, there were strong arguments for the development of a new instrument for the assessment of endurance capacity. This took the form of a standardised constant-paced field test based on the concept of the incremental shuttle walk test. The new test, the ESWT was complementary to the ISWT, the intensity of the endurance test was related

to the maximal performance assessed from the ISWT, and utilised the same 10 metre shuttle course. Initially three endurance intensities were examined which related to 75%, 85% and 95% of the predicted $\dot{V}O_{2peak}$. These high intensities were chosen for two reasons: firstly a number of studies had demonstrated patients with COPD were able to tolerate near maximal work intensities and had gained significant improvements following high intensity training programmes; secondly, it was necessary to develop a test which avoided lengthy testing periods since the test needed to be practical for the clinical situation, and not to onerous for the patient.

The exercise intensities chosen for the ESWT were related to percentages of the $\dot{V}O_{2peak}$ predicted from the ISWT. This was different from previous studies which have related submaximal exercise testing and training intensities to percentages of the maximal work rate achieved at initial testing (Ries 1987, Carter 1988, Punzal 1991). To date there is no consensus on the optimal exercise testing or training strategy for this patient group. In many reports the training programme is described in general terms and there is little indication of regular physiological monitoring. Examination of the cardio-respiratory response to endurance exercise on the treadmill, and described in chapter 7, revealed a wide range of responses in $\dot{V}O_2$, with few patients achieving a steady state, whilst many patients exceeded the target $\dot{V}O_2$. The lowest intensity examined, the 75% test, provoked a mean level of $\dot{V}O_2$ which related to 84% of the $\dot{V}O_{2peak}$. The energy expenditure for walking speeds of 2 mph has been estimated at < 1 $l.min^{-1}$ (Åstrand 1986), and this was close to the maximum $\dot{V}O_2$ available in this patient group. Thus for patients at the severe end of the COPD spectrum, low absolute levels of exercise were found to engage a high percentage of the maximum available $\dot{V}O_2$.

Many routine activities of daily living are likely to be associated with levels of energy expenditure similar to slow and moderate walking. In many cases patients avoid the most demanding tasks, proceed at a slower pace, or take frequent rests. However the studies presented in this thesis support the

contention that patients can tolerate exercise at a high level of $\dot{V}O_2$. Since untrained, healthy individuals would rarely sustain exercise at a similar intensity, the question of how patients achieve exercise at such a high relative intensity deserves consideration. The pathological changes associated with COPD are long term, and in many cases the decline in maximal capacity and functional capability occurs over a number of years. It is likely patients adapt to the loss of functional capacity in a continuous manner, and learn to tolerate high levels of breathlessness. Additional to this process is the loss of fitness, which further compounds the problem of breathlessness and exercise intolerance. It is at this point where an intervention of exercise training is likely to benefit.

In a recently published study, the exercise training intensities patients actually achieved during pulmonary rehabilitation were examined closely during a 12 week programme (Maltais 1997). Although patients were prescribed a target training intensity of 80% of their maximal work rate, few patients achieved this level and the mean intensity at the end of the 12 weeks, was 60% of the initial maximal work rate. Despite achieving a lower training intensity (60%) than the prescribed level (80%), the patients demonstrated significant improvements in $\dot{V}O_{2peak}$ and maximum work rate, and reductions in ventilation and blood lactate concentrations at equivalent pre-training work rates. The authors concluded the changes constituted a physiological adaptation to training, and most patients with severe COPD were unable to achieve higher intensity training targets. However, the $\dot{V}O_2$ was not measured during the training sessions in the study from Maltais (1997), and the findings described in chapter 7 demonstrated exercise intensities of 75% will engage a high proportion of the maximum available $\dot{V}O_2$. It is likely the 60% work rate training intensity achieved in the study from Maltais (1997) engaged high proportions of the $\dot{V}O_{2peak}$ in most of the patients.

In an earlier study Maltais (1996b) examined muscle biopsy material pre- and post-exercise training from 11 patients with severe COPD. There was a

significant increase in the activity of two oxidative enzymes and reductions in the blood lactic acid concentration. The training intensity achieved with these patients was 69% of the target work rate, and in this study, the original training intensity was related to $\dot{V}O_{2peak}$. Interestingly, the use of dyspnoea ratings for prescribing and regulating the intensity of exercise training in patients with COPD has been examined recently (Horowitz 1996). The study aimed to determine if patients were able to reproduce intensities of exercise, based on target levels of oxygen consumption, using dyspnoea ratings obtained from a previous exercise test. The study found patients were more successful at reproducing higher intensities of exercise (80% of $\dot{V}O_{2peak}$) than lower intensities (50% of $\dot{V}O_{2peak}$).

The findings from the aforementioned studies, and from the studies presented in this thesis raise a number of issues: significant improvements in exercise capacity have been measured following training at a variety of intensities. The ideal training level, and how this is determined, has yet to be elucidated. There may be a minimum intensity below which physiological adaptation in terms of skeletal muscle changes, lactic acid production and cardiac conditioning does not occur. However, the relative importance of such changes to the improvements in the exercise response for this patient group, with moderate to severe COPD, are unclear. Belman (1993) notes a large number of rehabilitation studies have employed an 'unstructured' approach to training and, despite many not documenting reductions in the blood lactate levels, have shown severely obstructed patients can be exercised safely, and show impressive gains in submaximal exercise endurance. There is a wide range of potential mechanisms of improvement, involving physiological, sensory and psychological factors, whilst the importance of each component is unresolved, and probably varies between patients.

The standardised field test for the assessment of endurance capacity was developed for two reasons: firstly many studies have demonstrated large improvements in endurance capacity following rehabilitation suggesting it is

more sensitive to change than the maximal capacity; secondly, the lack of standardisation of the 6 minute walk test renders the test difficult to regulate, and the imposition of a set time questions the validity of the test as a true test of endurance. The ESWT had standardised, externally regulated walking speeds and a clearly defined end-point. The intensity of the test was individualised and based on prior measurement of maximal capacity, evaluated during the similar incremental shuttle field test. Each patient experienced the same relative level of exertion i.e. 85% of the predicted $\dot{V}O_{2peak}$. The standardisation of intensity will act to improve inter-subject and intra-subject comparisons. There was a time limit to the ESWT test. However this was not revealed to any of the patients in the studies, and patients were instructed to keep walking for as long as possible until they felt too tired or too breathless to continue. In this respect the test was open ended and avoided setting external targets. In addition, most patients seemed to concentrate on maintaining the correct walking speed and few queried the time, thus suggesting there was little emphasis on any internal targets patients may have set themselves.

The substantial changes in the ESWT following the intervention of pulmonary rehabilitation suggests endurance capacity is particularly sensitive to improvement, and amplifies any training induced improvements. It also supports the use of the test as a worthwhile assessment tool and outcome measure for this patient group. Whether the exercise training component was singularly responsible for the improvements in endurance capacity, or the rehabilitation intervention as a whole, cannot be confirmed. The effects of presenting the educational component alone compared to a combined programme of education and exercise training have been examined (Toshima 1990, Ries 1995). Both studies demonstrated significant improvements in endurance capacity (time of treadmill walking) in the comprehensive rehabilitation groups, whilst there were non-significant changes in the education only group. In a meta-analysis of 14 randomised, controlled trials of a rehabilitation intervention there were significant improvements in dyspnoea and mastery, and maximal exercise capacity

(Lacasse 1996). Improvements in functional capacity, defined as changes in the 6 minute walk distance, were non-significant. The 14 trials analysed included lower limb exercise in the rehabilitation programme, whilst 5 trials included an additional educational component. The analysis found a strong degree of homogeneity amongst the results, which suggested all the programmes had produced significant improvements in mastery and dyspnoea, despite the differences in content and duration. The authors concluded pulmonary rehabilitation should include at least 4 weeks exercise training as part of the management for patients with COPD.

Since walking is central to many every day activities and normal functioning, improving the skill and duration of its performance, irrespective of the mechanisms which bring about the improvement would seem to be a valid outcome of the intervention. The magnitude of change in walking endurance, perceived by the patient as important, was not evaluated in the current studies. In the meta-analysis from Lacasse (1996) the size of the improvement in the 6 MWT was not significantly different from the minimally clinically important difference, defined as the smallest difference perceived as important by the average patient. Although the ESWT was examined for statistical repeatability, and this was good in both the short (2 weeks) and medium term (5 weeks), differences were not compared to subjective ratings of walking ability. This aspect of the test may warrant further investigation to gain a wider description of the application and clinical usefulness of the test. However the simple statistical repeatability revealed 95% confidence intervals of 0.6 to 29 s for short term repeatability, and -17 to 25 s for medium term repeatability, following one practice walk.

The changes in endurance capacity were positive, and large (minimum percentage improvement was +30%), for the majority of patients. Although it would be unwise to draw conclusions from the evidence of one patient, the lack of improvement in patient 10, and the subsequent events, suggested the test may be useful in the identification of deterioration, or for highlighting the presence of additional clinical problems, and which may require further

treatment. In a study of the effects of pulmonary rehabilitation in an outpatient community referred group of 68 patients with moderate to severe respiratory disease, 20% were found to have previously unsuspected cardiac disease at initial assessment (Holle 1988). Following cardiological evaluation 6 of the patients were placed on new medications and completed the rehabilitation, whilst 9 patients had significant arrhythmias and were closely observed throughout the programme. The patients in the current study were all referred from the Hospital respiratory clinics. However, the findings from the present study would indicate a small number of patients may have covert medical problems, and this additional aspect warrants further research.

In summary, the studies reported in this thesis have examined two aspects of the exercise performance in patients with COPD. Incremental threshold loading was found to be a repeatable indicator of respiratory muscle performance, and was significantly related to peak exercise ventilation. This association contrasted with the lack of a relationship between the static measure of respiratory muscle function, PI_{max}, and exercise ventilation. These findings would support a hypothesis in which dynamic measures of respiratory muscle performance were more closely associated with indices of whole body exercise performance than static measures of respiratory muscle function in severe COPD. The test appeared to be as efficient as other methods of respiratory muscle exercise at eliciting an increase in the blood lactate concentration, and additionally benefits from the use of standardised increments in work rate. The test performance did not improve following to an intervention of inhaled bronchodilator, though there were significant increases in the ventilatory response. The test was easy to perform and repeatable without the requirement of external breathing regulation. The variability in the measurement of the oxygen consumption during the test suggested the strategies adopted by patients to overcome the additional threshold load were varied, whilst the external work performed remained consistent.

The progress of the experimental work led to the examination of whole body endurance capacity in COPD and the development of a standardised field test of assessment. A range of exercise intensities were examined. The most practicable intensity for the field test related to 85% of the predicted $\dot{V}O_{2peak}$. At this intensity the ESWT was simple to perform, was not too onerous for the patient, and possessed a suitable margin for improvement. The heart rate response and Borg ratings following the field tests were not significantly different from those measured during equivalent treadmill testing. There was a wide variability in the pattern of the $\dot{V}O_2$ response to the treadmill endurance tests, whilst the cardio-respiratory responses to the 95% endurance test were not significantly different to incremental testing. In some patients, the heart rate and $\dot{V}O_2$ measured during the endurance tests were greater than the incremental values, suggesting high intensity endurance tests may be preferable to incremental tests for the measurement of peak values, in a number of patients. The 85% field test possessed good short and medium term repeatability, and was sensitive to an intervention of pulmonary rehabilitation. The field test has the advantage of avoiding costly treadmill or cycle ergometer assessments, and it is less likely to be associated with the anxiety of laboratory tests. The test was complementary to the ISWT, and did not involve additional resources, except the pre-recorded cassette tapes.

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Appendix 1

EQUIPMENT EVALUATION

A1.1 INTRODUCTION

The laboratory based studies involved the use of a computerised exercise testing system. The system (Oxycon Beta, Mijnhardt) had been evaluated by a group of workers at the University of Limberg, Holland (Keizer at al, unpublished). The evaluation involved a comparison of measurements with the classical Douglas bag method, and an assessment of measurement reproducibility over a wide range of expiratory flows including very high rates ($\dot{V}_E > 180$ l.min^{-1}). A copy of the report was made available to our laboratory. The study found no significant difference between the Oxycon Beta system and the Douglas bag method for $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ with both systems connected in series for simultaneous analysis, or when tests were performed on separate days. The reproducibility was also found to be acceptable (coefficient of variation for maximal $\dot{V}O_2 < 5\%$).

The accuracy, repeatability and quality control of any measurement involves the interaction of operator, protocol, equipment and environment. The aim of this experiment was to quantify the repeatability of HR, $\dot{V}O_2$ and $\dot{V}_E$ during an incremental maximal exercise test. Appendix 2 describes the on-going quality control of measurements throughout the study periods.

A1.2 METHODS

Six healthy subjects were recruited for the repeatability study (1 man, 5 women, mean age 29). Signed informed consent was obtained. Each subject performed a maximal incremental exercise test on a cycle ergometer (Jaeger, ER900) on three separate occasions (mean time between tests 9 days). The first test was considered a practice test and was excluded from analysis. All tests were repeated at the same time of day. Measurements of HR, $\dot{V}O_2$ and $\dot{V}_E$ were made at rest and continuously throughout the exercise period. The initial workload on the cycle ergometer was 25 watts, with increments of 25 watts every 2 minutes until the subject was unable to

sustain the correct pedalling rate (40-45 rpm), despite encouragement from the operator.

A1.3 **RESULTS**

The characteristics of the subject group are given in table A1.1. The mean maximal workload achieved was 175 watts (range 125 to 250) for both tests. The mean oxygen consumption for each workload (25 to 250 watts) during both tests is shown in figure A1.1. There were no significant differences between the measurements of $\dot{V}O_{2max}$, $\dot{V}_{Emax}$ or HR. The mean values for both tests are given in table A1.2. The mean differences between tests and the 95% confidence intervals are also shown in table A1.2. The mean (SE) % differences between repeat tests were 2.1 (0.8) % for $\dot{V}O_{2max}$, 5.4 (2.9) % for $\dot{V}_{Emax}$, and 0.8 (0.5) % for HR_{max}.

The limits of agreement (mean difference ±2SD), which provide an estimate of the widest deviation likely to be observed, were -11.7 to 13.5 $l.min^{-1}$ for $\dot{V}_{Emax}$, and -2.7 to 2.1 $ml.min^{-1}.kg^{-1}$ (-148 to 121 $ml.min^{-1}$) for $\dot{V}O_{2max}$. The range of differences about the mean for $\dot{V}O_{2max}$, and the limits of agreement, are illustrated in figure A1.2.

A1.4 **DISCUSSION**

In comparison to other published data the reapeatability of the exercise measurements was good. Jones (1979) carried out repeat steady state exercise tests on 9 subjects over 5 consecutive days and reported short term variabilities of 3.8%, 3.0% and 8.0% for $\dot{V}O_2$, HR and $\dot{V}_E$ respectively. In the current study the differences between repeat measurements for $\dot{V}O_{2max}$ and for HR_{max} represented less than 3 % of the actual measurements. There was slightly more variability for the measurement of $\dot{V}_{Emax}$ were the differences between repeat tests represented 5.4 % of the actual measurements. The on-going quality control of the system is described in Appendix 2.

Table A1.1 Characteristics of subject group (mean(SD))

Age	29 (7.7)
Height (m)	1.65 (0.05)
Weight (kg)	65 (13.8)

Table A1.2 Mean (SD) $\dot{V}O_{2max}$, $\dot{V}_{Emax}$ and HR at maximal workload for tests 1 and 2, and mean differences (SE) and 95% confidence intervals between repeat tests.

	$\dot{V}O_{2max}$ ($ml.min^{-1}.kg^{-1}$)	$\dot{V}_{Emax}$ ($l.min^{-1}$)	HR ($beats.min^{-1}$)
Test 1	38.4 (11.6)	84.8 (22.0)	178 (6.0)
Test 2	38.3 (11.1)	85.7 (18.9)	177 (6.6)
mean difference (SE)	0.27 (0.49)	0.9 (2.6)	-1.3 (0.8)
(95% CI)	(-1.47 - 0.93)	(-5.4 - 7.2)	(-3.3 - 0.7)

n=6

Mean (SD) $\dot{V}O_{2max}$ in $l.min^{-1}$: Test 1, 2.447 (0.812); Test 2, 2.433 (0.798)

mean difference (SE) $\dot{V}O_{2max}$ in $ml.min^{-1}$ = -14 (27) (95% CI, -81 - 53)

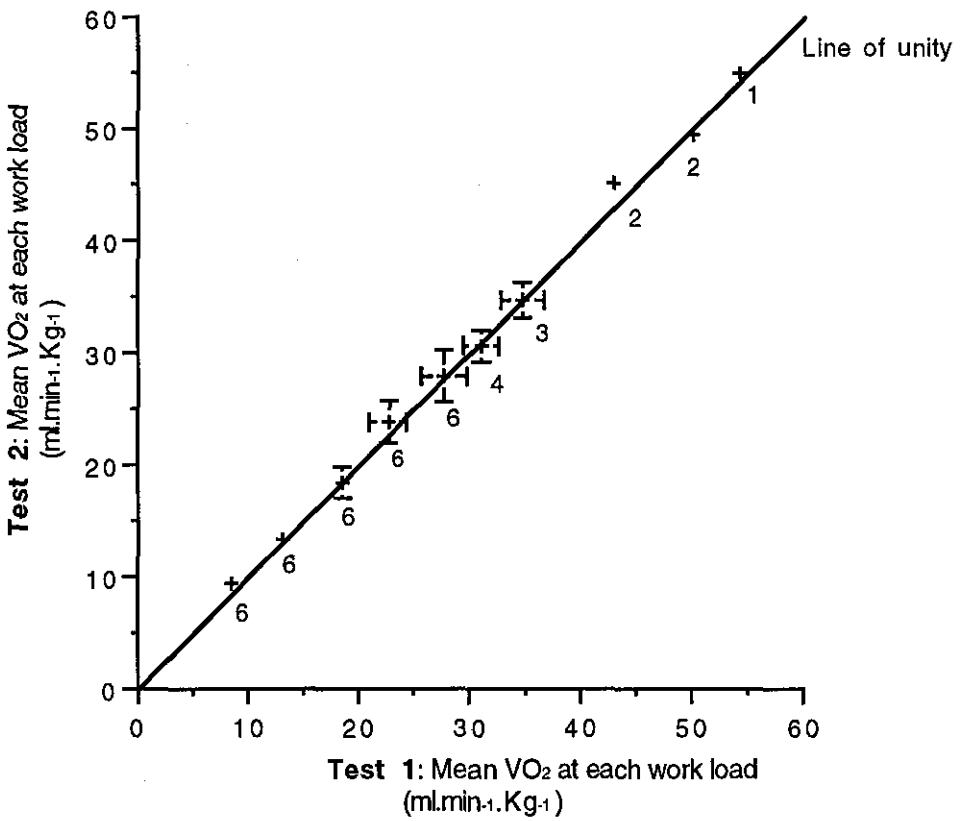

Figure A1.1: Mean oxygen consumption (VO_2) at 10 workrates
The number of subjects are indicated

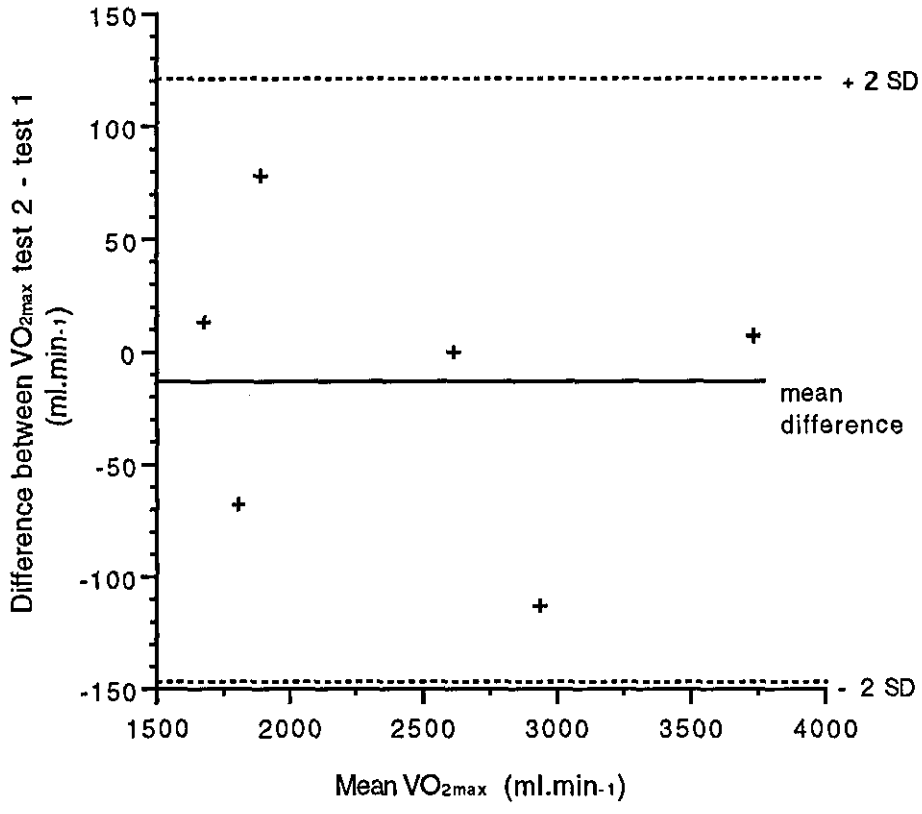

Figure A1.2 Differences in VO_{2max} (tests2 -1)

Appendix 2

QUALITY CONTROL OF THE EXERCISE TEST SYSTEM

The quality control of the integrated exercise system (i.e. treadmill, heart rate and gas analysis) used throughout the study periods consisted of a biological control performing repeat exercise tests on a regular basis. One subject (SMR) performed 4 x 2 minute increments on the treadmill throughout the study periods. Tests were performed on a weekly or two weekly basis depending on laboratory activity. Initially 5 tests were performed over 5 consecutive days to establish an average baseline. All subsequent data was compared to the baseline. The deviations of $\dot{V}O_2$ and heart rate values from the baseline were plotted on a graph to enable any trends in the equipment analysis to be identified. Figure A2.1 is an example of the quality control data obtained during one study period when the gas analysis system and treadmill were in regular use.

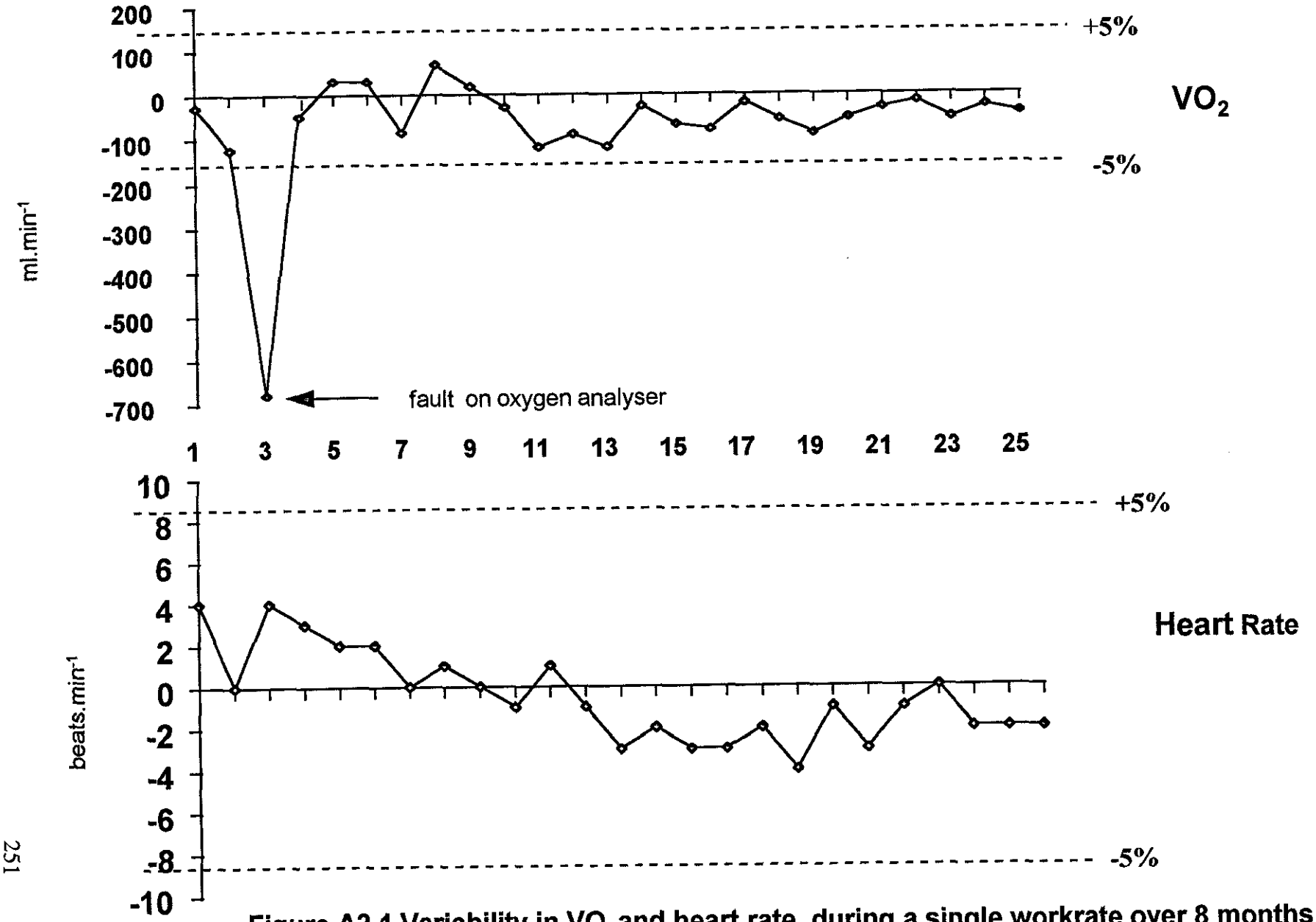

Figure A2.1 Variability in VO_2 and heart rate during a single workrate over 8 months

APPENDIX 3

TREADMILL CALIBRATION

The speed of the treadmill was checked at the start of a study period and periodically throughout. A marker was placed on the treadmill belt and 30 or 40 belt revolutions were timed over a range of walking speeds. For each set speed, the timing of the belt was measured twice and the average calculated. The speed of the belt was calculated and compared to the set speed. A sample of calibration checks is illustrated in table A3.1.

Table A3.1 Treadmill speed calibration

Date	Set Speed ($km.hr^{-1}$)	Measured Speed ($km.hr^{-1}$)	% error
15/8/95	1.50	1.528	1.9
	2.50	2.531	1.2
	3.50	3.538	1.1
	4.50	4.541	0.9
	5.50	5.542	0.8
7/12/95	1.50	1.530	2.0
	2.50	2.538	1.5
	3.50	3.538	1.1
	4.50	4.542	0.9
	5.50	5.544	0.8
26/2/96	1.50	1.530	2.0
	2.50	2.533	1.3
	3.50	3.537	1.1
	4.50	4.542	0.9
	5.50	5.539	0.7

Appendix 4

BLOOD LACTATE ASSAY

Blood lactate assays were performed using the fluorometric method described by Maughan (1982). The reaction depends on the release of NADH:

$$\text{Lactate} \xrightarrow[NAD^+]{LDH} \text{pyruvate} \quad (NADH)$$

In the conversion of lactate to pyruvate, catalysed by lactate dehydrogenase (LDH), the co-factor NAD^+ is reduced to NADH. NADH has a natural fluorescence, the intensity of which is an indication of the concentration of lactate. The actual values were established by relating each sample to a regression equation computed from a series of lactate standards of known concentration.

The process of analysis was as follows:

Solutions:

i) 2.5% perchloric acid

ii) Hydrazine buffer (1.1 $mmol.l^{-1}$, pH 9.4)

ii) Fresh reaction mixture: 2 mg NAD^+ and 10 µl LDH per ml of hydrazine buffer.

iv) Standard lactate solutions for calibration curve (concentrations of 1, 2, 3, 5 and 8 $mmol.l^{-1}$ were used throughout).

Procedure

1) 20 µl blood samples were de-proteinised by adding 200 µl of perchloric acid. The samples were mixed thoroughly and stored at minus 70°C for analysis in batches at a later date.

2) Samples were removed from the freezer and allowed to thaw at room temperature.

3) Samples were broken up with whirlimix and centrifuged for 4 minutes to separate the supernatant.

4) From each sample (including the standard solutions), in duplicate, 20 µl of supernatant was pipetted into a series of labelled, clean test tubes. 200µl of reaction mixture was then added.

5) The solutions were mixed and allowed to incubate at room temperature for 30 minutes.

6) The reaction was stopped with 1 ml of lactate diluent (0.07 M HCL), and mixed thoroughly.

7) 1 ml of each sample was transferred to a series of fluorometer tubes.

8) The samples were read against blanks and the standard solutions using fluorometer (Perkin Elmer 1000M).

9) The lactate concentration was established from the regression equation derived from the analysis of the standard solutions.

Determination of the coefficient of variation for the technique

Twelve aliquots from one blood sample were analysed and the coefficient of variation calculated:

Fluorometer Reading	Lactate concentration ($mmol.l^{-1}$)
116.5	7.01
118.9	7.16
119.2	7.18
116.6	7.01
118.1	7.11
118.5	7.14
119.8	7.22
121.3	7.32
118.8	7.16
124.8	7.55
114.1	6.85
127.8	7.75
	mean (SD) **7.21 (0.24)**
	coefficient of variation **3.3%**

Appendix 5

BORG SCALES

Scale to rate breathlessness		Scale to rate perceived exertion	
0	Nothing at all	6	
0.5	Very, Very Slight (Just Noticeable)	7	Very, Very Light
		8	
1	Very Slight		
		9	Very Light
2	Slight		
		10	
3	Moderate		
		11	Fairly Light
4	Somewhat Severe		
		12	
5	Severe		
		13	Somewhat Hard
6			
		14	
7	Very Severe		
		15	Hard
8			
		16	
9	Very, Very Severe (Almost Maximal)	17	Very Hard
10	Maximal	18	
		19	Very, Very Hard
		20	

Appendix 6

PREDICTION EQUATIONS

Variable		Reference
FVC (l)		Quanjer (1993)
Men	5.76H - 0.026A - 4.34	
Women	4.43H - 0.026A - 2.89	
FEV_1 (l)		Quanjer (1993)
Men	4.30H - 0.029A - 2.49	
Women	3.95H - 0.025A - 2.60	
PI_{max} (cm H_20)		Black (1969)
Men	143 - 0.55A	
Women	104 - 0.51A	
$\dot{V}O_{2max}$ ($ml.min^{-1}.kg^{-1}$)		Bruce (1973)
Men	57.8 - 0.445A	
Women	41.2 - 0.343A	
$\dot{V}_{Emax}$ ($l.min^{-1}$)		Spiro (1975)
	$19.7FEV_1 + 21.8$	
HR_{max} ($beats.min^{-1}$)		Wasserman (1994)
	220 - A	

(A Age in years; H Height in metres)

Appendix 7

THE ENDURANCE SHUTTLE WALK TEST

Instructions to the operator/patient:

Before you start the shuttle endurance walking test it is important to check that your cassette player and the tape are running at the correct speed. To help you with this we have recorded two accurately timed bleeps 60 seconds apart. *Check the timing now.*

Timed Minute

The object of the shuttle endurance test is to walk for as long as possible around the course keeping to the speed indicated by the bleeps on the cassette. You will hear these bleeps at regular intervals. You should walk at a steady pace aiming to turn around the cone at one end of the course when you hear the first bleep and at the other end when you hear the next bleep.

For the first two minutes your walking speed will be very slow, but you will need to speed up when you hear the triple bleep. You should maintain this faster pace for the remainder of the test. Your aim should be to follow the set rhythm for as long as you can. You should stop walking only when you become too breathless to maintain the required speed, or you can no longer keep up the set pace.

The walking speed for the first two minutes is fairly slow so don't go too fast. The test will start in 10 seconds so get ready at the start now. The test starts with a triple bleep after a 4 second count-down.