CHRONIC HEART FAILURE AND FACTORS CONTRIBUTING TO THE INCREASED VENTILATORY RESPONSE TO EXERCISE

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ABSTRACT

Patients with chronic heart failure are often limited by exertional dyspnoea and exercise intolerance. These patients also exhibit an increased ventilatory response to exercise. The precise mechanisms underlying these observations are not fully understood. This thesis sought to establish a further understanding of the ventilatory control of exercise in chronic heart failure patients.

The sensitivity of arterial chemoreceptors may be reset and may in part mediate the exercise hyperpnoea seen in this condition. Hitherto, the chemosensitivity of chronic heart failure patients was not known and was accordingly examined in the thesis. The effects of suppressing chemosensitivity with oxygen and a mild opiate, dihydrocodeine, on exercise ventilation and exercise tolerance were also studied. The effects of chronic hypoxaemia on chemosensitivity and on the ventilatory response to exercise, were also studied by examining a group of patients with cyanotic heart disease, either corrected or uncorrected.

Respiratory muscle weakness may cause exercise intolerance and breathlessness in chronic heart failure patients. The relationship between respiratory muscle strength, maximal oxygen consumption and the ventilatory response to exercise was investigated. The association between respiratory and quadriceps muscle weakness, the latter representative of locomotor skeletal myopathy, was also assessed.

Finally, airway hyperresponsiveness has been documented in chronic heart failure patients and may contribute to exertional dyspnoea. However, such a finding is often confounded by factors such as acute pulmonary congestion and smoking. The thesis therefore also sought to establish the presence of airway hyperresponsiveness in a group of stable and non-smoking chronic heart failure patients.

DEDICATION

This thesis is dedicated to my parents, Dato Chua Song Lim and Datin Koh Sai Eng, and to my wife, Jenny, for their love, tolerance and unfailing support.

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Erratum

Treadmill exercise testing in the various studies in this thesis was performed using a *modified* Bruce protocol with the addition of a Stage "0" (1.0 mph, 5% gradient). The word *"modified"* was inadvertently and regrettably omitted in the methods section of these studies (pages 61, 82, 113, 129, 144, 167 and 186). These errors are acknowledged.

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Chapter 1

INTRODUCTION

Background

Chronic heart failure is a complex clinical syndrome comprising the symptoms of breathlessness or fatigue, either at rest or during exertion, and oedema [Dargie & McMurray, 1993; Task Force on Heart Failure of The European Society of Cardiology, 1995]. It is a common condition with high morbidity and mortality comparable to malignancies. It has a prevalence of 4.5% of the population aged between 65 and 74 years and a 5-year survival rate of less than 40% [Ho *et al*, 1993]. In one study, chronic heart failure accounted for 4.9% of all admissions in a London district general hospital over a six-month period [Sutton, 1990] and when extrapolated to the United Kingdom as a whole, this gives an annual admission rate of 100 000 to 120 000 due to chronic heart failure.

The symptoms of chronic heart failure are debilitating. Exercise intolerance is common despite diuretic therapy and vasodilators. Patients with chronic heart failure also demonstrate hyperpnoea during exercise [Buller & Poole-Wilson, 1990]. This hyperpnoea is characterised by an increase in minute ventilation in relation to carbon dioxide output and may contribute to the perceived symptom of breathlessness [Rubin & Brown, 1984]. The mechanisms causing the increase in exercise ventilatory response are not fully understood [Clark & Coats, 1992]. To have a better insight into these mechanisms and before outlining the objectives of this thesis, it is pertinent to discuss the control of ventilation in health and the known pathophysiology of chronic heart failure.

Respiratory Centres

Respiration is controlled within the central nervous system by two functionally separate entities [Berger *et al*, 1977a, 1977b, 1977c]. Voluntary respiration is governed by higher cortical centres and automatic respiration by various centres in the brainstem with the spinal cord integrating the output of these two entities. The main respiratory centre in the brainstem consists of two bilateral aggregates of respiratory neurons known as the dorsal and ventral respiratory groups respectively. The dorsal respiratory group consists mainly of inspiratory neurons and is thought to maintain the activity of the diaphragm. The ventral respiratory group, on the contrary, contains both inspiratory and expiratory neurons with the former controlling the external intercostal muscles and also partially, the diaphragm whilst the latter the internal intercostal and abdominal muscles. From the effects of transection at different levels of the brainstem on the ventilatory patterns of anaesthesised animals, two other respiratory centres are known. These are the apneustic centre, which maintains an inspiratory termination mechanism, and the pneumotaxic centre, which modulates the activity of the apneustic centre.

There is also afferent input to the respiratory centres from different receptors forming various reflexes which modulate respiration. Amongst these receptors are the stretch receptors located within the smooth muscle of large and small airways which form an integral part of the Hering-Breuer reflex [Nunn, 1993a]. Hering and Breuer showed in 1868 that inflation of the lungs of anaesthesised animals decreases the frequency of inspiratory effort whilst abrupt deflation of the lungs was shown to do the opposite. While this reflex is not necessary for control of respiration, it may nevertheless be important in minimising the work of breathing by inhibiting large tidal volumes [Levitzky, 1995].

Control of Ventilation during Exercise

The control of ventilation during exercise in health remains the subject of intense study. In simplistic terms, the mechanisms underlying the control of ventilation during exercise may be divided into feedforward and feedback mechanisms [Cunningham *et al*, 1986].

A. Feedforward Mechanism

In the feedforward mechanism, it is proposed that central neurogenic control produces not only the locomotion but also simultaneously drives ventilation [Krogh & Lindhard, 1913]. This is particularly applicable to the initial immediate rise in ventilation with exercise which Dejours [1964] noted and termed the "neural" component of the ventilatory response to exercise. This fast ventilatory response may last 20 seconds following the onset of exercise before a slower increase in ventilation is noted until steady state is reached. This central neurogenic control may be in part a conditioned reflex and in part hypothalamic in origin. Beaver and Wasserman [1970] provided some evidence that this may be a learned response when they found that initial increases in ventilation were not always consistent in blindfolded subjects and may be influenced by conditioning. Eldridge *et al* [1985] demonstrated that electrically stimulating the hypothalamic motor area in the cat induced a rapid ventilatory response suggesting that the hypothalamus may have a role in the integrative response to exercise akin to its role in the "fight or flight" alarm reaction which causes an increase in ventilation, blood pressure, heart rate and also blood flow to muscles.

Some authors classify peripheral neurogenic signals as part of the feedforward mechanism but it is probably more appropriate to include these in the feedback

mechanisms since they involve the sensing of some form of stimuli from the periphery.

B. Feedback Mechanisms

i. Chemoreceptors

In the feedback mechanisms, the stimulation of breathing is achieved through sensory feedback after the onset of exercise. Since ventilation is approximately proportional to the required metabolic rate, humoral factors and metabolites acting on receptors in the brainstem, carotid bodies, lungs or blood vessels have been suggested as the source of the stimulus. These humoral factors include $[H^+]$, arterial blood gas tensions, catecholamines, potassium, adenosine and lactate. While central and peripheral arterial chemoreceptors in the medulla and carotid bodies have respectively been identified, that there is no significant change in pH or arterial blood gas tensions during exercise poses a potential limitation to the hypothesis that these chemoreceptors modulate exercise ventilation [Whipp, Ward & Wasserman, 1984]. However, such a mechanism may still be valid if chemoreceptors operate with an increased gain during exercise which indeed had been demonstrated to be the case [Weil *et al*, 1972] or if the chemoreceptors respond more to increased phasic changes in pH or arterial blood gases during exercise [Purves, 1966; Saunders, 1980; Cross *et al*, 1982]. The increased gain may well be achieved by the action of other humoral factors such as catecholamines, potassium and adenosine on the chemoreceptors. Hyperkalaemia has been shown to excite chemoreceptors [Linton & Band, 1985; Paterson & Nye, 1988] and also ventilation [Band *et al*, 1985]. Paterson *et al* [1989] demonstrated a close temporal relationship between a rise in arterial potassium and ventilation in healthy volunteers. Catecholamines have also been shown to excite chemoreceptors [Cunningham *et al*, 1963] and so has

adenosine [McQueen & Ribiero,1983; Maxwell *et al*, 1986].

Lugliani and colleagues [Lugliani *et al*, 1971; Wasserman *et al*, 1975] demonstrated that there was a initial reduction in the ventilatory response to exercise such that the steady state ventilation was delayed in subjects who had carotid bodies removed as part of treatment of asthma although the eventual ventilation reached was not significantly different from controls. That the steady state ventilation during exercise is comparable to controls does not diminish the role of chemoreceptors in the control of exercise ventilation because it may be that several reflex mechanisms are at play given the importance of respiration, so that if a particular reflex is removed, another reflex system becomes more dominant and takes over to preserve homeostasis.

The role of lactate in the control of ventilation is controversial. Wasserman and Whipp [1975] suggested that the ventilatory threshold seen during heavy exercise is due to the release of lactate which is subsequently buffered by plasma bicarbonate. The release of lactate, causing an acidosis, is also thought to cause the further rise in ventilation with respect to carbon dioxide output. This may also be mediated at the level of peripheral chemoreceptors because in subjects with carotid bodies removed, such a ventilatory threshold is not seen [Wasserman *et al*, 1975]. Interestingly, however, in subjects with McArdle's syndrome in whom there is myophosphorylase deficiency and the inability to produce lactate, a ventilatory threshold is seen during heavy exercise [Hagberg *et al*, 1982] although a subsequent study has suggested otherwise [Riley *et al*, 1993].

ii. Cardiodynamic Mechanisms - Mixed Venous Chemoreceptors & Cardiac Mechanoreceptors

Wasserman *et al* [1974] also proposed the presence of rapidly responding

pulmonary chemoreceptors to explain the initial fast ventilatory response to exercise. They argued that if there was only a neural component to the initial increase in ventilation, then there would be a drop in the end-tidal carbon dioxide tension, just as there would in hyperventilation, which is not the case. They showed that by pacing or by isoprenaline infusion in dogs, which increased cardiac output and thus flow in the lungs, there was an immediate ventilatory response with end-tidal carbon dioxide tension remaining constant. They proposed that the increase in cardiac output, in the absence of an initial increase in ventilation, caused the carbon dioxide tension in the pulmonary vascular tree to rise which in turn stimulated the pulmonary chemoreceptors located in the pulmonary artery, causing an abrupt hyperpnoea. Thus, ventilation became matched again with perfusion as before exercise and this explains the constant respiratory exchange ratio and the end-tidal carbon dioxide tension. However, the search for pulmonary chemoreceptors, sometimes also known as mixed venous chemoreceptors, has been futile over the years [Dawes & Comroe, 1954; Cropp & Comroe, 1961; Coleridge *et al*, 1967; Gonzalez *et al*, 1977]. Subsequently, it was proposed the receptors responsible for this so-called "cardiodynamic" mechanism of increased ventilatory response to exercise may indeed be mechanoreceptors in the right atrium or ventricle which have afferents in the sympathetic nerve fibres [Uchida, 1975 & 1976; Jones *et al*, 1982].

iii. Muscle and Joint Mechanoreceptors

Another feedback mechanism is that from mechanoreceptors arising from muscle spindles [Gautier *et al*, 1969; Leitner & Dejours, 1971] and joints [Comroe & Schmidt, 1943]. By inhibiting the muscle spindle activity pharmacologically, Flandrois *et al* [1967]

demonstrated the reduction in the ventilatory response to passive motion of the limbs. Similarly, by anaesthesising the articular surface of the knee, exercise ventilation was also reduced. It therefore appears that reflexes arising from both muscle spindles and joints play a role in mediating exercise ventilation.

iv. Metaboreceptors/Ergoreceptors

Kao *et al* [1963] and Tibes *et al* [1977] introduced the concept of a metaboreflex, also termed as an ergoreflex, in the ventilatory control of exercise. Such a reflex is sensitive to the metabolic changes related to work of skeletal muscles [Clark *et al*, 1995a]. This is therefore another feedback mechanism and may influence the ventilatory response to exercise.

v. Pulmonary stretch receptors (J receptors)

Pulmonary stretch receptors (J receptors) may also be involved in the control of exercise ventilation (Paintal, 1969 & 1977). These receptors are located in the interstitial tissue between pulmonary capillaries and the alveoli and are stimulated by the increased alveolar interstitial volume consequent to raised pulmonary capillary pressures. This in turn causes hyperpnoea and also the sensation of dyspnoea. During exercise, the increase in cardiac output and the associated rise in pulmonary capillary pressure [Bevegard *et al*, 1963] may stimulate the J receptors leading to hyperpnoea. Paintal [1977] also proposed the "J reflex" as part of the ventilatory control of exercise based on the findings that stimulation of J receptors was found to inhibit somatic muscles [Deshpande & Devanandan, 1970] and thus may contribute to the termination of exercise.

It is likely that both feedforward and feedback mechanisms contribute to the

control of exercise ventilation in health. It is thus not surprising that in a disease state, such as chronic heart failure, these mechanisms may be affected by, and indeed contribute to, the pathophysiology of the condition. An overview of the pathophysiology of chronic heart failure in terms of haemodynamic, autonomic, neurohormonal, pulmonary and skeletal muscle abnormalities will be presented next.

Pathophysiology of Chronic Heart Failure

A. Haemodynamic, Autonomic and Neurohumoral Abnormalities

Heart failure has traditionally been regarded as a disorder in which the ventricles fail to pump adequate quantities of blood to meet the demands of peripheral organs [Packer, 1992]. To compensate for the loss of ventricular function, both haemodynamic, autonomic and neurohormonal mechanisms are activated. With the failure of the ventricle to empty normally, diastolic tension on the non-injured parts of the heart is increased. This increased tension enhances contraction in accordance to the Frank-Starling principle. However, there is a limit to this compensatory mechanism since the ventricular function curve is depressed due to the loss of myocardial contractility in heart failure. There is a reflex increase in sympathetic activity which is initially beneficial but this becomes ineffective in the long term because of the downregulation of ß-receptors [Bristow *et al*, 1982] and the uncoupling of ß-receptors from adenylate cyclase, the effector enzyme [Bristow *et al*, 1990]. An abnormal baroreflex function may also contribute to the persistently increased sympathetic activity probably because the baroreceptors are less able to inhibit the vasomotor centres leading to enhanced sympathetic outflow [Dibner-Dunlap & Thames, 1989; Wang *et al*, 1990; Mancia *et al*, 1992]. The resultant sympathetic overactivity leads to peripheral vasoconstriction increasing ventricular

preload and afterload, and further adding to the vicious cycle of heart failure. There is also, at the same time, a reduction in parasympathetic activity. With increased sympathetic activity and the reduction in renal blood flow, the renin-angiotensin-aldosterone system is activated leading to sodium and fluid retention. This further increases preload and worsens the haemodynamic abnormalities.

There are other vasoconstrictor hormones activated in chronic heart failure which include arginine vasopressin [Francis *et al*, 1990], neuropeptide Y [Maisel *et al*, 1989] and endothelins [McMurray *et al*, 1991; Pacher *et al*, 1993; Wei *et al*, 1994] all contributing to the pathophysiology of chronic heart failure. There is also the release of cytokines such as tumour necrosis factor [Packer *et al*, 1989; McMurray *et al*, 1991] which is not only a marker of the disease process but may also be partly responsible for the generalised wasting seen in this disease. However, not all neurohormonal responses are detrimental; there are increased levels of vasodilator hormones such as atrial natriuretic factors [Gottlieb *et al*, 1989], prostaglandins [Dzau *et al*, 1984] and dopamine [Minami *et al*, 1964] which may counterbalance the effects of the vasoconstrictor hormones. Increased erythropoietin production is also seen in chronic heart failure probably in response to reduced peripheral perfusion [Herrlin & Sylven, 1991].

In general, however, there is a dissociation between exercise tolerance and resting haemodynamic measurements in chronic heart failure [Franciosa *et al*, 1981; Szlachcic *et al*, 1985; Lipkin & Poole-Wilson, 1986; Fink *et al*, 1986; Metra *et al*, 1990; Gibbs *et al*, 1990]. More recently, attention has been directed towards the peripheral abnormalities of chronic heart failure such as pulmonary and skeletal muscle changes which may be important in the genesis of exercise intolerance in these patients. These will accordingly be discussed.

B. Pulmonary Abnormalities

The amount of review literature which focuses primarily on pulmonary pathophysiology in chronic heart failure remains limited [Smulyan *et al*, 1974; Hertz, 1976; Murray, 1985; Szidon, 1989; Faggiano, 1994]. Because one of the cardinal symptoms of chronic heart failure is breathlessness, pulmonary factors may be especially relevant [Kraemer *et al*, 1993].

A large part of the pulmonary abnormalities seen in chronic heart failure is consequent upon chronic pulmonary oedema [Szidon, 1989]. With a failing left ventricle, the left ventricular diastolic pressure becomes elevated which in turn causes increased left atrial, pulmonary venous and pulmonary capillary pressures [Gazetopoulos *et al*, 1966]. Pulmonary artery pressure may initially be normal but is often elevated during exercise [Sullivan *et al*, 1988a]. These changes in pulmonary haemodynamics lead to three sequential stages of lung water accumulation [Ayers, 1982]. Initially, there is pulmonary vascular congestion without the development of interstitial oedema despite more transcapillary fluid transfer because this excess fluid is removed by increased lymphatic clearance. When the lymphatic clearance reaches its limit, fluid starts to accumulate in the peribronchial tissues, perivascular tissues and interstitial spaces. Since the pulmonary lymphatics drain into the systemic veins, any elevation of central systemic venous pressure will tend to decrease this lymphatic clearance. If the progressive accumulation of interstitial fluid is not reversed, alveolar oedema ensues.

Chronic elevation of pulmonary venous pressure causes parenchymal and structural changes in the lungs. This is especially well-documented in patients with mitral stenosis [Parker & Weiss, 1936; Heath & Edwards, 1959; Kay & Edwards, 1973]. The pulmonary vessels develop thickening of the media and intima [Smith et al, 1954].

Persistent peribronchial, perivascular and alveolar septal oedema lead to fibroblast proliferation and connective tissue deposition with consequent fibrosis. These changes together with the capacious lymphatics [Heath & Hicken 1960; Uhley *et al*, 1962] may explain the relative resistance to the development of alveolar oedema in chronic heart failure patients compared with those unaccustomed to raised pulmonary venous pressure. It has also been confirmed that pulmonary microvascular permeability is reduced in severe chronic heart failure, which is consistent with this [Davies *et al*, 1992].

Airway Function

Most studies on airway function in patients with chronic heart failure have demonstrated a restrictive pattern in chronic heart failure based on the reduction in total lung capacity, forced vital capacity and increased ratio of forced expiratory volume in 1.0 second to forced vital capacity (FEV_1/FVC) [Collins *et al*, 1975; Ries *et al*, 1986; Hosenpud *et al*, 1990; Wright *et al*, 1990; Naum *et al*, 1992]. The restrictive pattern is thought to be due to the loss of lung volume secondary to increased cardiac size, alveolar and interstitial fluid formation and the presence of pleural effusion. Stiffening of the lung parenchyma due to fluid engorgement may also be relevant. This restrictive dysfunction generally improves after treatment of chronic heart failure either by drug therapy [Faggiano *et al*, 1993] or following cardiac transplantation [Hosenpud *et al*, 1990; Ravenscraft *et al*, 1993] and is thought to be due to the reduction in lung water, and also in cardiac size particularly after cardiac transplantation. Both the reduction in forced vital capacity and total lung capacity correlate with raised pulmonary capillary wedge pressure [Ries *et al*, 1986]. Hosenpud *et al* [1990] calculated the reduction in cardiac volume after cardiac transplantation by radiographic means and showed that the decrease in cardiac

size accounted for 69% of the improvement in forced vital capacity.

Light and George [1983], on the contrary, reported a predominant obstructive pattern in their study. This observation may be due to different patient characteristics. Their study was performed on twenty-eight patients admitted with acute heart failure in contrast to patients with stable chronic heart failure in whom a predominant restrictive airway dysfunction was noted. Similarly, significant airway obstruction was reported by Petermann and colleagues [1987] in sixty patients admitted acutely for treatment of severe left heart failure. In another study which assessed the effects of treatment of heart failure on pulmonary function in a group of patients with severe congestive cardiac failure, restrictive, obstructive or mixed patterns of pulmonary dysfunction were seen [Faggiano *et al*, 1993]. In all these studies, airway obstruction generally improved following the treatment of heart failure. Light and George [1983] also showed that airway obstruction did not change with bronchodilator therapy and that the obstructive pattern persisted for a long time, even in non-smokers, despite some initial improvement, with a mean follow-up duration of 310 days.

The predominant airway dysfunction seen is probably related to whether the heart failure is acute or chronic; with decompensated chronic heart failure also resembling acute heart failure in contrast to adequately treated and stable chronic heart failure. Airway obstruction may be attributable to peribronchial vascular congestion or oedema causing increased airway resistance [Hogg *et al*, 1972]. On the other hand, in stable chronic heart failure, peribronchial oedema may be less important and other abnormalities such as increased cardiac size, stiffening of the lung parenchyma and the presence of fluid-filled alveolar spaces may account for the predominant restrictive defect.

The possible importance of airway function in determining exercise tolerance in chronic heart failure patients was demonstrated by the significant correlation between both FEV_1 and forced vital capacity and peak oxygen consumption in fifty patients [Kraemer *et al*, 1993].

Diffusion abnormalities

The diffusion characteristics of the lung is typically assessed using carbon monoxide. By definition, the uptake of carbon monoxide per minute per unit partial pressure gradient of carbon monoxide is its diffusing capacity, D_LCO. The rate of uptake of carbon monoxide depends on the volume of blood coming in contact with the inhaled carbon monoxide, which is the pulmonary capillary blood volume, and also the diffusing capacity of the alveolar-capillary membrane [Cotes, 1993a]. A low D_LCO may result from the reduction in the number of alveolar capillaries, for example, in pulmonary embolism or in fibrosis due to destruction of the vascular bed. On the other hand, increased pulmonary capillary blood volume may increase the D_LCO. The diffusing capacity of the alveolar capillary membrane is a measure of the total surface area of alveolar membrane available for gas exchange and of the permeability of the membrane, the latter influenced by the thickness of the membrane.

Most studies show that D_LCO is reduced in chronic heart failure [Wright *et al*, 1990; Naum *et al*, 1992; Ravenscraft *et al*, 1993; Ohar *et al*, 1993]. Various explanations have been offered including the reduction of lung volume (hence less effective surface area for gas diffusion), the presence of pulmonary oedema and alveolar-capillary membrane thickening. However, there appears to be little correlation between D_LCO and forced vital capacity in chronic heart failure, as would be expected if the

diffusion impairment were predominantly due to reduction in lung volume [Wright *et al*, 1990; Ravenscraft *et al*, 1993; Ohar *et al*, 1993]. Siegel and colleagues [1990] found that D_LCO is only reduced in patients with rales but normal in those without, suggesting that lung oedema is a more important causative factor. This is supported by the correlation between D_LCO and pulmonary capillary wedge pressure in one study [Naim *et al*, 1992].

Puri *et al* [1994 & 1995] demonstrated that pulmonary capillary blood volume is increased in chronic heart failure, consistent with raised pulmonary venous pressure. This is however offset by the greater reduction in alveolar-capillary membrane diffusing capacity, probably due to increased alveolar-capillary membrane thickness, effectively lowering D_LCO. This also explains why D_LCO is normal in acute heart failure [Light & George, 1983]. In this situation, the rise in pulmonary capillary volume is sufficient to render D_LCO normal despite the presence of pulmonary oedema but with chronicity, there may be an alteration of the physical characteristics of the alveolar-capillary membrane affecting its diffusing capacity which causes a decrease in D_LCO.

Whatever the mechanisms of the reduced D_LCO may be, it remains debatable whether this is functionally significant since significant arterial oxygen desaturation is uncommon in chronic heart failure even during exercise [Wilson & Ferraro, 1983; Sullivan *et al*, 1988a; Clark & Coats, 1994]. However, one study has shown a close relation between D_LCO and maximal oxygen consumption during exercise [Kraemer *et al*, 1993].

Airway hyperresponsiveness

Non-specific airway hyperresponsiveness is classically seen in bronchial asthma [Snashall & Chung, 1991]. This is usually assessed using an aerosol of histamine or

methacholine, an analogue of acetylcholine and the bronchoconstrictor response to provocation can be monitored in terms of forced expiratory volume [Cotes, 1993b]. Several reports show that non-specific airway hyperresponsiveness is present in chronic heart failure [Cabanes *et al*, 1989; Pison *et al*, 1989; Sasaki *et al*, 1990] although this is not a unanimous finding [Eichacker *et al*, 1988; Siebert *et al*, 1989]. It appears that airway hyperresponsiveness in chronic heart failure is not a function of pre-existing bronchial obstruction [Cabanes *et al*, 1989; Pison *et al*, 1989] or pulmonary haemodynamic variables [Sasaki *et al*, 1990]. Cabanes *et al* [1989] also demonstrated that inhalation of the vasoconstrictor methoxamine, an alpha-receptor agonist, prevented or attenuated the methacholine-induced airway hyperresponsiveness. They suggested that airway wall oedema caused by the inherent vasodilatory effect of methacholine on bronchial vessels and also by the vascular congestion due to chronic heart failure itself, is partly responsible for the airway hyperresponsiveness. This may be explained on the basis of simple geometric considerations in which the effect of spasm on airway narrowing in an already narrowed airway is amplified, even if the tone of smooth muscle contraction is no more than normal [Moreno *et al*, 1986]. Another possible mechanism is that the c-nerve fibres, through pulmonary stretch (J) receptors [Paintal, 1969], in the bronchial wall are stimulated by raised pulmonary venous pressure leading to increased reactivity to non-specific stimuli [Kikuchi *et al*, 1984]. In any case, the influence of confounding factors such as smoking and acute decompensation of heart failure has not been properly addressed since many of these studies included smokers and patients with a recent history of pulmonary oedema. In one study, diuretic treatment was witheld before various tests were carried out which again may have affected the results [Sasaki *et al*, 1990]. Smoking is also known to directly cause airway hyperresponsiveness

[Gerrard *et al*, 1980; Sparrow *et al*, 1984; Cerveri *et al*, 1989; Paoletti *et al*, 1995].

Another manifestation related to airway hyperresponsiveness is exercise-induced bronchospasm. Uren *et al* [1993] showed a small improvement in peak oxygen consumption associated with an improvement in FEV_1 following a single nebulised dose of salbutamol and ipratropium bromide in a group of 10 chronic heart failure patients. However, there was no reduction in FEV_1 with exercise following nebulised placebo which would have been expected had there been exercise-induced bronchospasm in these patients. The improvement in FEV_1 with nebulised bronchodilators is probably not peculiar to chronic heart failure patients but applies generally to all subjects in view of the bronchodilatory properties of these drugs. There were unfortunately no controls in this particular study.

Respiratory Muscle Strength

Reduced respiratory muscle function may play a role in causing breathlessness and exercise intolerance in chronic heart failure. Research however remains limited. Using near-infrared spectroscopy, a technique based on the differences in light absorption of oxygenated and deoxygenated haemoglobin, it has been shown that there is respiratory muscle deoxygenation during exercise in heart failure patients but not in normal subjects [Mancini *et al*, 1991]. Although this deoxygenation could well cause respiratory muscle fatigue, this has not been demonstrated [Mancini *et al*, 1992a]. This may be related to a delay in the assessment of respiratory muscle function following exercise. Indeed, respiratory muscle strength, assessed by measuring mouth pressures during maximum inspiratory and expiratory effort, has been shown to be reduced in chronic heart failure [Mancini *et al*, 1992a; McParland *et al*, 1992; Hammond *et al*, 1990]. There is also a

significant correlation between respiratory muscle weakness and the perceived ratings of dyspnoea [Mancini *et al*, 1992a; McParland *et al*, 1992]. The work of breathing is probably greater in chronic heart failure as suggested by the increased diaphragmatic work in heart failure patients observed in one study [Mancini *et al*, 1992a]. The relationship between respiratory muscle strength and exercise tolerance was not known in chronic heart failure patients at the time research was inititiated in this thesis.

Ventilation-Perfusion Inequality

Lung abnormalities, increased pulmonary venous pressures, reduced cardiac output and increased pulmonary vascular resistance in chronic heart failure may all cause an increase in ventilation-perfusion ($\dot{V}/\dot{Q}$) inequality. In the normal lung, the intrapleural pressure is less negative at the base due to its weight and consequently, it is relatively compressed in its resting state at the base than at the apex. During inspiration, this causes more expansion and thus larger ventilation per unit alveolar volume at the basal regions of the lung [West, 1990]. Similarly, due to the effect of gravity, blood flow is more at the base of the lung. In short, both ventilation and blood flow distribution are influenced by gravity, giving rise to a range of $\dot{V}/\dot{Q}$ ratios from 0.6 to 3 with an overall value of 0.85 in the normal lung [Cole & Mackay, 1991]. In chronic heart failure, there is flow redistribution with relatively more blood flow to the apical regions of the lungs due to raised pulmonary venous pressure and other pulmonary structural changes [Ingram & Braunwald, 1992]. This has been shown radiographically and also by radionuclide lung perfusion scans [Mohsenifar *et al*, 1989]. Because of this flow redistribution and other lung abnormalities described earlier, there is potentially a wider range of $\dot{V}/\dot{Q}$ distribution and increased mismatch.

From alveolar-arterial oxygen partial pressure difference, there is a small degree of shunting in normal subjects and this arises from the anatomical shunt involving the bronchial and thebesian circulation [Nunn, 1993b]. Using the multiple inert gas elimination technique (MIGET), a technically laborious method which employs the introduction of six inert gases of different solubilities to the circulation and the numerical analysis of the retention and elimination of the gases to obtain the ventilation and perfusion distribution in relation to a range of $\dot{V}/\dot{Q}$ ratios in a 50-compartment lung model, there is no *intrapulmonary* shunt seen in normal young adults [Wagner *et al*, 1974a; Wagner *et al*, 1974b]. Adnot *et al* [1991] used this technique to assess the effect of vasodilator therapy in chronic heart failure. Prior to treatment with vasodilators, the percentage of cardiac output supplying areas with low $\dot{V}/\dot{Q}$ (<0.1) and shunt was 2.1% and 1.6% respectively. This suggests there are modest airway and alveolar abnormalities impairing ventilation, such as reduced alveolar distensibility and air trapping. It has also been shown that cardiomegaly itself impairs left lower lobe ventilation by causing regional atelectasis and alveolar collapse [Alexander *et al*, 1992].

From the Bohr equation*, the ratio of physiological dead space to tidal volume (VD/VT ratio) ranges between 20.8% to 36.3% in resting normal subjects [Harris *et al*, 1973]. The physiological dead space is predominantly due to the anatomical dead space since in normal subjects, the alveolar dead space is small [Nunn, 1993b]. In chronic heart failure, the VD/VT ratio is both elevated at rest and during exercise compared with

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* Bohr equation: $V_D/V_T = (P_aCO2 - P_ECO2)/P_aCO2$, where P_aCO2 is the arterial carbon dioxide partial pressure and P_ECO2 the mixed expired carbon dioxide partial pressure.

normal subjects [Sullivan *et al*, 1988a; Rubin & Brown, 1984; Rajfer *et al*, 1987], suggesting that there are areas of high $\dot{V}/\dot{Q}$ ratios and alveolar dead space due to underperfusion.

During exercise, ventilation rises faster in patients with chronic heart failure than in normal subjects such that the slope relating ventilation ($\dot{V}_E$) to carbon dioxide production ($\dot{V}CO_2$) is increased [Buller & Poole-Wilson, 1990]. Sullivan *et al* [1988a] showed a strong relationship between $\dot{V}_E/\dot{V}CO_2$ ratio and VD/VT both at rest as well as during exercise and suggested that increased dead space is an important factor causing exercise hyperpnoea in chronic heart failure. In other words, ventilatory efficiency is decreased due to the increased dead space and a greater minute ventilation is thus required to maintain eucapnia. Although this may well be one of the mechanisms causing the increased ventilatory response to exercise seen in chronic heart failure patients, it remains to be answered how this increased dead space is sensed by the body considering that arterial blood gases are not significantly changed in chronic heart failure patients compared with normals [Wilson & Ferraro, 1983; Sullivan *et al*, 1988a; Clark & Coats, 1994]. One possibility may be that the increased dead space ventilation causes a change in the amplitude of oscillations about the mean partial pressure of arterial blood gases. This is then sensed by arterial chemoreceptors, altering their sensitivity.

C. Skeletal Muscle Abnormalities

Muscle fatigue is a cause of exercise intolerance in patients with chronic heart failure [Mancini *et al*, 1992b; Coats *et al*, 1994]. Other than loss of skeletal muscle bulk

and strength, skeletal muscle abnormalities documented include changes in histochemistry, skeletal muscle blood flow and metabolism. It has also been established that exercise rehabilitation can improve the exercise capacity of patients with chronic heart failure and this may be due to improvement in muscle function [Sullivan *et al*, 1988b; Coats *et al*, 1990; Minotti *et al*, 1990; Coats *et al*, 1992]. It is therefore relevant that skeletal muscle abnormalities are discussed.

Abnormal Histochemistry

Microscopically, skeletal muscle fibres can be categorised into three types, 1, 2a and 2b using three main histochemical staining reactions for myosin ATPase, mitochondrial enzyme activities and glycolytic activity [Jones & Round,1990]. In terms of size and contractile properties such as speed and fatiguability, skeletal muscle may also be divided into two groups of motor unit, small, slow-twitch and fatigue-resistant or large, fast-twitch and fatiguable. The former conveniently consists of type 1 muscle fibres and has oxidative enzyme activity while the latter consists of generally type 2b and shows predominant glycolytic enzyme activity. Type 2a units are seen in a range of size and fatigue resistance and have a combination of glycolytic as well as oxidative enzyme activity.

Lipkin *et al* [1988] found an increased variation in muscle fibre size including atrophic fibres and also a shift to type 2 fibres in quadriceps muscle needle biopsies of chronic heart failure patients. Such findings were consistent with other studies [Mancini *et al*, 1989; Sullivan *et al*, 1990a; Drexler *et al*, 1992]. The volume density of mitochondria and surface density of mitochondrial cristae were reduced especially in patients with exercise intolerance [Drexler *et al*, 1992]. Oxidative enzymes such as

cytochrome oxidase, succinate dehydrogenase and citrate synthase were reduced [Sullivan *et al*, 1990a & 1991; Ralston *et al*, 1991]. Broqvist *et al* [1992] also reported reductions in high energy metabolic substrates including ATP, phosphocreatine and glycogen. In short, there is a general shift away from type 1 slow-twitch aerobic fibres towards type 2 fast-twitch anaerobic fibres with the accompanying biochemical changes such as the reduction in oxidative capacity. The precise cause of these changes are not known but may be related to prolonged periods of reduced muscular activity and deconditioning [Astrand & Rodahl, 1986a; Hambrecht *et al*, 1995], malnutrition [Blackburn *et al*, 1977; Carr *et al*, 1989; Broqvist *et al*, 1994] and also to neurohormonal changes mentioned earlier such as tumour necrosis factor release. Insulin resistance which has been demonstrated in chronic heart failure patients may also play a role [Swan *et al*, 1994].

Abnormal Skeletal Muscle Blood Flow

In chronic heart failure, there is an altered distribution of blood flow in the body [Zelis *et al*, 1968, 1974, 1975 & 1982; Wilson *et al*, 1986a; Levine & Levine, 1990]. There may be a 5-fold reduction in skeletal muscle blood flow during exercise compared with normal [Poole-Wilson *et al*, 1992] suggesting an increase in resistance in the vascular bed. The cause of the increased in resistance is not known but may be related to the increased sympathetic activity and the activation of the renin-angiotensin system causing increased vasoconstriction. An impairment of normal vasodilator mechanisms during exercise may also be responsible [Katz *et al*, 1992]. Central haemodynamics seem to be less important as suggested by the lack of immediate reversal of vascular resistance following cardiac transplantation [Sinoway *et al*, 1988].

It has been reported that skeletal muscle changes parallel changes in muscle blood

flow [Drexler *et al*, 1992; Sullivan *et al*, 1991]. Indeed, peak oxygen consumption and exercise capacity have been shown to correlate with leg blood flow [Weber *et al*, 1982; Wilson *et al*, 1984; Sullivan *et al*, 1989] although subsequent studies suggested otherwise [Wilson *et al*, 1993; Volterrani *et al*, 1994]. This may be due to different patient selection and the methodology of assessing blood flow. Some studies quantitate absolute blood flow using thermodilution methods whilst in others, blood flow is assessed per unit tissue volume using venous occlusion plethysmography. The former may be reduced in chronic heart failure secondary to skeletal muscle wasting.

Abnormal Muscle Metabolism

Intrinsic muscle abnormalities and underperfusion result in excessive lactate production and early onset of intramuscular acidosis as suggested by increased arterial and venous lactate levels at a given workload in heart failure [Weber *et al*, 1985a; Sullivan *et al*, 1988a & 1989; Wilson *et al*, 1993]. Using ^{31}P magnetic resonance spectroscopy, it has been shown that chronic heart failure patients develop greater reductions in phosphocreatine and intracellular pH than controls for a given workload [Wiener *et al*, 1986; Massie *et al*, 1987a & 1987b]. Phosphocreatine represents a rapidly available energy reserve and can be transferred to ADP for the anaerobic regeneration of ATP. The increased phosphocreatine depletion and lower intracellular pH are associated with fatigue. Mancini and colleagues [1989] suggested that this increased phosphocreatine depletion may be related in part to muscle atrophy since for a given workload, the muscle fibres in atrophied muscle experience greater workloads relative to normal muscle and hence greater metabolic changes.

Muscle Strength and Fatiguability

Lipkin *et al* [1988] and Buller *et al* [1991] demonstrated reduced quadriceps muscle strength in chronic heart failure. Early quadriceps muscle fatiguability has also been demonstrated [Buller *et al*, 1991; Minotti *et al*, 1991]. Traditionally, muscle underperfusion is thought to be the main cause of fatigue but it has been shown that fatiguability is independent of blood flow [Wilson *et al*, 1984]. One study showed the improvement in exercise capacity following physical training was not dependent on an increase in blood flow [Minotti, 1991] but another demonstrated it may be associated with it [Hambrecht *et al*, 1995]. Thus, it may be that intrinsic muscle changes are the predominant determinants of fatiguability in chronic heart failure; blood flow *per se* does not affect fatiguability but improvement of flow, in the longer term, may affect the intrinsic muscle changes leading to better exercise tolerance.

Relationship to Ventilation

Abnormal muscle metabolism may be sensed by metaboreceptors causing increased exercise ventilation. As mentioned earlier, physical training can improve the exercise capacity of patients with chronic heart failure [Sullivan *et al*, 1988b; Coats *et al*, 1990; Minotti *et al*, 1990; Coats *et al*, 1992]. Other than improvement in exercise capacity, there is also reversal in autonomic abnormalities and reduction in exercise ventilation [Coats *et al*, 1992]. It plausible that these may be related to the a reduction in the metaboreflex which is known to increase sympathetic tone [Shepherd, 1987; Floras 1993] and also stimulate ventilation [Kao, 1963]. Indeed, Piepoli *et al* [1994] have shown that forearm training reduced the metaboreflex effects in heart failure patients. As discussed earlier, potassium may be important in the control of ventilation. This is

released from exercising muscle and it has been shown that potassium handling may be abnormal in chronic heart failure with higher levels at matched workloads compared with normals [Barlow *et al*, 1994]. Increased arterial potassium may be sensed both by arterial chemoreceptors and muscle metaboreceptors increasing their gain and causing the hyperpnoea seen in this condition. Although the increase in arterial potasium parallels that in ventilation in chronic heart failure, the non-linear increase in ventilation at high workloads is not matched by a similar break-point in arterial potassium, suggesting that other metabolites are probably also involved [Clark *et al*, 1995b]. Other than potassium, it is also conceivable that the early onset of intramuscular acidosis due to excessive lactate production may stimulate the metaboreflex.

OBJECTIVES

The objectives of this thesis are to investigate the mechanisms of increased ventilatory response to exercise in patients with chronic heart failure, the basis of which remains poorly understood. They may also provide an insight into the understanding of the mechanisms of exercise limitation and breathlessness in this condition. In brief, the investigations carried out in this thesis focused on several aspects of chronic heart failure which hitherto have not been studied or remained to be explored due to limited research including:

i. the part played by peripheral and central arterial blood gas chemosensitivity in mediating the increased ventilatory response to exercise in chronic heart failure patients;

ii. the effects of altered chemosensitivity on the exercise tolerance of these patients;

iii. the role of respiratory muscles in determining exercise capacity and their

relationship with the ventilatory response to exercise and also with locomotor muscle strength in chronic heart failure;

iv. the presence of airway hyperresponsiveness in non-smoking stable chronic heart failure patients.

Because the assessment of the functional capacity of subjects in this thesis was objectively made by means of cardiopulmonary exercise testing with metabolic gas exchange analysis, this will be described in detail in Chapter 2 under the general methods section whilst methods used specifically in the course of investigations will be discussed as necessary in the relevant chapters. The investigations on chemosensitivity in chronic heart failure and interventions to alter this are included in Chapters 3, 4 and 5. This is followed by a chapter describing the effects of chronic hypoxaemia on chemosensitivity in relation to the ventilatory response to exercise in a group of cyanotic univentricular patients. This may further aid our understanding of the part played by the chemoreflex in the control of ventilation. The role of the respiratory muscles in determining exercise capacity and their relationship with locomotor muscle strength will be investigated in Chapter 7. Finally, the significance of airway hyperresponsiveness in chronic heart failure patients not confounded by factors such as smoking and acute decompensation is discussed in Chapter 8.

Chapter 2

GENERAL METHODS - CARDIOPULMONARY EXERCISE TESTING

Introduction

Symptoms of chronic heart failure such as dyspnoea and muscle fatigue are limiting and manifest especially during exertion. Although indices such as left ventricular ejection fraction, left ventricular dimensions and haemodynamic measurements reflect the degree of cardiac dysfunction, there is little correlation between these and exercise capacity [Franciosa *et al*, 1979; Higginbotham *et al*, 1983; Franciosa *et al*, 1984; Sullivan *et al*, 1988]. Thus exercise testing remains an objective assessment of the functional capacity of patients with this condition [Franciosa, 1984; Weber & Janicki, 1985; Lipkin, 1987; McElroy *et al*, 1988; McKelvie & Jones, 1989; Wasserman, 1990]. While electrocardiographic and haemodynamic changes during maximal exercise testing are sufficient for the assessment of patients with ischaemic heart disease, coupling metabolic gas exchange analysis to maximal exercise testing provides a more objective test in chronic heart failure patients [Weber *et al*, 1982; Matsumara *et al*, 1983; Lipkin *et al*, 1984; Wilson *et al*, 1986; Wasserman, 1990].

In this thesis, cardiopulmonary exercise testing is used to assess the functional capacity of patients and their ventilatory response to exercise. It is therefore relevant to present an overview of the various parameters measured during testing and to give a summary of the known patterns of metabolic gas exchange in chronic heart failure. Having discussed this, the method used to analyse metabolic gas exchange in our exercise laboratory will be presented.

Background

According to the Fick principle, cardiac output is equal to oxygen consumption divided by the arteriovenous oxygen difference. The arteriovenous oxygen difference represents oxygen extraction by the peripheral tissues which increases to a maximum during exercise. By rearranging the Fick equation above, it can be seen that as the arteriovenous oxygen difference reaches a constant value during peak exercise, the total body oxygen consumption becomes a function of cardiac output. Therefore not only does cardiopulmonary exercise testing help assess functional capacity, it also reflects cardiac output during maximal exercise.

During the cardiopulmonary exercise test, the patient wears a nose clip and breathes through a respiratory valve that separates inspired and expired air. Measurements of oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and minute ventilation ($\dot{V}_E$) are made either breath-by-breath using mass spectrometry and a pneumotachograph [Beaver *et al*, 1981] or using the inert gas dilution method with mass spectrometry alone [Davies & Denison, 1979]. Simultaneous electrocardiographic and blood pressure monitoring is performed. From the oxygen consumption, carbon dioxide output and minute ventilation, a series of derivatives may be obtained including anaerobic threshold, respiratory exchange ratio (R), the ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}O_2$ ratio), the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$ ratio), oxygen pulse and the ventilatory response to exercise, as characterised by the regression slope relating minute ventilation to carbon dioxide output during exercise.

Maximal Oxygen Consumption

This may be defined as the oxygen consumption which has reached a plateau

despite increases in work rate [Taylor *et al*, 1955]. As this reflects the cardiac output, the maximal oxygen consumption is reduced in chronic heart failure patients compared with normal subjects. Patients with a maximal oxygen consumption of 16 to 20 ml/kg/min are considered to have mild to moderate functional impairment, those with a value of 10 to 16 ml/kg/min moderate to severe functional impairment and those with a maximal oxygen consumption of less than 10 ml/kg/min severe functional impairment. On a similar basis, these patients can also be categorised into groups A - D (A >20 ml/kg/min; B 16-20 ml/kg/min; C 10-16 ml/kg/min; D <10 ml/kg/min) according to their maximal oxygen consumption [Weber & Janicki, 1985b; McElroy *et al*, 1988]. Figure 2.1 shows a graph of oxygen consumption during incremental exercise of two patients with different severity of chronic heart failure compared with an age-matched normal subject obtained in our laboratory.

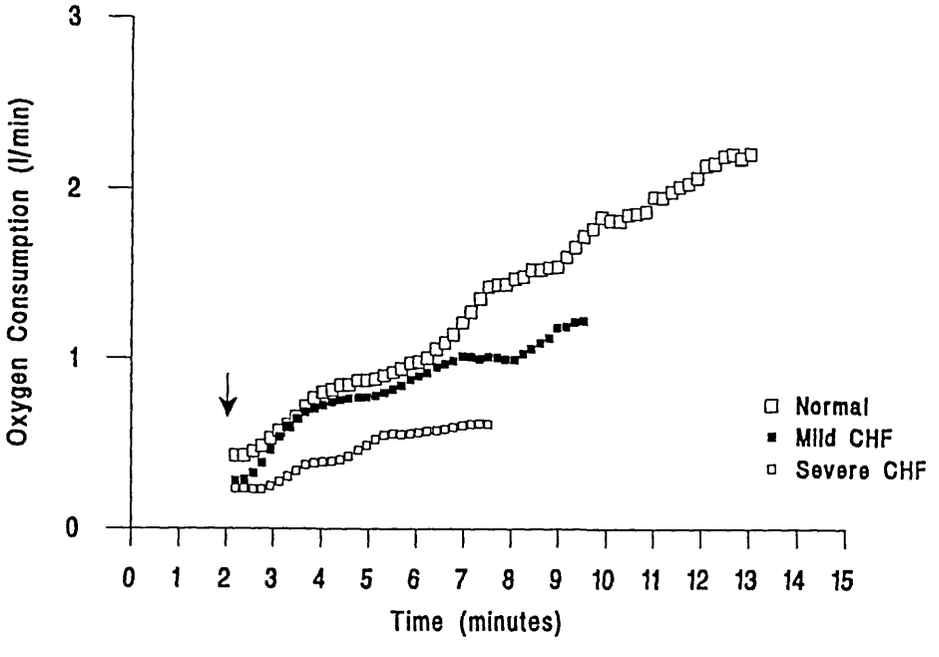

Figure 2.1 The graph shows the oxygen consumption of two chronic heart failure (CHF) patients and an age-matched healthy subject during incremental exercise. Arrow denotes start of exercise.

Lipkin *et al* [1984] found that maximal oxygen consumption was related to functional class as assessed by the New York Heart Association criteria although other investigators have not [Weber *et al*, 1982; Franciosa, 1984]. Franciosa [1984] suggested that the lack of correlation between New York Heart Association functional class II and III and maximal oxygen consumption in his study indicated that cardiopulmonary exercise testing was more discriminating in categorising patients according to functional impairment.

It is not always clear whether the oxygen consumption has reached a plateau because of a small upward drift especially in normal subjects [Myers *et al*, 1989] and by the same token, in patients with mild disease. In such instances, supplementary criteria to define maximal exercise independent of volition may be useful. These include the attainment of predicted maximal heart rate and a respiratory exchange ratio of >1.1 [Sharkey, 1991; McKelvie & Jones, 1989].

Buller and Poole-Wilson [1988] used a mathematical model relating $\dot{V}O_2$ and $\dot{V}CO_2$ to derive an estimate of maximal oxygen consumption independent of exercise duration. The pattern of the metabolic gas exchange data points during exercise is best described by the equation $y = ax\text{-}bx^2$ (Equation 1), where x is carbon dioxide output, y oxygen consumption and the values a and b that provide the "best fit" curve are obtained mathematically as shown diagramatically in Figure 2.2. From equation 1, $dy/dx = a - 2bx$ (Equation 2); thus, when $dy/dx = 0$ and oxygen consumption reaches a plateau, $x = a/2b$ (Equation 3). Substituting equation 3 into equation 1, $y = a^2/4b$ which they have termed *the extrapolated maximal oxygen consumption.* This is useful in instances when a true plateau in oxygen consumption is not seen. It is relatively independent of exercise duration and may help avoid variation due to differences in

motivation (Clark, Poole-Wilson & Coats, 1994).

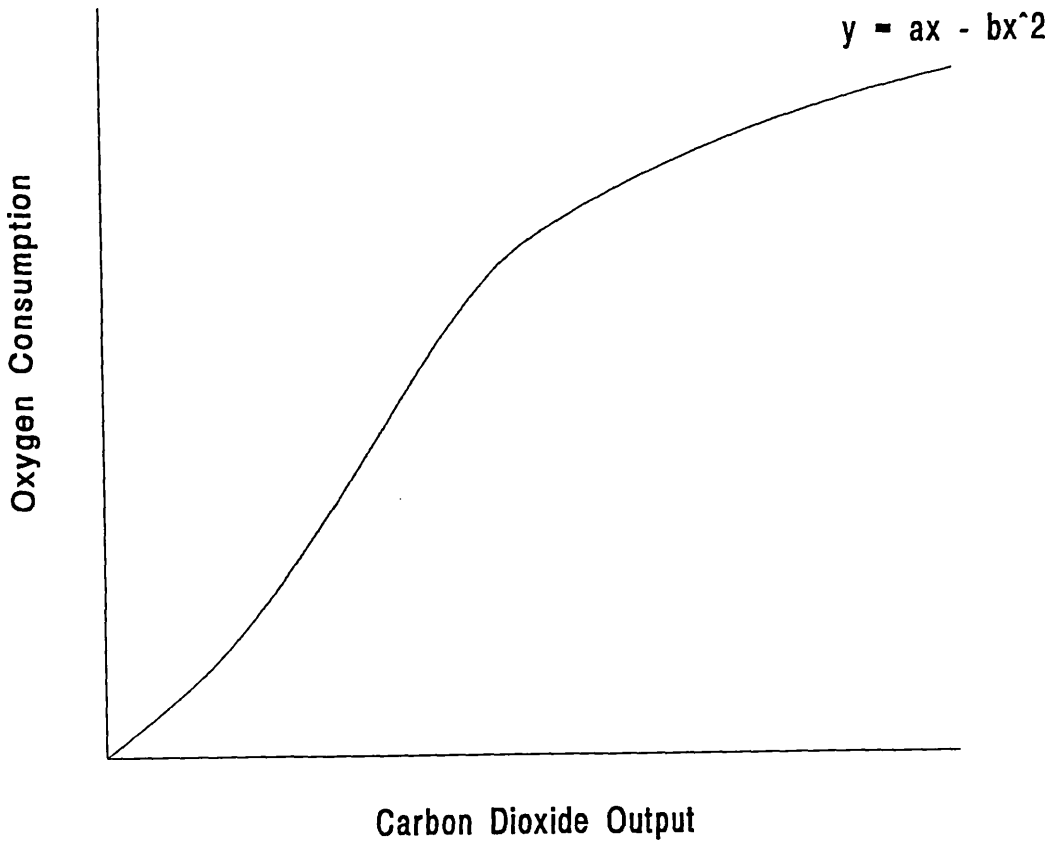

Figure 2.2 The curve relating oxygen consumption to carbon dioxide output during cardiopulmonary exercise testing is best described by the equation $y = ax - bx^2$ and is used to derive the *extrapolated maximal oxygen consumption.*

Anaerobic Threshold

Wasserman and McIlroy [1964] introduced the concept of anaerobic threshold to measure cardiopulmonary capacity. This may be defined as the level of oxygen consumption during exercise above which aerobic energy production is supplemented by anaerobic mechanisms. Above this threshold, there is a sustained rise in blood lactate due to increased production by exercising muscle with an associated increase in ventilation.

The blood lactate is buffered by plasma bicarbonate causing an increase in carbon dioxide production [Wasserman *et al*, 1967]. Because the anaerobic threshold is usually reached at 60 to 70% of maximal oxygen consumption, it may be used as a marker that the patient is on the way to a maximal cardiopulmonary test.

The anaerobic threshold can be determined visually and non-invasively by observing the disproportionate increase in carbon dioxide output and ventilation in relation to oxygen consumption as shown in Figure 2.3; there is also a concomitant steeper rise in the respiratory exchange ratio and in end-tidal oxygen concentration due to the disproportionate increase in ventilation [Wasserman *et al*, 1973]. However. there is much reviewer variability and frequently it is not obtainable [Lipkin *et al*, 1985; Cowley AJ *et al*, 1990].

The anaerobic threshold may also be assessed invasively by determining the onset of blood lactate accumulation [Wasserman *et al*, 1973; Matsumara *et al*, 1983; Wilson *et al*, 1983; Simonton *et al*, 1988; Sullivan & Cobb, 1990; Metra *et al*, 1990] although again, it is not always possible to establish this [Yeh *et al*, 1983]. This has also led to the concept of anaerobic threshold and its linkage to lactate accumulation being questioned. Lactate production is also known to occur in aerobic conditions and anaerobic metabolism can be present at rest [Davis, 1985; Brooks, 1985]. In general, its use in cardiopulmonary exercise testing is limited because of the variability in determining its value.

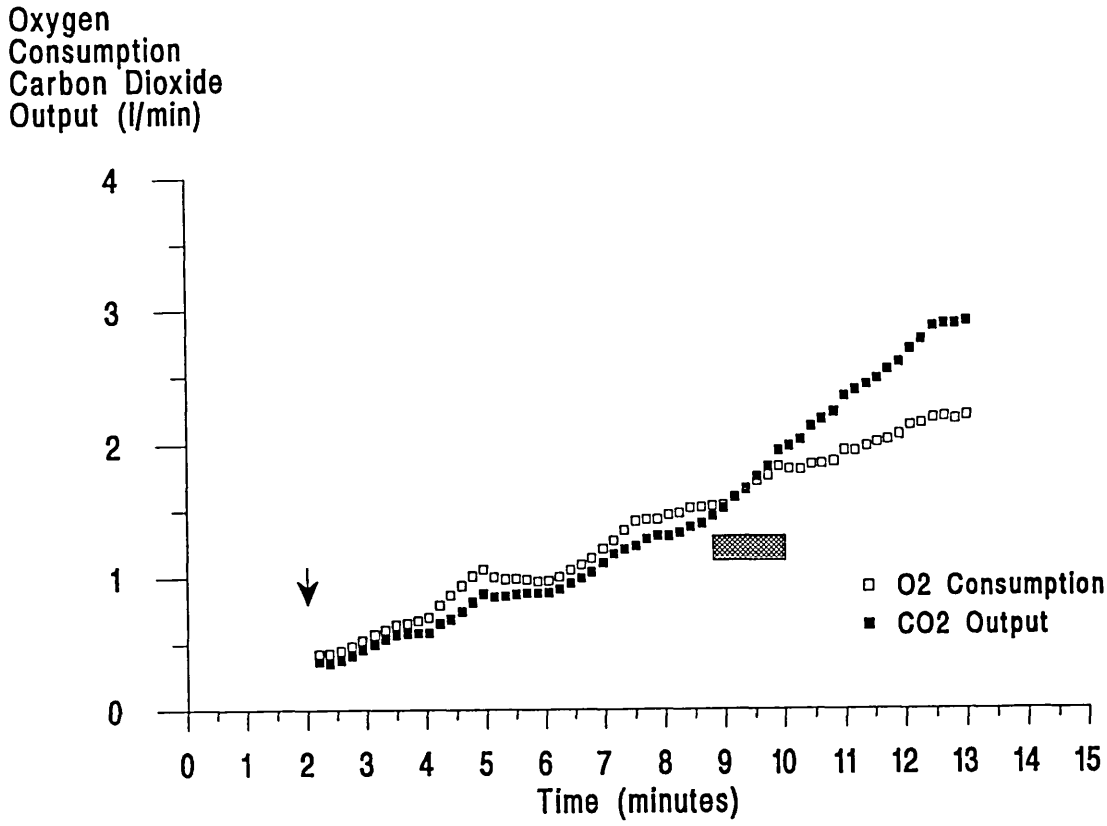

Figure 2.3 The graph shows the oxygen consumption and carbon dioxide output of a healthy subject during cardiopulmonary exercise testing. Arrow denotes start of exercise. The grey area represents the start of anaerobic metabolism, the precise onset may sometimes be indeterminate as discussed in the text.

Respiratory Exchange Ratio

The respiratory exchange ratio is the ratio of carbon dioxide output to oxygen consumption. This is about 0.8 at rest (250 ml/min for resting carbon dioxide output and 300 ml/min for oxygen consumption) [Otis, 1964]. During early exercise, oxygen consumption and carbon dioxide output increase at the same rate as seen in Figure 2.3. At about 60 to 70% of maximal oxygen consumption, carbon dioxide output and minute ventilation begin to increase at a greater rate than oxygen consumption, heralding the onset of anaerobic threshold, with the respiratory exchange ratio also increasing more

steeply. As mentioned earlier, exercising subjects to a respiratory exchange ratio of greater that 1.1 provides a guide that the subjects are near a maximal cardiopulmonary exercise test.

Minute Ventilation

Minute ventilation increases in proportion to both oxygen consumption and carbon dioxide production during incremental exercise until the onset of anaerobic threshold [Wasserman *et al*, 1973]. In fact for work increments of one minute, it increases in proportion to carbon dioxide output for about two minutes after anaerobic threshold; this period is also known as the isocapnic buffering period, after which ventilation increases further due to increasing lactic acidosis [Wasserman, 1978]. The relationship between minute ventilation and carbon dioxide output is more linear and less variable than that between minute ventilation and oxygen consumption [Wasserman & Whipp, 1975]. As such, an index of ventilatory drive can be obtained by calculating the slope relating minute ventilation to carbon dioxide output ($\dot{V}_E$-$\dot{V}CO_2$ regression slope) using linear regression analysis [Wasserman & Whipp, 1975; Buller & Poole-Wilson, 1990]. Chronic heart failure patients often have an excessive exercise ventilatory response and show a steeper $\dot{V}_E$-$\dot{V}CO_2$ regression slope. The $\dot{V}_E$-$\dot{V}CO_2$ slope has also been shown to be inversely related to maximal oxygen consumption and is itself a measure of the severity of chronic heart failure [Buller & Poole-Wilson, 1990]. Figure 2.4 illustrates the relation between minute ventilation and the rate of carbon dioxide production of two chronic heart failure patients of different severity compared with a normal subject. It shows a steeper $\dot{V}_E$-$\dot{V}CO_2$ slope in the more severe patient.

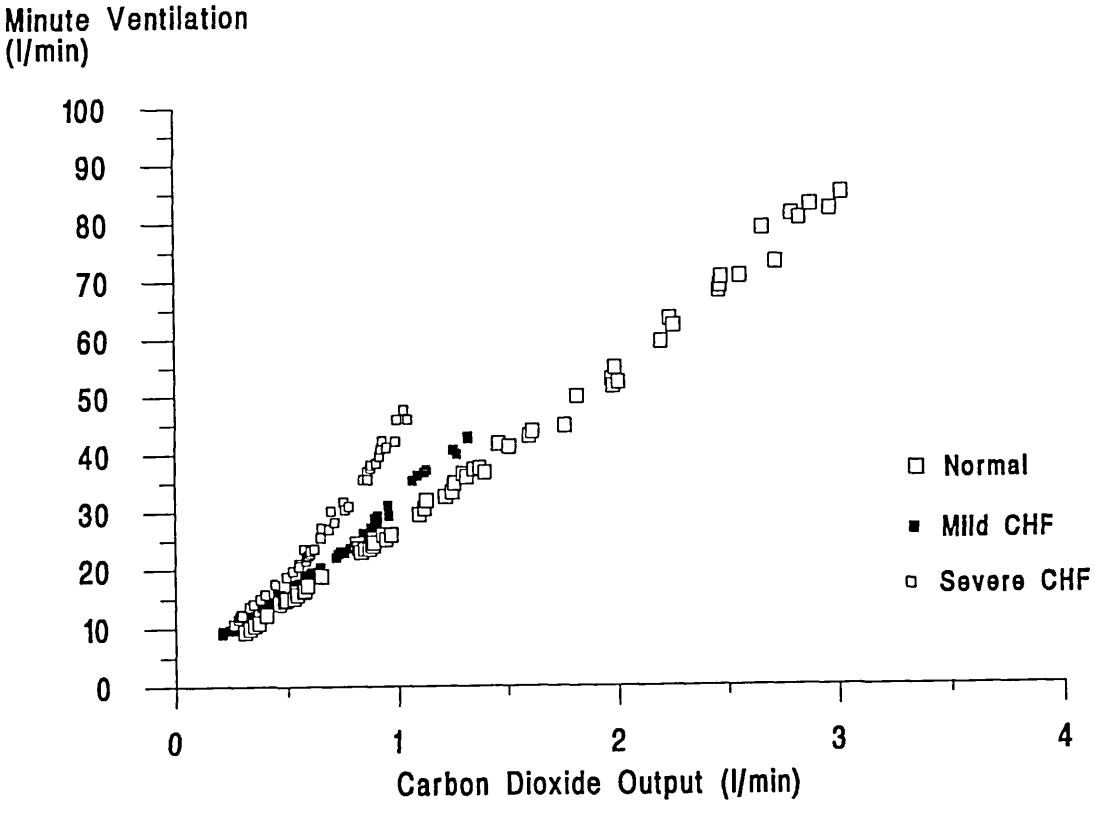

Figure 2.4 Severe chronic heart failure (CHF) patients have a steeper slope of the regression line relating minute ventilation and carbon dioxide output as illustrated in this figure.

If the $\dot{V}_E/\dot{V}CO_2$ ratio (i.e. the ventilatory equivalent for carbon dioxide) at a particular instant in time is plotted against work rate, $\dot{V}_E/\dot{V}CO_2$ ratio is seen to decrease until a plateau in normal subjects and in mild chronic heart failure patients [Clark *et al*, 1993]. This is thought to be due to a reduction in dead space ventilation consequent to improved perfusion of hitherto poorly perfused regions of the lungs during incremental exercise. In those with more severe chronic heart failure, this $\dot{V}_E/\dot{V}CO_2$ ratio may decrease initially and then rise at the end of exercise [Clark *et al*, 1993]. An increase in dead space ventilation [Sullivan *et al*, 1988; Sovijarvi *et al*, 1992] and possibly a non-carbon dioxide drive to ventilation may account for this [Clark & Coats, 1992].

Oxygen Pulse

This is derived by dividing oxygen consumption by heart rate. Since cardiac output is equal to heart rate multiplied by stroke volume and from the Fick equation, cardiac output is also equal to oxygen consumption divided by arteriovenous oxygen difference, oxygen pulse therefore represents *stroke volume* during maximal exercise. Oxygen pulse is reduced at peak exercise in chronic heart failure [Nery *et al*, 1983; Lipkin *et al*, 1984; Sovijarvi *et al*, 1992]. The possibility of downregulation of beta-receptors in chronic heart failure [Bristow et al, 1982] and the concurrent use of digoxin in patients have however made the measurement of heart rate not a reliable index in chronic heart failure patients. Thus oxygen pulse, like target heart rate, in heart failure may have its limitation.

Summary

Cardiopulmonary exercise testing offers an objective way to assess the functional capacity of chronic heart failure patients. The expected abnormalities in metabolic gas exchange data and their derived parameters are accordingly summarised in Table 2.1.

	Chronic Heart Failure
Maximal Oxygen Consumption	Reduced
Anaerobic Threshold	Reduced
$\dot{V}_E$-$\dot{V}CO_2$ regression slope	Increased
Oxygen Pulse	Reduced
Arterial Oxygen Desaturation	Negligible

Table 2.1 Summary of observed patterns of respiratory gas exchange during exercise in chronic heart failure

Mass Spectrometry

Having given an overview of cardiopulmonary exercise testing, it is relevant to discuss the analysis of metabolic gas exchange variables in our exercise laboratory. The measurement of gases using mass spectrometry is central in such analysis.

The principle of mass spectrometer was first developed by Aston in 1919 and uses the application of magnetic and electric fields to measure the relative concentrations of gases. The gas mixture to be analysed is first introduced to a vacuum (about 10^{-6} mm Hg) and ionised by an electron beam as shown in Figure 2.5. The positive ions which are formed are then accelerated in an electric field by an amount directly proportional to their charge and inversely proportional to their mass. A magnetic field at right angle to the accelerating positive ions deflects them by an amount dependent on their charge/mass ratio so that the heavier the ions, the less the deflection and the more the

charge, the greater the deflection. A gas mixture will thus disperse as a function of charge/mass ratio of its constituent ions. A secondary electron multiplier amplifies the electric charge accumulated by the collecting electrode and a voltage is recorded at each charge/mass ratio characteristic of the respective constituents of the gas mixture. The voltage signal can be converted to a concentration by reference to a relative signal from known calibration gases. For calibration gases in our laboratory, a gas mixture is obtained from the British Oxygen Company comprising 0.5% helium, 15% oxygen, 5% carbon dioxide, 1% argon and the remainder, nitrogen. A typical mass spectrum of the calibration gases is shown in Figure 2.6.

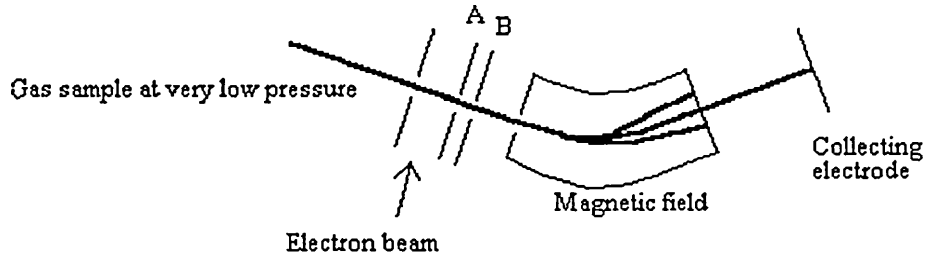

Figure 2.5 The principle of mass spectrometry. Positive ions created by the electron beam are accelarated by the electric field between A and B. They are then deflected by a magnetic field according to their charge/mass ratio as discussed in the text.

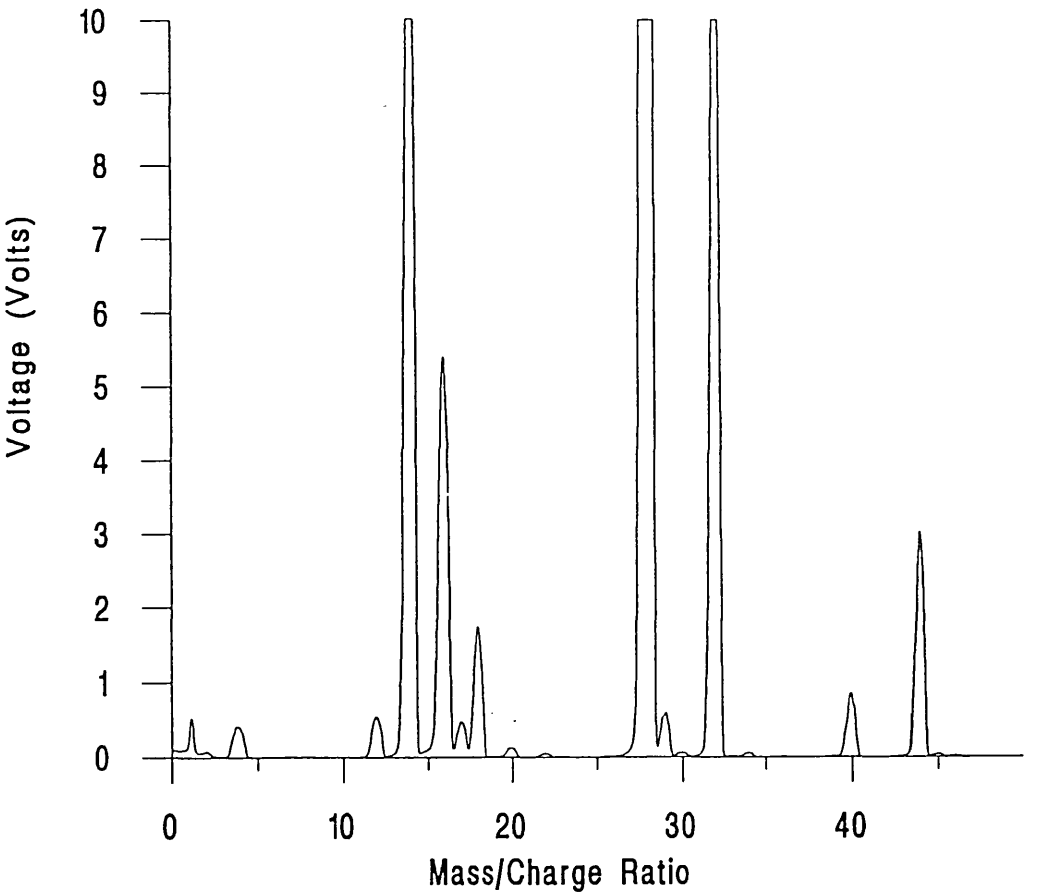

Figure 2.6 Mass spectrum of the calibration gases which consisted of helium (mass/charge=4), oxygen (atomic and molecular, 16 & 32), nitrogen (14 & 28), argon (40) and carbon dioxide (44). Peaks for hydrogen (1 & 2), carbon (12) and water (18) are also seen.

The mass spectrometer and its accompanying software used in this thesis is an Amis 2000 system (Innovision, Odense, Denmark). The system was calibrated each time before use. In order to assess the reliability of the system following calibration with calibration gases above, two experiments were performed to see if the mass spectrometer was able to measure the concentration of aliquots of 100% oxygen and of 13% carbon dioxide serially diluted with pure nitrogen. The results are shown in Figures 2.7 and 2.8 with the mass spectrometer measurements similar to the known concentrations of the gases, giving a correlation coefficient of 0.99 respectively.

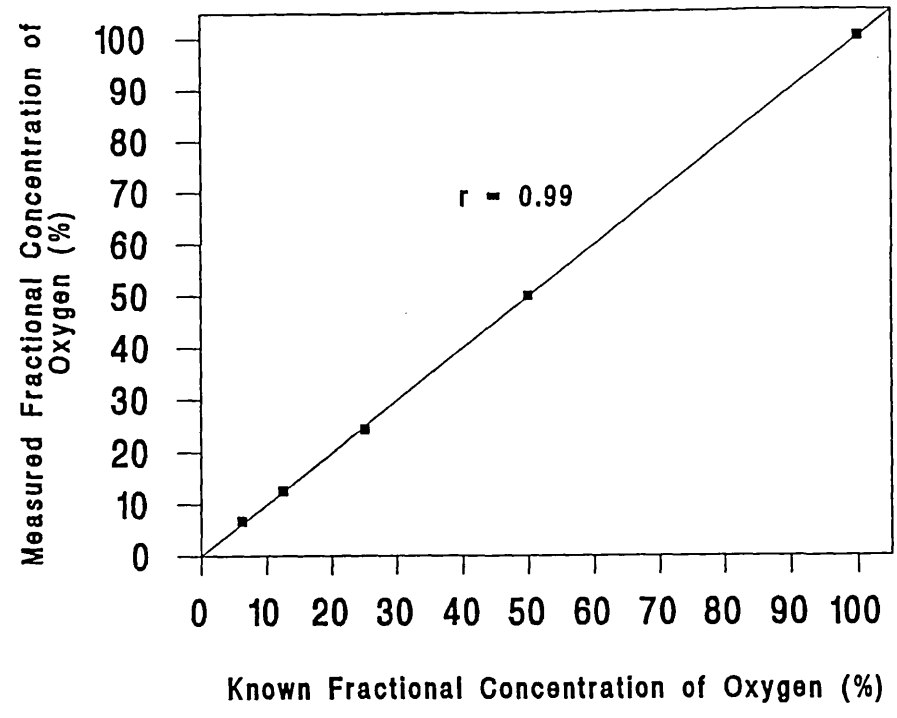

Figure 2.7 Known concentrations of oxygen are measured with mass spectrometry. The measured values correlate well with the known concentrations as shown in this figure.

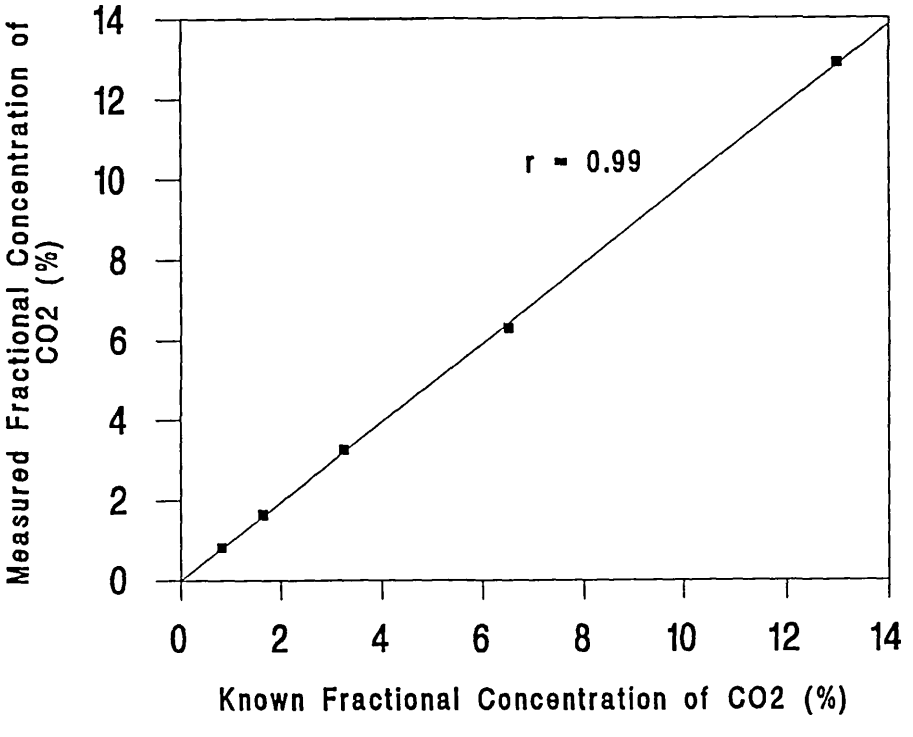

Figure 2.8 Known concentrations of carbon dioxide are measured with mass spectrometry. The measured values again correlate well with the known concentrations as shown in this figure.

Derivation of Gas Exchange Variables

The derivation of gas exchange variables in this thesis was mainly done using the inert indicator gas dilution technique [Denison & Davies, 1989]. Helium was the indicator gas used. Subjects wore a nose clip and breathed through a respiratory valve that separated inspired and expired air, the latter being collected in a mixing box containing baffles. The expired air was evenly mixed with the inert indicator gas introduced at a rate of 100 ml/min. Inspired air was sampled at the mouth while expired air and the indicator gas were sampled at the outlet of the mixing box every 10 seconds and analysed by mass spectrometry.

From the inspired gas concentration, the flow rate of indicator gas and the concentration of expired and indicator gases at the mixing box, the metabolic gas exchange variables and ventilation were derived on line (see Appendix 1 for the principles of derivation).

An experiment was also performed to assess whether the mixing box technique closely measures the rate of air flow into it. Different volumes of air per minute was passed into the mixing box using a calibration syringe (Vitalograph, USA) by varying the volume per stroke and also the number of strokes emptied per minute. This is shown in Figure 2.9 with a correlation coefficient of 0.99 and illustrates the reliability of the method.

Apart from the inert gas dilution technique to measure gas exchange variables, another method may be used based on the breath-by-breath analysis of the inspired and expired gas concentrations at the mouth and the measurement of air flow using a pneumotachometer to derive minute ventilation. The latter is derived by means of integrating the flow rate as measured by the pneumotachometer and the duration per

breath. The disadvantage of this method is that it generates much raw data since it analyses each and every breath and therefore requires much computing memory. The measurement of metabolic gas exchange variables in this thesis was made using the inert gas dilution method unless stated otherwise.

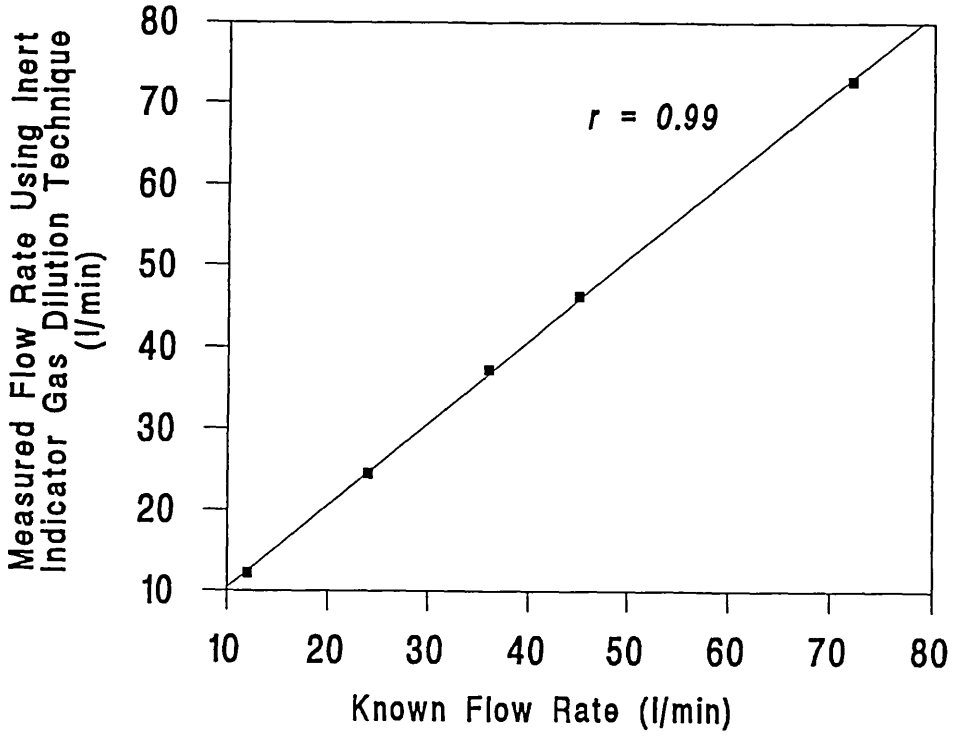

Figure 2.9 Known rates of air flow are measured with the inert indicator gas dilution technique. The measured values correlate well with the known rates of air flow as shown in this figure.

Exercise Protocols

It must be borne in mind that various exercise methods and protocols will elicit a different maximal oxygen consumption because of the different size of muscle groups involved. Treadmill exercise testing produces a 5 to 8 per cent higher maximal oxygen consumption than cycle ergometer [Astrand & Rodahl, 1986b]. Thus while some subjects may find it easier to go on a cycle ergometer than a treadmill, the maximal oxygen consumption must be assessed in relation to the method and exercise protocol used [Froelicher *et al*, 1974]. In this thesis, treadmill exercise testing using the Bruce Protocol [Bruce *et al*, 1963] with 3-minute work increments and the addition of a Stage "0" (1.0 mph, 5% gradient) was used. All subjects exercised until they could not continue because of exhaustion, guided by the attainment of R value of at least 1.1.

Reproducibility Studies

To assess the reproducibility of the metabolic gas exchange parameters including maximal oxygen consumption, anaerobic threshold, extrapolated oxygen consumption and $\dot{V}_E$-$\dot{V}CO_2$ regression slope, 4 normal volunteers and 8 chronic heart failure patients exercised until exhaustion on two occasions within 2 weeks apart, with a similar respiratory exchange ratio on each occasion.

The results are illustrated graphically in Figures 2.10 to 2.13. The coefficient of variation which is a measure of variability in relation to the mean of the various metabolic gas exchange variables [Bland, 1987] is given in Tables 2.2 to 2.5.

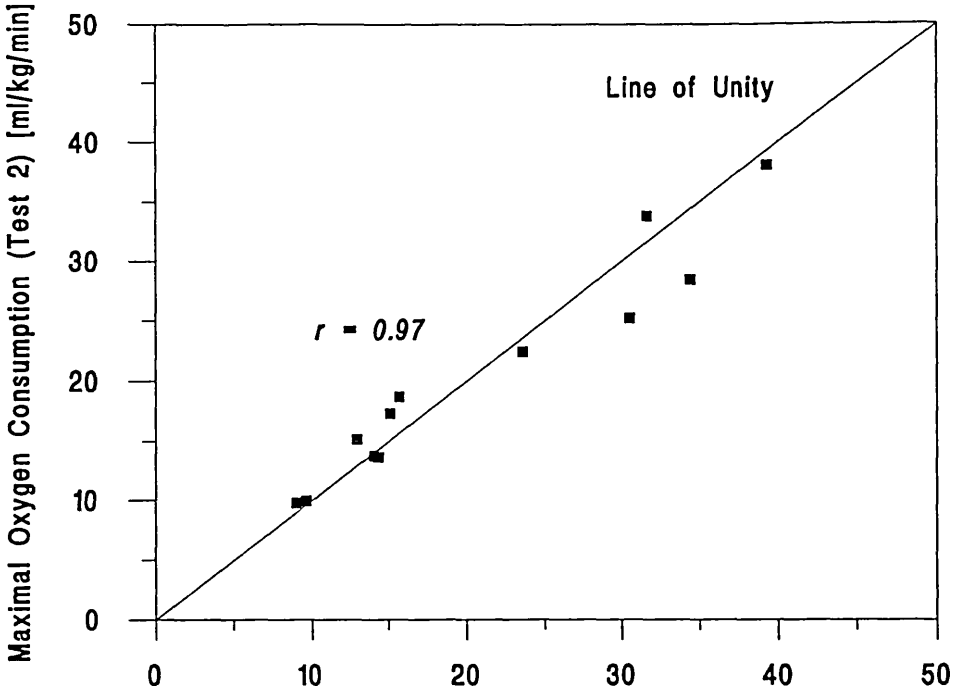

Figure 2.10 Reproducibility studies of maximal oxygen consumption in 12 subjects.

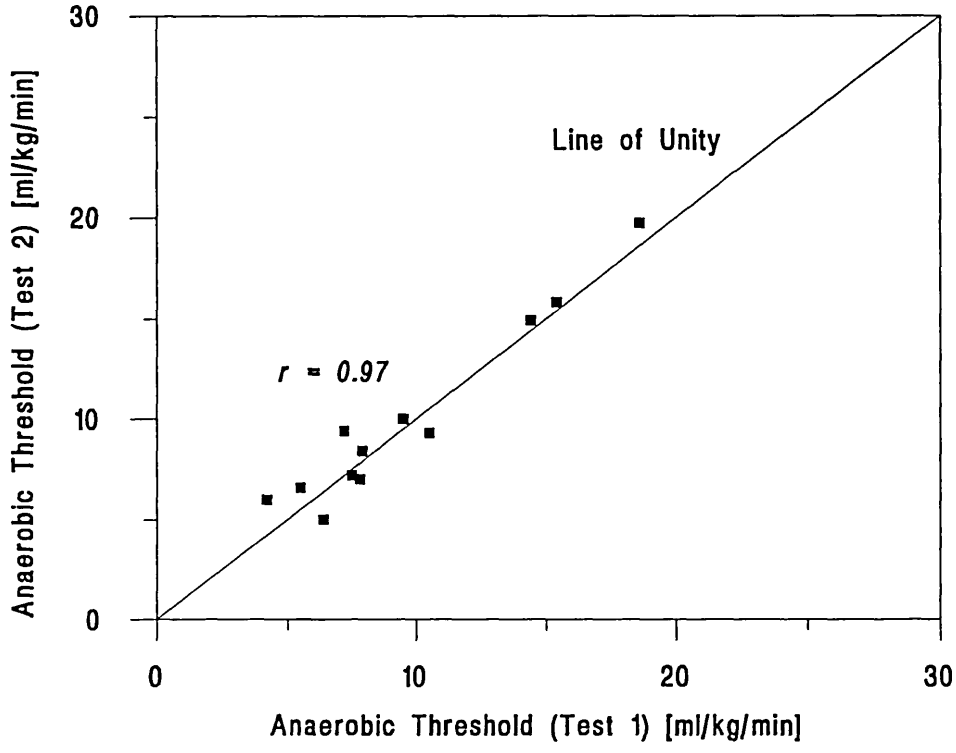

Figure 2.11 Reproducibility studies of anaerobic threshold in 12 subjects.

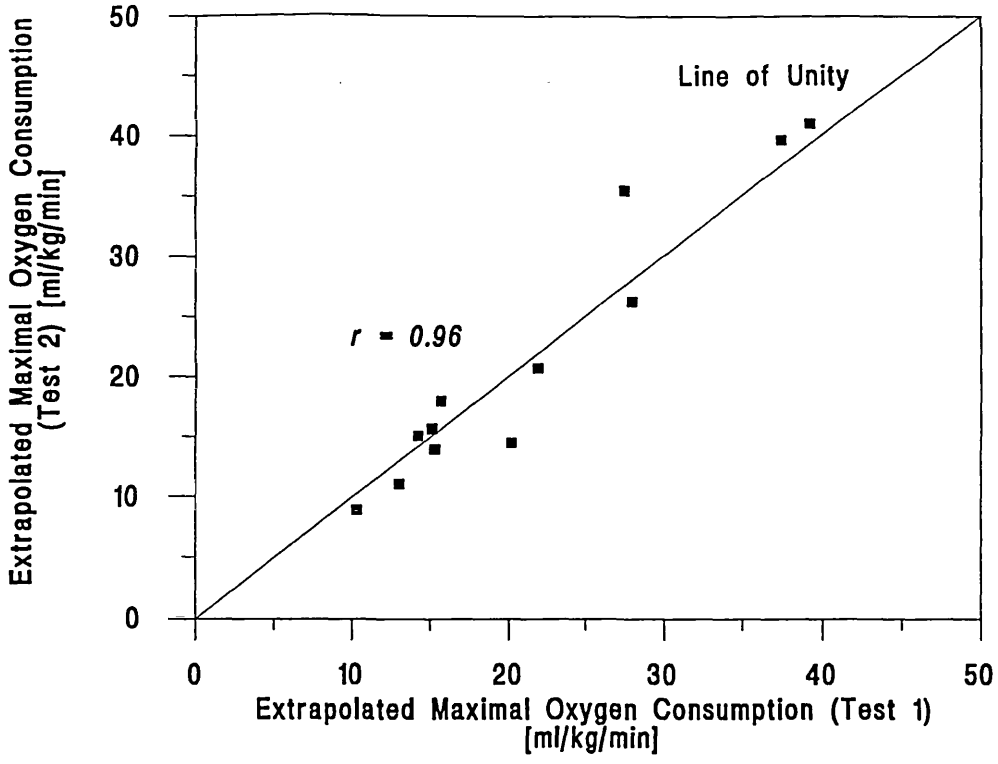

Figure 2.12 Reproducibility studies of extrapolated maximal oxygen consumption in 12 subjects.

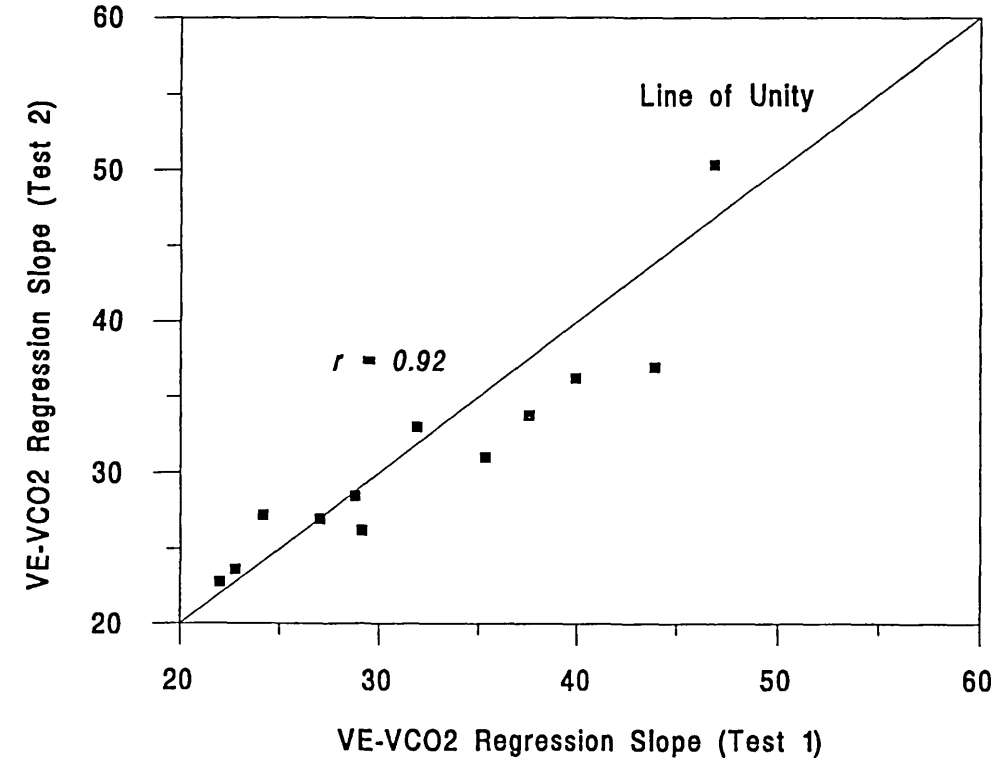

Figure 2.13 Reproducibility studies of the $\dot{V}_E$-$\dot{V}CO_2$ regression slope in 12 subjects.

Subject (n=12)	R(1)	R(2)	$m\dot{V}O_2$ (1) (ml/kg/min)	$m\dot{V}O_2$ (2) (ml/kg/min)	Mean [$m\dot{V}O_2$ (1) & (2)] (ml/kg/min)	Difference [$m\dot{V}O_2$(1)-$m\dot{V}O_2$(2)]	Square of Difference
1	1.20	1.11	14.3	13.5	13.9	0.8	0.64
2	1.17	1.11	12.9	15.1	14.0	-2.2	4.84
3	1.10	1.10	15.7	18.7	17.2	-3.0	9.0
4	1.10	1.12	15.1	17.3	16.2	-2.2	4.84
5	1.17	1.10	9.6	9.9	9.75	-0.3	0.09
6	1.13	1.21	9.0	9.8	9.4	-0.8	0.64
7	1.07	1.06	14.0	13.7	13.85	0.3	0.09
8	1.08	1.20	16.8	17.3	17.05	-0.5	0.25
9	1.18	1.15	30.5	25.2	27.85	5.3	28.09
10	1.17	1.17	31.6	33.7	32.65	-2.1	4.41
11	1.25	1.15	39.3	38.0	38.65	1.3	1.69
12	1.20	1.23	23.6	22.4	23.0	1.2	1.44
Mean	**1.15**	**1.14**	**19.4**	**19.6**	**19.5**	**-0.18**	
Total							**55.95**
SD							= square root of [Total/2n] = **1.53**
CV							= [SD / Overall Mean $m\dot{V}O_2$] X 100 = **7.85%**

R, respiratory exchange ratio; $m\dot{V}O_2$, maximal oxygen consumption; SD, standard deviation; CV, coefficient of variation.

Table 2.2 The coefficient of variation of maximal oxygen consumption in 12 subjects who had the cardiopulmonary exercise testing on 2 occasions. Subjects 1-8 were patients with chronic heart failure. The number in parentheses indicates the first and second test respectively.

Subject ($n=12$)	$R(1)$	$R(2)$	AT (1) (ml/kg/min)	AT (2) (ml/kg/min)	Mean [AT(1) & AT(2)] (ml/kg/min)	Difference [AT(1)-AT(2)] (ml/kg/min)	Square of Difference
1	1.20	1.11	7.9	8.4	8.15	-0.5	0.25
2	1.17	1.11	5.5	6.6	6.05	-1.1	1.21
3	1.10	1.10	7.2	9.4	8.3	-2.2	4.84
4	1.10	1.12	7.8	7.0	7.4	0.8	0.64
5	1.17	1.10	4.2	6.0	5.1	-1.8	3.24
6	1.13	1.21	7.5	7.2	7.35	0.3	0.09
7	1.07	1.06	6.4	5.0	5.7	1.4	1.96
8	1.08	1.20	9.6	9.6	0	0	0
9	1.18	1.15	10.5	9.3	9.9	1.2	1.44
10	1.17	1.17	15.4	15.8	15.6	-0.4	0.16
11	1.25	1.15	14.4	14.9	14.65	-0.5	0.25
12	1.20	1.23	9.5	10.0	9.75	-0.5	0.25
Mean	**1.15**	**1.14**	**8.8**	**9.1**	**8.95**	**-0.27**	
Total							**14.09**
SD							= square root of [Total/2n] = **0.77**
CV							= [SD / Overall Mean AT] X 100 = **8.54%**

R, respiratory exchange ratio; AT, anaerobic threshold; SD, standard deviation; CV, coefficient of variation.

Table 2.3 The coefficient of variation of anaerobic threshold in 12 subjects who had the cardiopulmonary exercise testing on 2 occasions. Subjects 1-8 were patients with chronic heart failure. The number in parentheses indicates the first and second test respectively.

Subject (n=12)	R(1)	R(2)	EMOC (1) (ml/kg/min)	EMOC (2) (ml/kg/min)	Mean EMOC (1) & (2) (ml/kg/min)	Difference [EMOC(1)-EMOC(2)]	Square of Difference
1	1.20	1.11	15.3	14.0	14.65	1.3	1.69
2	1.17	1.11	15.1	15.7	15.4	-0.6	0.36
3	1.10	1.10	15.7	18.0	16.95	-2.3	5.29
4	1.10	1.12	14.2	15.1	14.65	-0.9	0.81
5	1.17	1.10	12.0	11.1	11.55	0.9	0.81
6	1.13	1.21	10.3	9.0	9.65	1.3	1.69
7	1.07	1.06	15.2	14.5	14.85	0.7	0.49
8	1.08	1.20	16.7	16.1	16.4	0.6	0.36
9	1.18	1.15	28.0	26.2	27.1	1.8	3.24
10	1.17	1.17	39.2	40.9	40.05	-1.7	2.89
11	1.25	1.15	37.4	39.5	38.45	-2.1	4.41
12	1.20	1.23	21.9	20.7	21.3	1.2	1.44
Mean	**1.15**	**1.14**	**20.08**	**20.07**	**20.075**	**0.017**	
Total							**23.48**
SD							= square root of [Total/2n] = **0.99**
CV							= [SD / Overall Mean EMOC] X 100 = **4.93%**

R, respiratory exchange ratio; EMOC, extrapolated maximal oxygen consumption; SD, standard deviation; CV, coefficient of variation.

Table 2.4 The coefficient of variation of extrapolated maximal oxygen consumption in 12 subjects who had cardiopulmonary exercise testing on 2 occasions. Subjects 1-8 were patients with chronic heart failure. The number in parentheses indicates the first and second test respectively.

Subject (n=12)	R(1)	R(2)	$\dot{V}_E$-$\dot{V}CO_2$ (1)	$\dot{V}_E$-$\dot{V}CO_2$ (2)	Mean $\dot{V}_E$-$\dot{V}CO_2$ (1) & (2)	Difference [$\dot{V}_E$-$\dot{V}CO_2$(1)-$\dot{V}_E$-$\dot{V}CO_2$ (2)]	Square of Difference
1	1.20	1.11	27.02	26.96	26.99	0.06	0.0036
2	1.17	1.11	31.91	32.98	32.45	-1.07	1.14
3	1.10	1.10	39.89	36.21	38.05	3.68	13.54
4	1.10	1.12	43.90	36.94	40.42	6.96	48.44
5	1.17	1.10	37.51	33.76	35.64	3.75	14.06
6	1.13	1.21	35.31	30.99	33.15	4.32	18.66
7	1.07	1.06	46.86	50.37	48.62	-3.51	12.32
8	1.08	1.20	45.87	40.99	43.43	4.88	23.81
9	1.18	1.15	29.13	26.22	27.68	2.91	8.47
10	1.17	1.17	22.0	22.75	22.38	-0.75	0.56
11	1.25	1.15	28.8	28.5	28.65	0.3	0.09
12	1.20	1.23	24.13	27.19	25.66	-3.06	9.36
Mean	**1.15**	**1.14**	**34.36**	**32.82**	**33.59**	**1.54**	
Total							**150.48**
SD							= square root of [Total / 2n] = **2.50**
CV							= [SD / Overall Mean $\dot{V}_E$-$\dot{V}CO_2$] X 100 = **7.45%**

R, respiratory exchange ratio; $\dot{V}_E$-$\dot{V}CO_2$ slope, regression slope relating minute ventilation to carbon dioxide output; SD, standard deviation; CV, coefficient of variation.

Table 2.5 The coefficient of variation of the regression slope relating minute ventilation to carbon dioxide output in 12 subjects who had cardiopulmonary exercise testing on 2 occasions. Subjects 1-8 were patients with chronic heart failure. The number in parenthesis indicates the first and second test respectively.

Discussion

Cardiopulmonary exercise testing offers an objective way to assess the functional capacity of chronic heart failure patients. The expected abnormalities in metabolic gas exchange data and their derived parameters were accordingly summarised in Table 2.1 earlier. The reproducibility of maximal oxygen consumption, anaerobic threshold, extrapolated maximal oxygen consumption and the $\dot{V}_E$-$\dot{V}CO_2$ regression slope was good, all giving a mean coefficient of variation of $<10\%$. The reproducibility of maximal oxygen consumption agrees closely with other studies [Bruce *et al*, 1973; Weber *et al*, 1982; Dickstein *et al*, 1988; Lipkin *et al*, 1985; Elborn *et al*, 1990]. The reproducibility may improve further with repeated exercise testing as the subject becomes more familiar with the test [Elborn *et al*, 1990] although many of the patients in this thesis have already had previous cardiopulmonary exercise testing performed in the past. As expected, the coefficient of variation for anaerobic threshold was the highest probably due to reviewer variability as discussed earlier.

In the following chapters, cardiopulmonary exercise testing is used repeatedly as a means to assess the functional capacity and the ventilatory response to exercise of chronic heart failure patients.

Chapter 3

CHEMOSENSITIVITY AND THE VENTILATORY RESPONSE TO EXERCISE IN CHRONIC HEART FAILURE

Introduction

In the last chapter, the proportional increase in ventilation ($\dot{V}_E$) with oxygen consumption and in particular, with carbon dioxide output ($\dot{V}CO_2$) during exercise was noted [Wasserman & Whipp, 1975; Buller & Poole-Wilson, 1990]. This suggests that the stimulus to exercise ventilation may be humoral and that arterial chemoreceptors may play a central role. It has also been documented previously that in normal subjects, the ventilatory response to exercise correlates positively with chemosensitivity [Rebuck *et al*, 1972; Martin *et al*, 1978]. As a corollary to this, the increased ventilatory response to exercise seen in chronic heart failure patients and characterised by the steeper regression slope relating minute ventilation to carbon dioxide output may be related to an increased chemosensitivity. On a more theoretical basis, it has been suggested that the generalised sympathetic activation in chronic heart failure may not only be due to a reduced input from inhibitory baroreceptors but also to an increased input from excitatory chemoreceptors [Shepherd, 1987; Floras, 1993]. Based on these considerations, it was hypothesized that the sensitivity of chemoreceptors may be reset and may in part mediate the exercise hyperpnoea seen in this condition. The purpose of the experiments in this chapter was, therefore, primarily to examine both the peripheral and central chemosensitivity of chronic heart failure patients which hitherto has not been evaluated and also to assess their relationship with the ventilatory response to exercise.

Peripheral chemosensitivity is generally measured by assessing the ventilatory

response to hypoxia and three major techniques are available. These are the steady state [Cormack *et al*, 1957], progressive [Weil *et al*, 1970; Rebuck & Campbell, 1974] and transient hypoxic methods [Edelman *et al*, 1973]. They all correlate well with each other [Kronenberg *et al*, 1972; Shaw *et al*, 1982]. However, persistent hypoxia especially with the first two methods may result in the depression of ventilation due to direct central effects. There are also the potential risks of prolonged hypoxic exposure especially in chronic heart failure patients. Thus in this thesis, the transient hypoxic method was used.

Because a small and an early component of the hypercapnic chemosensitivity is mediated by the peripheral chemoreceptors, McClean *et al* [1988] also reported the use of the single-breath carbon dioxide ventilatory response test as an alternative method of assessing peripheral chemoreflex and highlighted its relative safety. However, the relationship between the hypoxic and single-breath carbon dioxide ventilatory response tests of peripheral chemoreflex has never been assessed.

Central chemosensitivity is measured using steady state hypercapnia [Severinghaus, 1976; Lumb & Nunn, 1991] or by the rebreathing of carbon dioxide [Read, 1966]. Both give comparable results [Read, 1966]. The rebreathing technique was used in this thesis because of the ease and the brevity of performing the test.

This chapter is divided into 3 parts. In the first, the reproducibility of the transient hypoxic and the peripheral hypercapnic (single-breath carbon dioxide) ventilatory response tests was assessed. Since the relationship between these two tests of peripheral chemosensitivity is not known, this was examined accordingly in a group of healthy subjects. The reproducibility of the carbon dioxide rebreathing test of central chemosensitivity was assessed in the second part. In the third part of this chapter, the peripheral and central chemosensitivity of chronic heart failure patients were specifically

examined. All the studies were approved by the local ethics committee and all subjects gave informed consent.

Part 1

Reproducibility and Comparability of the Transient Hypoxic and Single-breath Carbon Dioxide Ventilatory Response Tests

Fifteen healthy subjects, 11 men and 4 women, participated in this study. They were 31 to 73 years of age and were either staff members of the National Heart & Lung Institute or friends of patients of the affiliated Royal Brompton Hospital. None had respiratory symptoms and all except two were non-smokers. All were told to avoid caffeinated products on the morning of the tests. Subject characteristics including results of spirometry tests are summarised in Table 3.1.

Number of Subjects	Age (years)	Height (cm)	Weight (kg)	FEV_1 (% predicted)	FVC (% predicted)
15 [11 men]	54.9±3.0 (31-73)	169.5±2.4 (156-180)	73.9±4.1 (45-93)	105.9±4.6 (82-140)	112.1±4.9 (91-144)

Values expressed as mean±SEM (range).

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 3.1 Characteristics of subjects who participated in the study assessing the reproducibility and comparability of the transient hypoxic and single-breath carbon dioxide ventilatory response tests.

All 15 subjects underwent both the transient hypoxic ventilatory drive test and the single-breath carbon dioxide response test on separate occasions within a week. In addition, the transient hypoxic ventilatory drive test and the single-breath carbon dioxide response test were repeated once within a month in seven subjects respectively for the assessment of within-subject reproducibility.

Transient Hypoxic Ventilatory Response Test

The method of performing the transient hypoxic test was described by Edelman *et al* [1973]. This was performed while subjects were seated and after a period of quiet breathing. They were encouraged to relax in a quiet environment and were allowed to read. Each subject wore a noseclip and breathed through a pneumatic respiratory valve (Innovision, Odense, Denmark) which separated the expirate from the inspirate. The inspirate port was further connected to a T-valve placed behind the subject and depending on the position of the T-valve, the subject breathed either room air or pure nitrogen from a four-litre reservoir bag. This bag was quietly refilled from a gas cylinder containing pure nitrogen with a valve mechanism (Intersurgical Complete Respiratory Systems, Wokingham, U.K.) which prevented overfilling and pressure from building up in the bag. Minute ventilation was measured breath-by-breath using a heated pneumotachograph by integrating the flow over one whole expiration and dividing by the duration of the breath. This was done on line. Continuous monitoring of oxygen and carbon dioxide was done at the mouth by mass spectrometry as described in the last chapter (Amis 2000, Innovision, Odense, Denmark). The pneumotachometer and mass spectrometer were calibrated before each test. Arterial oxygen saturation was measured using a pulse oximeter (Model N-200E, Nellcor, Hayward, California, U.S.A.) set at fast mode with

a response time of 2 to 3 seconds and a lightweight ear-probe clipped gently on the subject's right ear lobe.

After the subject breathed room air for several minutes, the T-valve was turned surreptitiously and unknown to the subject during the expiratory phase of the previous breath so that pure nitrogen was inhaled for two to eight breaths. This was repeated ten to fifteen times so as to provide a wide range of arterial oxygen saturations from 75% to 100%. End-tidal oxygen was monitored during the testing for safety reasons to prevent extreme hypoxia. Each transient was preceded by a period of air breathing during which time oxygen saturation and end-tidal carbon dioxide were allowed to return to the subject's baseline. The average of 2 largest consecutive breaths which gave the highest ventilation after the hypoxic stimulus was used to calculate maximal minute ventilation as shown in Figure 3.1. This value was plotted against the lowest arterial oxygen desaturation reached for that period of nitrogen inhalation. The ventilatory response to transient hypoxia was expressed as the slope which related ventilation to arterial oxygen saturation, calculated by least-squares linear regression analysis, in terms of litres per minute per percent oxygen saturation (l/min/%SaO_2).

Single-Breath Carbon Dioxide Ventilatory Response Test

The method used was similar to that described by McClean *et al* [1988]. The apparatus including the T-valve was the same as for the transient hypoxic ventilatory drive test above. A smaller 2-litre reservoir bag was used which was quietly refilled after each inhalation with a gas mixture containing 13% carbon dioxide in air instead of pure nitrogen. After a period of quiet breathing, the T-valve was again turned in a surreptitious manner during the expiratory phase of the previous breath such that the

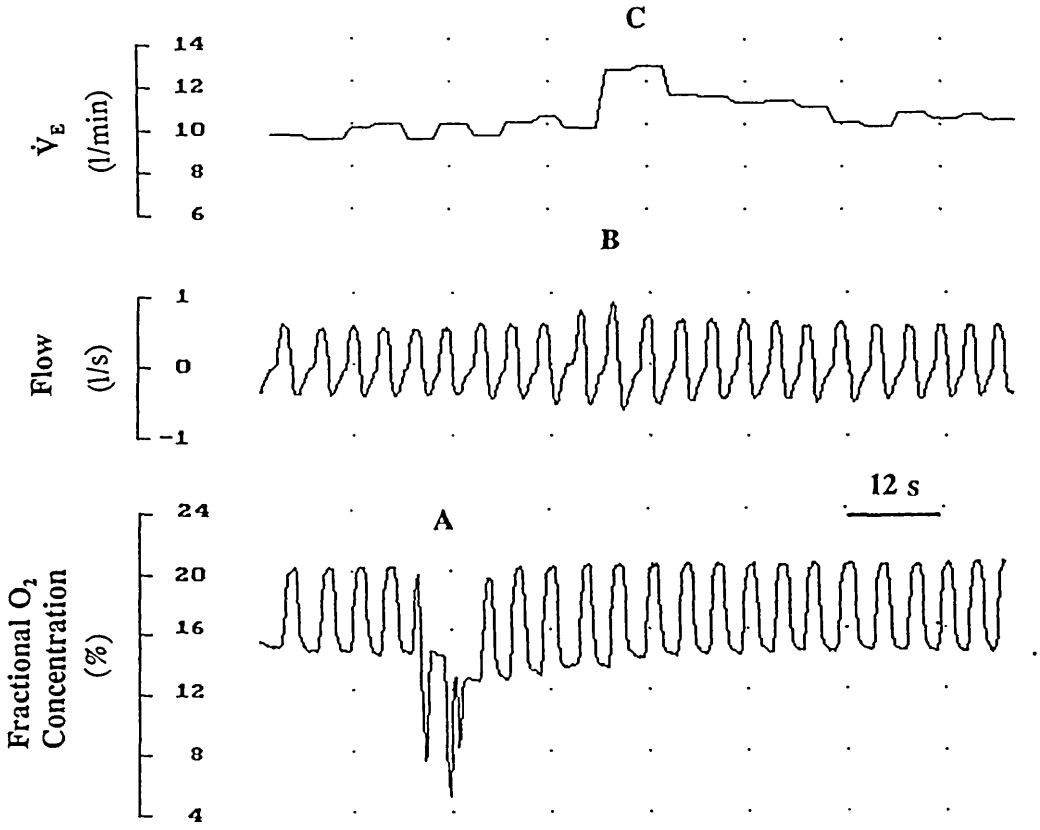

Figure 3.1 The diagram shows two breaths of pure nitrogen (A) causing a ventilatory response which manifested in an increase in air flow (B) and integrated on line to give the corresponding minute ventilation. The maximal minute ventilation following each period of nitrogen inhalation is obtained by averaging the two largest consecutive breaths (C).

subject inhaled a single breath of gas mixture high in carbon dioxide content. On average, 10 single breaths of carbon dioxide were administered at approximately 2-minute intervals. As before, minute ventilation was measured breath-by-breath using a heated pneumotachograph and continuous monitoring of carbon dioxide was done at the mouth by mass spectrometry.

The mean of the minute ventilation of the preceding 5 breaths before the stimulus carbon dioxide breath was calculated and taken as the control ventilation [$\dot{V}(C)$] as shown in Figure 3.2. The mean end-tidal fraction of carbon dioxide of these breaths was also calculated and taken as the control end-tidal fraction of carbon dioxide [$F_{ETCO2}(C)$]. The response ventilation after the stimulus carbon dioxide breath [$\dot{V}(S)$] was calculated by averaging the 2 largest consecutive breaths but unlike hypoxic testing, breaths 20 seconds following the stimulus breath were excluded. This is because breaths beyond this time limit were assumed to be affected by changes in central chemoreceptor drive and thus excluded [McClean *et al*, 1988]. The end-tidal carbon dioxide concentration after the stimulus breath was considered the stimulus end-tidal fraction of carbon dioxide [$F_{ETCO2}(S)$].

The single-breath carbon dioxide response was accordingly calculated as follows:

$$= \frac{\dot{V}(S) - \dot{V}(C)}{[F_{ETCO2}(S) - F_{ETCO2}(C)] \times (P_B - 47)}$$

where P_B is the atmospheric pressure in mmHg and 47 is the saturated water vapour pressure in mm Hg. The mean of 10 responses was considered the subject's single-breath carbon dioxide response and expressed in litres per minute per mm Hg (l/min/mmHg).

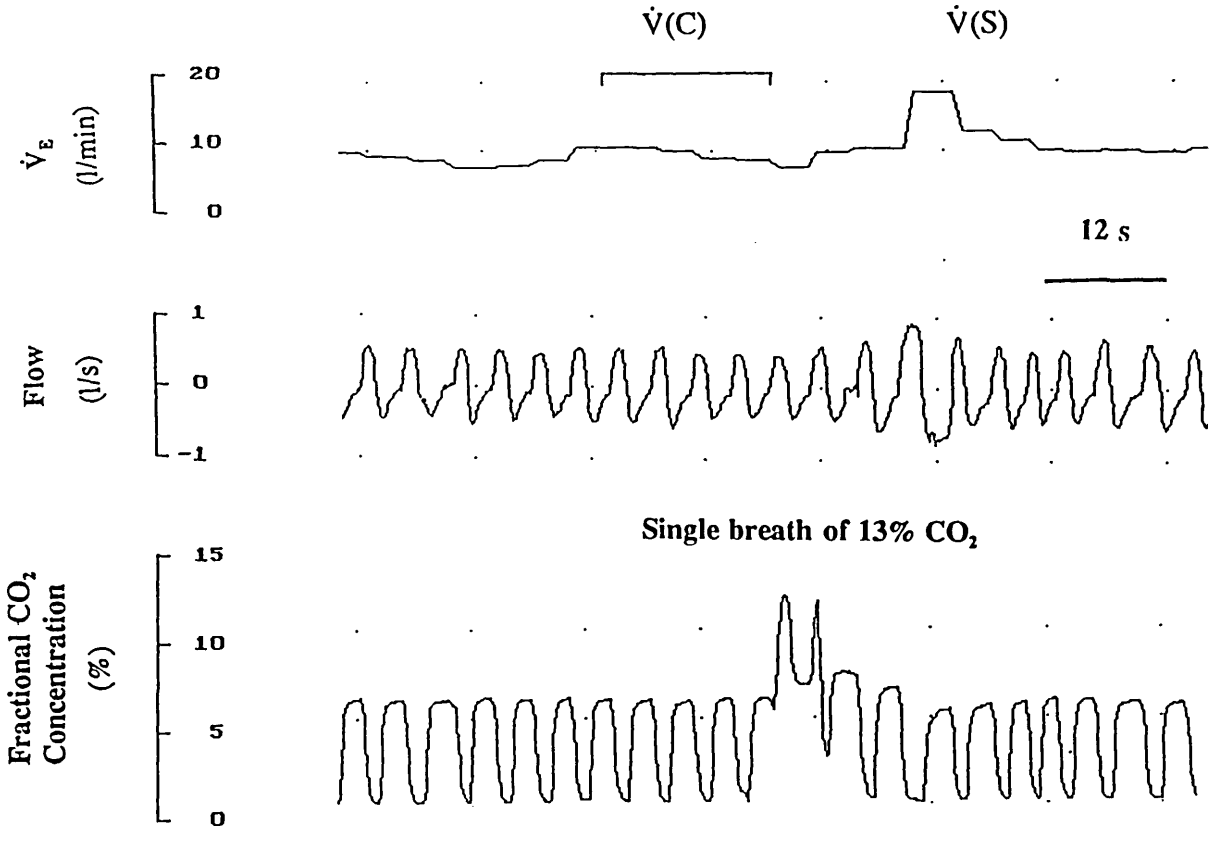

Figure 3.2 The diagram shows the ventilatory response following a single breath of 13% carbon dioxide in air. The control ventilation, $\dot{V}(C)$, is the average of the 5 breaths preceding the stimulus breath of carbon dioxide. The maximal ventilation following the stimulus breath is obtained by averaging the two largest consecutive breaths, $\dot{V}(S)$, but within 20 seconds following the stimulus breath of carbon dioxide. Responses after this time interval are excluded as they may be affected by central chemoreceptors.

Statistical Analysis

The results are presented as means±SEM. Studies of reproducibility within subjects was assessed by linear regression analysis and the coefficients of variation of the tests calculated. The relation between the transient hypoxic and single-breath carbon dioxide tests was also assessed by linear regression analysis. $P < 0.05$ was considered significant.

Part 2

Reproducibility of the Carbon Dioxide Rebreathing Test

The carbon dioxide rebreathing test was performed twice within a month in 6 healthy subjects aged between 29 and 61 years (mean 43.8±5.3[SEM] years; 5 men) to assess the reproducibility and the coefficient of variation. This test was done using the rebreathing of 7% carbon dioxide in 93% oxygen as described below.

Carbon Dioxide Rebreathing Test

During the carbon dioxide rebreathing test, expired carbon dioxide is constantly returned to the lungs and as carbon dioxide accumulates, this provides a progressive carbon dioxide stimulus to ventilation. After a period of quiet breathing, subjects rebreathed through a 6-litre bag containing a gas mixture of 7% carbon dioxide in oxygen for 4 minutes as described by Read [1966]; the test was stopped sooner if they were too breathless to continue or if end-tidal carbon dioxide fraction exceeded 10%. It has been shown that by rebreathing of 7% carbon dioxide (which approximates to venous carbon dioxide tension) in oxygen, a carbon dioxide equilibrium is developed rapidly in the mixed venous blood, arterial blood, gas in the lung and gas in the breathing bag

[Read, 1966]. Thus, the carbon dioxide tension in any one of these compartments is representative of the other compartments, including the brain tissue. With the high oxygen tension, the peripheral hypercapnic response is known to be very small or negligible [Gelfand *et al*, 1973; Sebert *et al*, 1990]. Minute ventilation was measured breath-by-breath and continuous monitoring of oxygen and carbon dioxide was done at the mouth by mass spectrometry. The central hypercapnic chemosensitivity was obtained as the slope which related minute ventilation to end-tidal carbon dioxide concentration calculated by linear regression analysis and expressed in terms of litres per minute per mm Hg (l/min/mmHg). This is schematically represented in Figure 3.3.

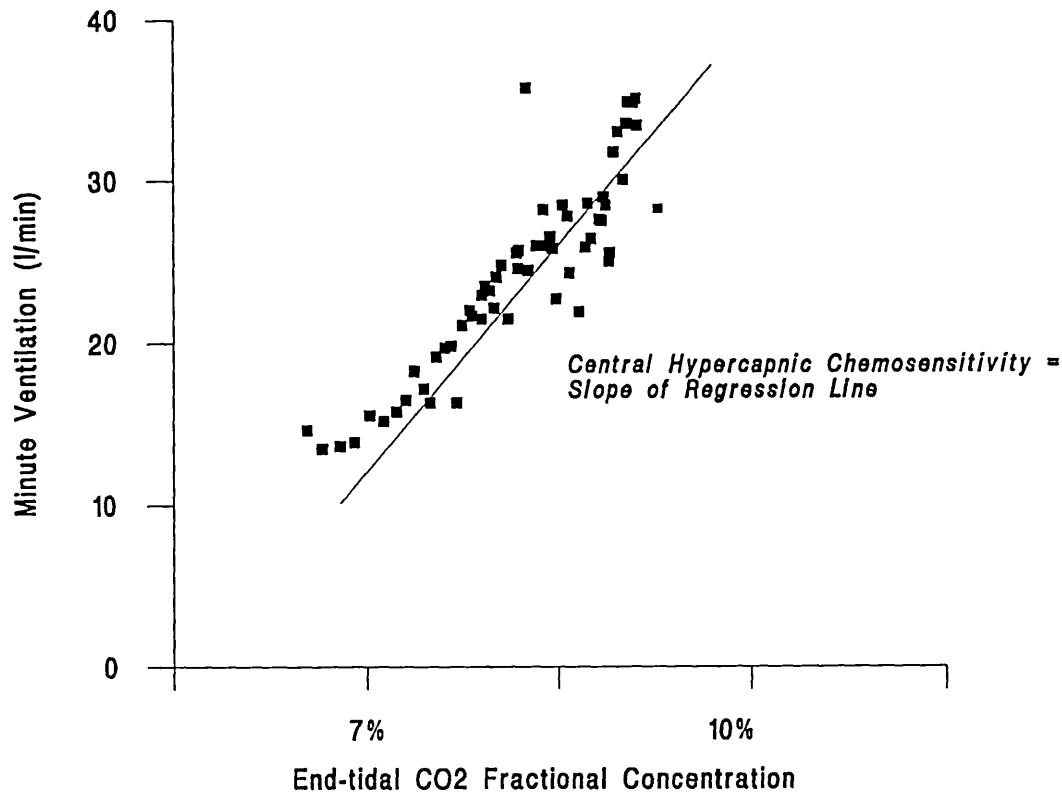

Figure 3.3 Schematic representation showing the derivation of central chemosensitivity using the rebreathing of 7% carbon dioxide. The test is performed for 4 minutes or until the end-tidal carbon dioxide concentration reaches 10% or if the subject is too breathless to continue.

Statistical Analysis

As before, the study of reproducibility within subjects was assessed by linear regression analysis and the coefficient of variation of the test calculated. $P < 0.05$ was considered significant.

Part 3

Chemosensitivity and the Ventilatory Response to Exercise in Chronic Heart Failure Patients

The chemosensitivity of chronic heart failure patients was measured using the transient hypoxic, single-breath carbon dioxide and carbon dioxide rebreathing tests, the methodology of which was described above. In addition to these tests being performed at rest, the transient hypoxic and single-breath carbon dioxide tests were also carried out during mild exercise to investigate the change in hypoxic and peripheral hypercapnic chemosensitivity with exercise, as will be described in more detail later. The carbon dioxide rebreathing test was not performed during exercise because of the uncertainties of carbon dioxide equilibrium during exercise in all the compartments (mixed venous blood, arterial blood, gas in the lung and gas in the breathing bag) using the same mixture of 7% carbon dioxide in oxygen and because it is very unpleasant and quite intolerable for subjects, controls and patients alike, to have this test performed during exercise. The ventilatory response to exercise was also assessed with treadmill cardiopulmonary exercise testing to assess its relationship with chemosensitivity.

Subjects and Methods

Thirty-eight chronic heart failure patients between 40 and 75 years of age (mean 60.2 ± 1.3 years; 35 men) participated in this part of the study. Patients with a known

history of pulmonary and neurological disease were excluded. All patients had been in heart failure for more than three months. They were all treated with diuretics and most received angiotensin-converting enzyme inhibitors. Nineteen patients were in New York Heart Association functional class II and 16 in class III, the definition of which is given in Appendix 2. None of the patients was limited by angina. Patient characteristics are summarised in Table 3.2. A control group of 15 healthy subjects (age range 31-73 years, mean 54.9$\pm$3.0 years; 11 men) as described in Part 1 above was also studied.

Hypoxic and peripheral hypercapnic chemosensitivity were assessed at rest in all subjects. The first 15 consecutive chronic heart failure patients recruited also had these assessments made during mild exercise on a cycle ergometer (Tunturi, Piispanristi, Finland) at 25 W for 10 minutes on two separate occasions to evaluate the change in chemosensitivity with exercise. A fixed external workrate was used, based on the observation that for a particular workrate, chronic heart failure patients have a higher ventilatory response compared with normals [Weber *et al*, 1982]. During exercise, on average, only 6 episodes of transient hypoxia were given in view of the duration of exercise. A delay of 3 minutes after the onset of exercise was given before the hypoxic chemosensitivity testing to allow steady state [Wasserman *et al*, 1994; Sietsema *et al*, 1994]. For safety reasons, the degree of arterial oxygen desaturation was deliberately kept above 80% and all patients were monitored electrocardiographically during exercise. Similarly, on average, only 6 single breaths of carbon dioxide were administered during exercise (given at shorter time intervals in view of increased minute ventilation and circulation during exercise).

Central hypercapnic chemosensitivity was assessed using the rebreathing of carbon dioxide in 10 controls and 25 patients to assess the role of central chemoreceptors.

	Normal Controls (n=15)	Chronic Heart Failure (n=38)
Age (years)	54.9±3.0	60.2±1.3
Sex (M/F)	11/4	35/3
Height (cm)	169.5±2.4	172.1±1.2
Weight (kg)	73.9±4.1	79.5±2.4
Spirometry		
FEV_1 (% predicted)	105.9±4.6	85.3±2.9
FVC (% predicted)	112.1±4.9	89.2±2.7
Aetiology of Chronic Heart Failure		IHD 22 DCM 12 Others* 4
Symptoms (NYHA)		I 1 II 19 III 16 IV 2
Left Ventricular Ejection Fraction (%)		25.7±2.3
Treatment		
Diuretics		n = 38
(Dose of frusemide or its equivalent**)		(64.2±5.2 mg)
ACE Inhibitors		n = 35
Digoxin		n = 10

Values expressed as mean±SEM.

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NYHA, New York Heart Association classification of symptoms; IHD, ischaemic heart disease; DCM, idiopathic dilated cardiomyopathy; ACE inhibitors, angiotensin-converting enzyme inhibitors.

*Two were due to valvular heart disease, one alcohol-related and one hypertension-related cardiomyopathy.

**1 mg bumetanide was taken as equivalent to 40 mg frusemide.

Table 3.2 Characteristics of normal subjects and chronic heart failure patients who participated in the study assessing chemosensitivity and the ventilatory response to exercise.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing was performed in all subjects on a separate day to determine the exercise ventilation. All were exercised to exhaustion (respiratory exchange ratio >1.1) using the Bruce protocol [Bruce *et al*, 1963], with the addition of a "Stage 0" at 1.0 mph and 5% gradient for the chronic heart failure patients. Respiratory gas exchange analysis was carried out by means of mass spectrometry (Amis 2000, Innovision, Odense, Denmark) using the inert gas dilution technique [Davies & Denison, 1979] as described in Chapter 2. The slope of the regression line relating minute ventilation to carbon dioxide output was used as an index of the ventilatory response to exercise [Whipp *et al*, 1984; Buller & Poole-Wilson, 1990].

Statistical Analysis

The results are presented as mean$\pm$SEM. Two-tailed Student's *t-test* was used where appropriate to assess the significance of results. The relationship between variables was assessed using linear regression analysis. $P<0.05$ was considered significant.

Results

Part 1

Reproducibility and Comparability of the Transient Hypoxic and Single-breath Carbon Dioxide Ventilatory Response Tests

The results of the transient hypoxic and single-breath carbon dioxide ventilatory response tests are summarised in Table 3.3. The mean transient hypoxic ventilatory response was 0.293 ± 0.056 l/min/%SaO_2 and the mean single-breath carbon dioxide response 0.310 ± 0.050 l/min/mmHg. The transient hypoxic responses correlated

significantly with height (r=0.57, P=0.03) but not with weight (r=0.41, P=0.14). There was an association between single-breath carbon dioxide responses and height although this did not achieve statistical significance (r=0.51, P=0.06). No correlation was found between single-breath carbon dioxide responses and weight (r=0.30, P=0.75). Neither transient hypoxic nor single-breath carbon dioxide responses correlated with age or spirometric measurements. There was no significant correlation between the transient hypoxic and single-breath carbon dioxide responses as shown in Figure 3.6 (r=0.25, P=0.37).

Subject	Age (Years)	Sex	Hypoxic Ventilatory Response (l/min/%SaO_2)	Single-breath CO_2 Ventilatory Response (l/min/mmHg)
1	50	F	0.182	0.390
2	64	F	0.082	0.110
3	64	M	0.615	0.268
4	56	M	0.183	0.092
5	58	F	0.186	0.081
6	31	M	0.236	0.495
7	69	M	0.222	0.446
8	42	M	0.299	0.182
9	64	M	0.265	0.232
10	41	M	0.168	0.501
11	45	M	0.018	0.270
12	58	M	0.718	0.309
13	61	F	0.157	0.083
14	73	M	0.687	0.406
15	47	M	0.383	0.787
Mean	55.9		0.293	0.310
SEM	3.1		0.056	0.050

Table 3.3 Results of transient hypoxic and single-breath carbon dioxide ventilatory response tests.

The reproducibility between two tests taken on different days are shown in Tables 3.4 and 3.5. The coefficient of variation calculated from the results of two transient hypoxic tests in seven subjects was 21.9%. Figure 3.4 shows a graphical representation of the reproducibility of the transient hypoxic test (r=0.96, P<0.001). The coefficient of variation obtained from the results of two single-breath carbon dioxide tests in seven subjects was 17.2% as shown in Table 3.5. Figure 3.5 shows the results of the two single-breath carbon dioxide tests plotted graphically (r=0.84, P=0.02).

The mean value and the coefficient of variation of the hypoxic and single-breath carbon dioxide tests obtained in this study show that they compare favourably with previous data [Edelman *et al*, 1973; Shaw *et al*, 1982; McClean *et al*, 1988; Sebert *et al*, 1990]. The results indicate that both tests are adequately reproducible. There has been no previous published study of reproducibility of the transient hypoxic ventilatory drive test but one study using the progressive hypoxic test based on the Rebuck and Campbell technique [1974] showed a coefficient of variation of 23.1% [Shaw *et al*, 1982]. This is comparable to the mean coefficient of variation of 21.9% seen in this study. The coefficient of variation for the single-breath CO_2 response test was 17.2% in this study and is again compatible with that of 25% obtained by McClean *et al* [1988].

Subject (n=7)	Response 1 (l/min/%SaO_2)	Response 2 (l/min/%SaO_2)	Mean (Response 1 & 2) (l/min/%SaO_2)	Difference (Response 1 - 2)	Square of Difference
4	0.183	0.138	0.161	0.045	0.0020
6	0.237	0.172	0.205	0.065	0.0042
7	0.222	0.148	0.185	0.074	0.0055
8	0.299	0.481	0.390	-0.182	0.0331
10	0.168	0.195	0.182	-0.027	0.0007
12	0.718	0.820	0.769	-0.102	0.0104
14	0.687	0.894	0.791	-0.207	0.0429
Mean	**0.359**	**0.407**	**0.383**	**-0.048**	
Total					**0.0989**
SD					**0.0840**
CV					**21.9%**

SD, standard deviation (=square root of [Total/2n]); CV, coefficient of variation (SD/overall mean multiplied by 100).

Table 3.4 Reproducibility of transient hypoxic ventilatory drive test in 7 healthy subjects.

Subject (n=7)	Response 1 (l/min/mmHg)	Response 2 (l/min/mmHg)	Mean Response 1 & 2 (l/min/mmHg)	Difference (Response 1 - 2)	Square of Difference
1	0.390	0.369	0.380	0.021	0.0004
2	0.110	0.255	0.183	-0.145	0.0210
6	0.495	0.412	0.454	0.083	0.0069
7	0.446	0.410	0.428	0.036	0.0013
8	0.182	0.233	0.208	-0.051	0.0026
9	0.232	0.271	0.252	-0.039	0.0015
10	0.501	0.635	0.568	-0.134	0.0180
Mean	**0.337**	**0.369**	**0.353**	-0.033	
Total					**0.0517**
SD					**0.0608**
CV					**17.2%**

SD, standard deviation (= square root of [Total/2n]); CV, coefficient of variation (= SD/overall mean multiplied by 100).

Table 3.5 Reproducibility of the single-breath CO_2 response test in 7 healthy subjects.

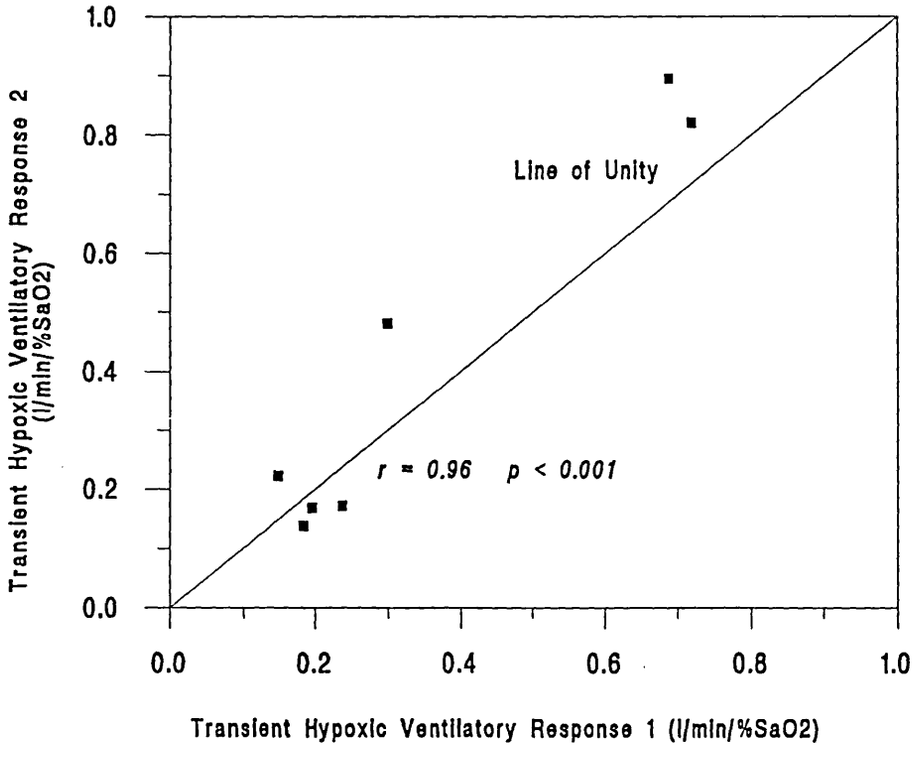

Figure 3.4 Reproducibility studies of the transient hypoxic ventilatory response test in 7 subjects.

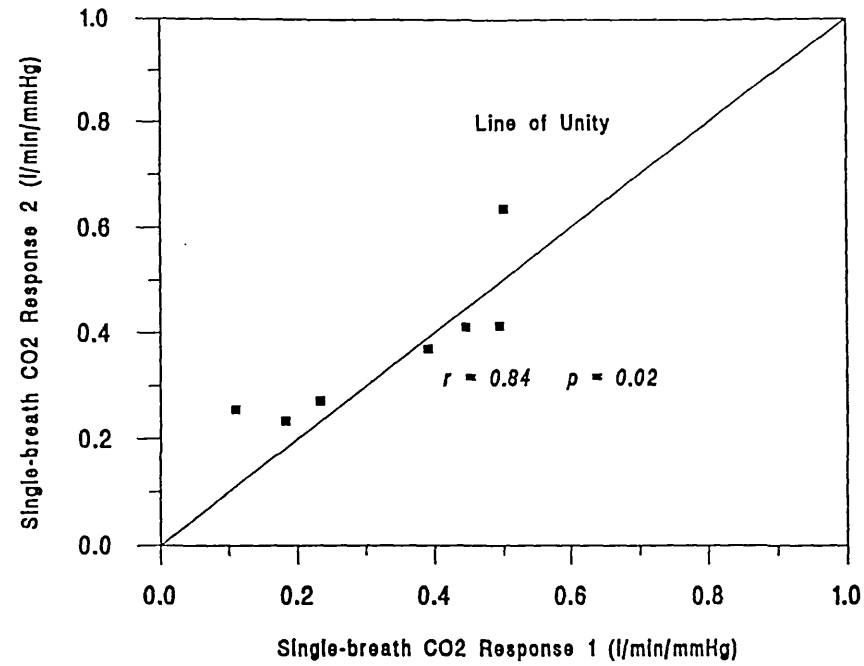

Figure 3.5 Reproducibility studies of the single-breath CO_2 response test in 7 healthy subjects.

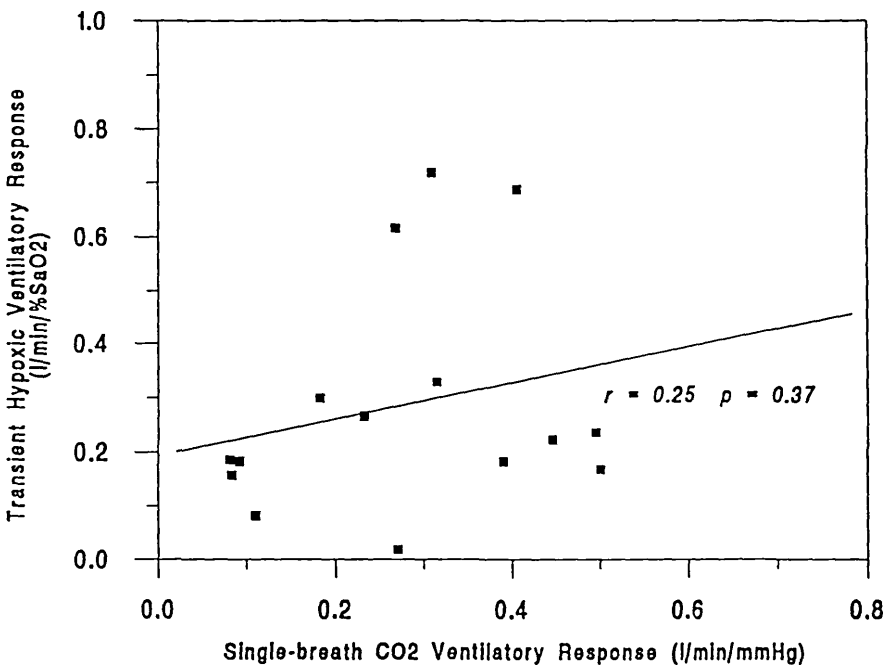

Figure 3.6 Scatter plot showing the absence of a significant correlation between the transient hypoxic and the single-breath CO_2 ventilatory response tests in 7 healthy subjects.

Part 2

Reproducibility of the Carbon Dioxide Rebreathing Test

The reproducibility between two tests of carbon dioxide rebreathing taken on different days is shown in Figure 3.7 with satisfactory correlation between the repeated measurements (r=0.86, P=0.02). The coefficient of variation calculated from the results of the two tests in 6 healthy subjects was 17.7%, comparable to previous data [Read, 1966].

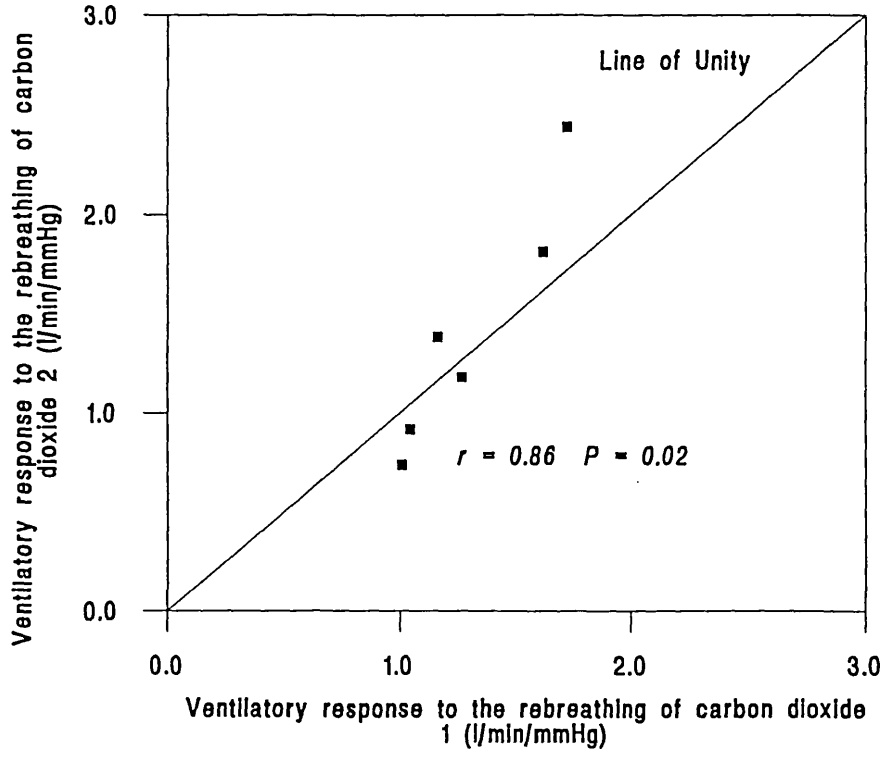

Figure 3.7 Reproducibility studies of the carbon dioxide rebreathing test in 6 healthy subjects.

Part 3

Chemosensitivity and the Ventilatory Response to Exercise in Chronic Heart Failure Patients

Cardiopulmonary Exercise Testing

The mean age, height and weight of controls and chronic heart failure patients did not differ significantly (Table 3.2). As shown in Table 3.6, the chronic heart failure patients had a lower maximal oxygen consumption ($P<0.0001$) and higher ventilatory response to exercise as judged by the higher ventilation-carbon dioxide output regression slope compared with the controls ($P<0.0001$). There was no significant difference in maximal oxygen consumption (16.4±0.8 v 17.3±2.3 ml/kg/min), ventilation-carbon dioxide output regression slope (38.13±1.70 v 34.60±3.40) or left ventricular ejection fraction (27.1±2.8 v 22.7±4.5%) between patients with chronic heart failure due to ischaemic heart disease and idiopathic dilated cardiomyopathy who participated in the study.

Chemosensitivity

Figure 3.8 shows a significantly higher transient hypoxic ventilatory response in chronic heart failure patients (0.707±0.076 l/min/%SaO_2) than in controls (0.293±0.056 l/min/%SaO_2). When the results of the transient hypoxic ventilatory test were analysed separately for patients with chronic heart failure due to ischaemic heart disease and idiopathic dilated cardiomyopathy, there was no significant difference between the two groups (0.642±0.088 v 0.819±0.14 l/min/%SaO_2, $P=0.3$).

The peripheral hypercapnic chemosensitivity was higher in chronic heart failure patients (0.388±0.04 v 0.310±0.051 l/min/mmHg) but this did not reach statistical significance (Figure 3.9). In contrast, when central hypercapnic chemosensitivity

	Controls	Chronic Heart Failure		
	(n=15)	All Causes (n=38)	IHD (n=22)	DCM (n=12)
Maximal Oxygen Consumption (ml/kg/min)	29.7±2.2	16.6±0.9	16.4±0.8	17.3±2.3
$\dot{V}_E$-$\dot{V}CO_2$ Slope	26.54±1.40	37.15±1.5	38.13±1.70	34.60±3.40
Left Ventricular Ejection Fraction (%)		25.7±2.3	27.1±2.8	22.7±4.5

IHD, ischaemic heart disease; DCM, idiopathic dilated cardiomyopathy; $\dot{V}_E$- $\dot{V}$ CO_2 slope is the regression slope relating minute ventilation and carbon dioxide output.

Table 3.6 Exercise capacity and the ventilatory response to exercise in controls and chronic heart failure patients as characterised by maximal oxygen consumption and the ventilation-carbon dioxide output ($\dot{V}_E$-$\dot{V}CO_2$) regression slope respectively during cardiopulmonary exercise testing. Patients with chronic heart failure due to ischaemic heart disease (IHD) and idiopathic dilated cardiomyopathy (DCM) who participated in this study have comparable maximal oxygen consumption, $\dot{V}_E$-$\dot{V}CO_2$ slope and left ventricular ejection fraction.

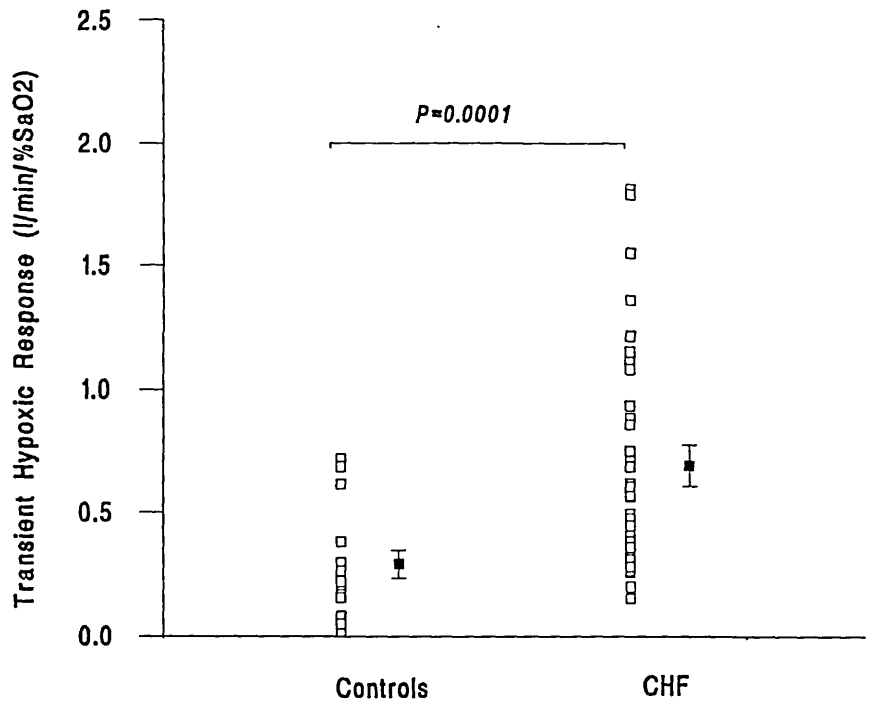

Figure 3.8 Transient hypoxic ventilatory response in chronic heart failure patients compared with normals.

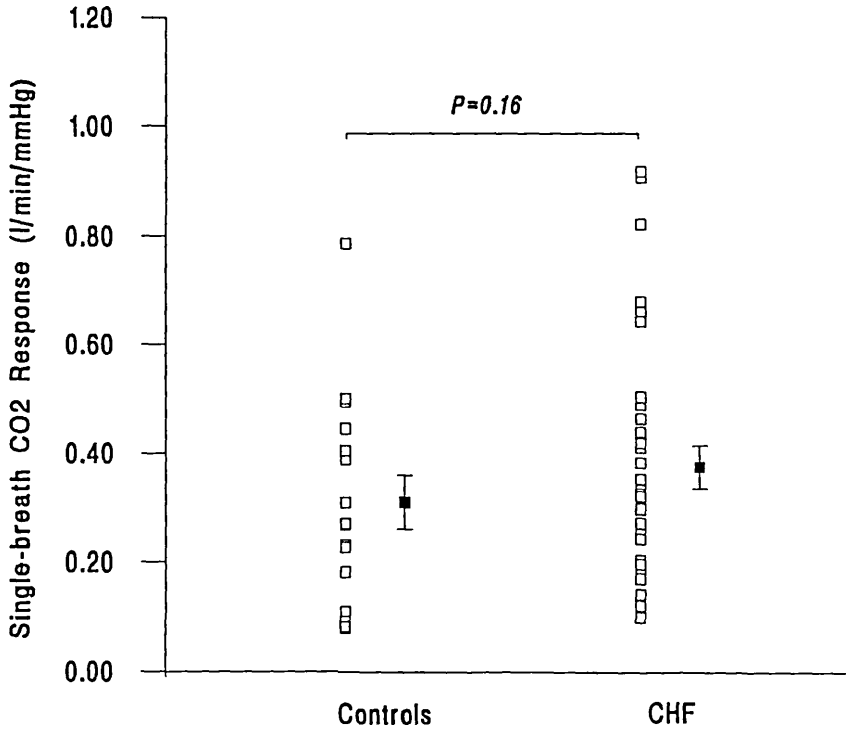

Figure 3.9 Single-breath carbon dioxide response in chronic heart failure patients compared with normal subjects.

was assessed in 25 of the chronic heart failure patients, there was a significant difference between patients and controls (3.15±0.41 v 2.02±0.25 l/min/mmHg, P=0.018; Figure 3.10). These 25 patients had similar age (57.7±1.7 years), maximal oxygen consumption (17.8±1.1 ml/kg/min), ventilation-carbon dioxide output regression slope (37.8±2.0) and left ventricular ejection fraction (23.4±2.8%) when compared with the patient population described for the hypoxic and single-breath carbon dioxide tests. Fourteen patients had ischaemic heart disease and 9 had idiopathic cardiomyopathy. There was no difference in the central hypercapnic chemosensitivity between these two groups of patients [3.20±0.51 v 3.27±0.83 l/min/mm Hg, P=0.95]. Of these 25 patients, there were 11 in New York Heart Association functional class II and 13 in class III.

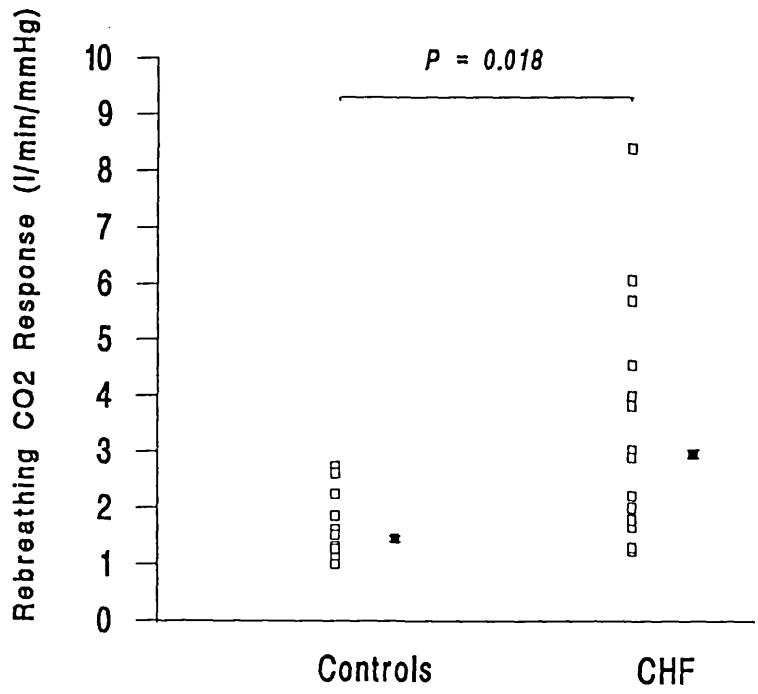

Figure 3.10 Central hypercapnic chemosensitivity as measured by the carbon dioxide rebreathing test in chronic heart failure patients compared with normals.

Chemosensitivity and Functional Impairment

To see if there was any relationship between hypoxic and central hypercapnic chemosensitivity and functional impairment, we compared the respective chemosensitivity in patients with New York Heart Association functional class II and class III patients as shown in Figure 3.11. Although the hypoxic chemosensitivity was higher in class III than class II patients, this was not statistically significant (0.724 ± 0.10 v 0.600 ± 0.11 l/min/%SaO_2, $P=0.41$). In contrast, central hypercapnic chemosensitivity tended to be more discriminatory with class III patients having a significantly higher chemosensitivity than class II patients (4.17 ± 0.66 v 2.00 ± 0.14 l/min/mm Hg, $P=0.007$) also shown in Figure 3.12.

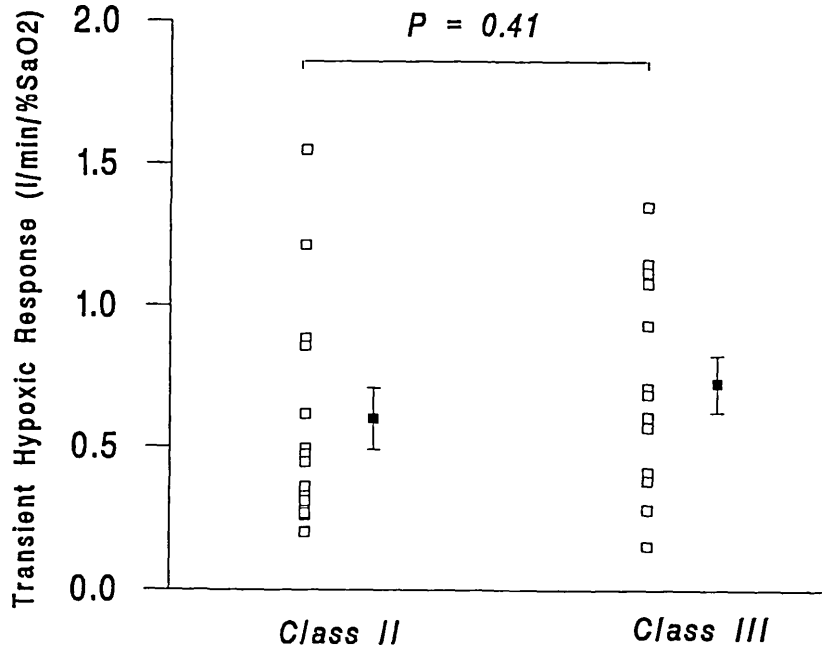

Figure 3.11 Hypoxic chemosensitivity and functional capacity as defined by the New York Heart Association functional class, showing lack of significant difference between class II and III patients. See text for discussion.

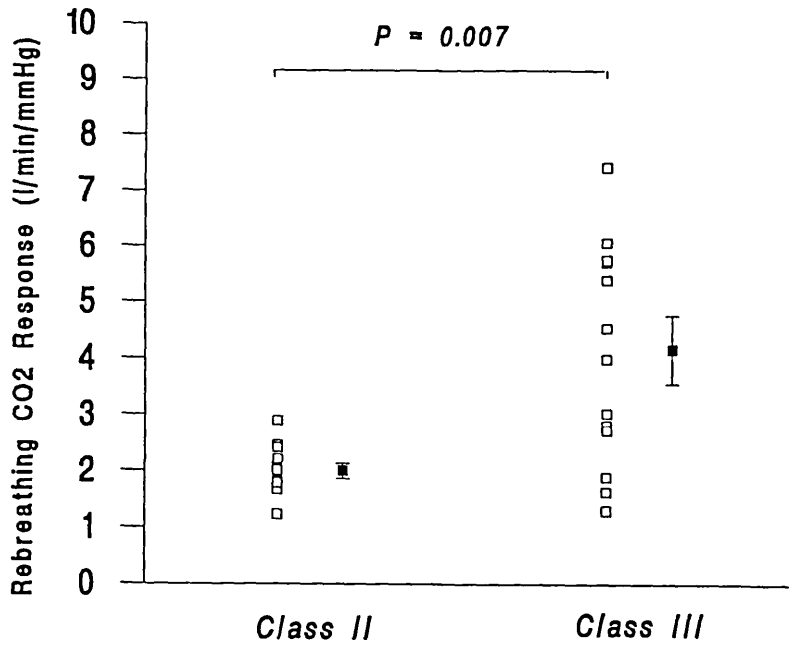

Figure 3.12 Central hypercapnic chemosensitivity and functional capacity as defined by the New York Heart Association functional class, showing a significant difference in central hypercapnic chemosensitivity between class II and III patients.

Relationship between Chemosensitivity and the Ventilatory Response to Exercise

A significant correlation was seen between the ventilatory response to exercise and hypoxic chemosensitivity as shown in Figure 3.13 (r=0.44, P=0.001). There was also a significant correlation between the ventilatory response to exercise and central hypercapnic chemosensitivity as shown in Figure 3.14 (r=0.66, P<0.001). There was no correlation between the ventilatory response to exercise and the peripheral hypercapnic chemosensitivity (r=0.08, P=0.94).

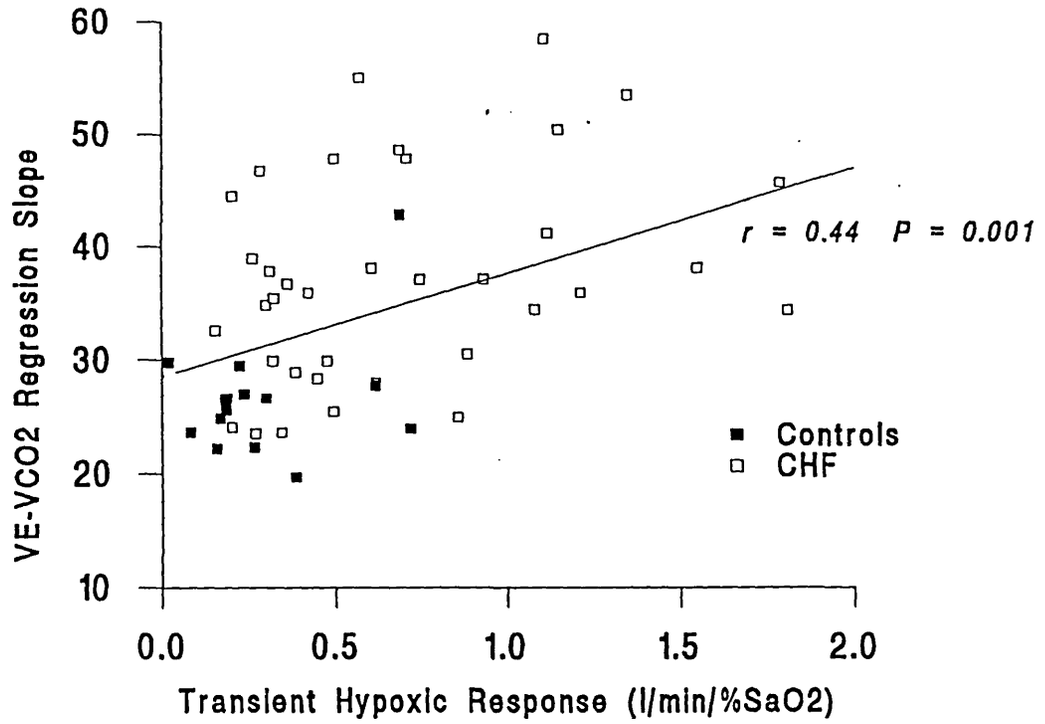

Figure 3.13 Relationship between hypoxic chemosensitivity measured at rest and the ventilatory response to exercise ($\dot{V}_E$-$\dot{V}CO_2$ regression slope).

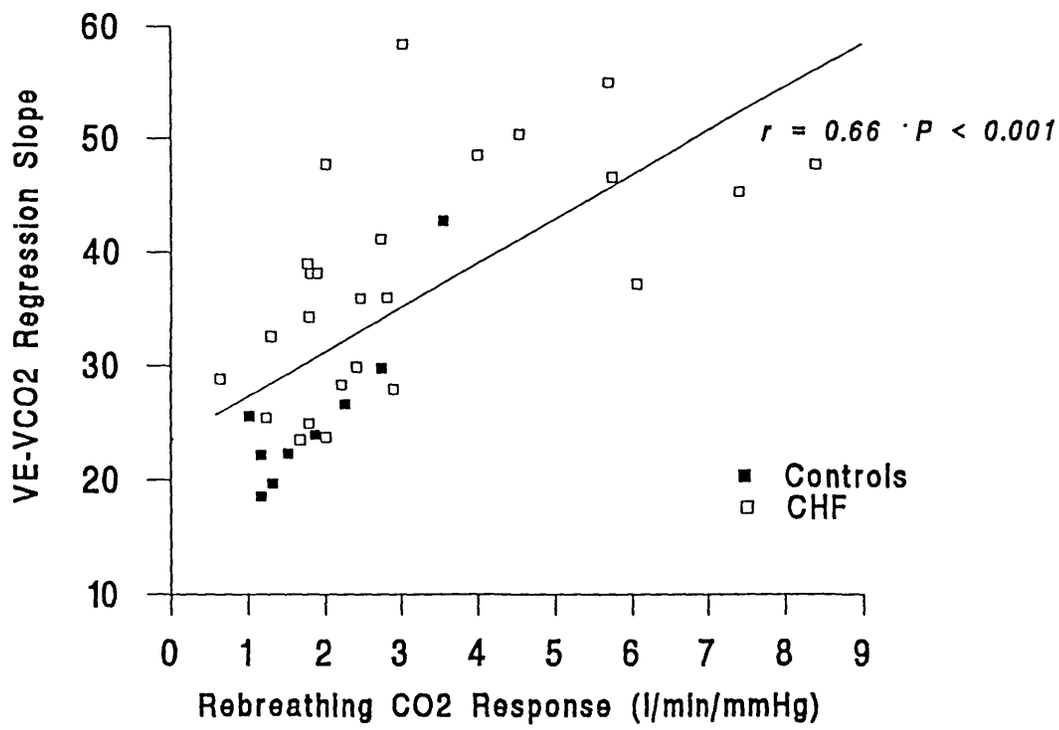

Figure 3.14 Relationship between central hypercapnic chemosensitivity measured at rest and the ventilatory response to exercise ($\dot{V}_E$-$\dot{V}CO_2$ regression slope).

Augmentation in Chemosensitivity with Exercise

The 15 chronic heart failure patients who had their chemosensitivity assessed during mild exercise showed similar baseline characteristics (age 60.7±1.3 years; maximal oxygen consumption 17.9±1.4 ml/kg/min; ventilation-carbon dioxide output regression slope 34.13±2.30; left ventricular ejection fraction 27.5±3.6%) when compared with all the chronic heart failure patients as a group. As shown in Table 3.7, the transient hypoxic response during exercise in these 15 patients was 1.530±0.270 l/min/%SaO_2 compared with 0.685±0.120 l/min/%SaO_2 in normals. Despite augmentation of the hypoxic chemosensitivity during exercise in both controls and chronic heart failure patients, the transient hypoxic response remained significantly higher in patients. Also shown in Table 3.7, the peripheral hypercapnic chemosensitivity was also augmented during exercise in controls and patients but there was still no significant difference between the two groups. The augmentation of the hypoxic and peripheral hypercapnic chemosensitivity in chronic heart failure patients is shown graphically in Figure 3.15.

When the hypoxic chemosensitivity measured during mild exercise was correlated with ventilation-carbon dioxide output regression slope, the relationship between these two variables remained intact with a correlation coefficient of 0.41 (P=0.024) as shown in Figure 3.16. A weak association between the single-breath carbon dioxide response during exercise and ventilation-carbon dioxide output regression slope was also seen (r=0.34, P=0.07) as shown in Figure 3.17.

Chemosensitivity	Normal Controls (n=15)	Chronic Heart Failure (n=15)	*P Value*
Transient Hypoxia (l/min/%SaO_2)			
Rest	0.293±0.056	0.684±0.130	0.012
Mild Exercise (25W)	0.685±0.120	1.530±0.270	0.01
Mean Augmentation during exercise*	3.05±0.62	2.66±0.37	0.60
Single-breath CO_2 (l/min/mmHg)			
Rest	0.310±0.051	0.324±0.046	0.84
Mild Exercise (25W)	0.507±0.052	0.534±0.084	0.79
Mean Augmentation during exercise*	2.31±0.42	2.05±0.43	0.67

*This was obtained as a mean of all the individual augmentation during mild exercise expressed as a factor of the resting value.

Table 3.7 Summary of chemosensitivity results at rest and during mild exercise of normal controls and 15 chronic heart failure patients.

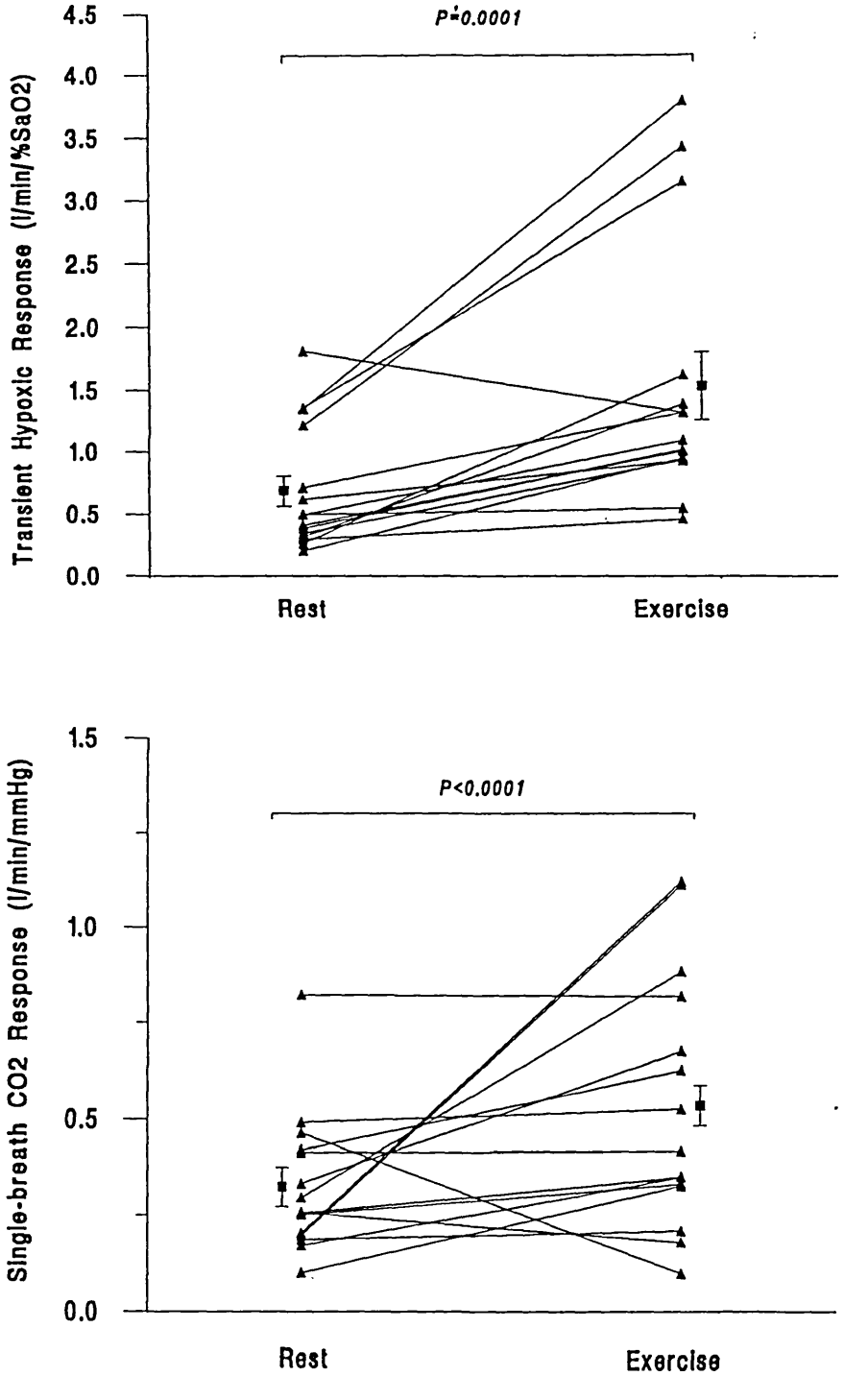

Figure 3.15 Augmentation of hypoxic chemosensitivity (top graph) and peripheral hypercapnic chemosensitivity during mild exercise in chronic heart failure patients.

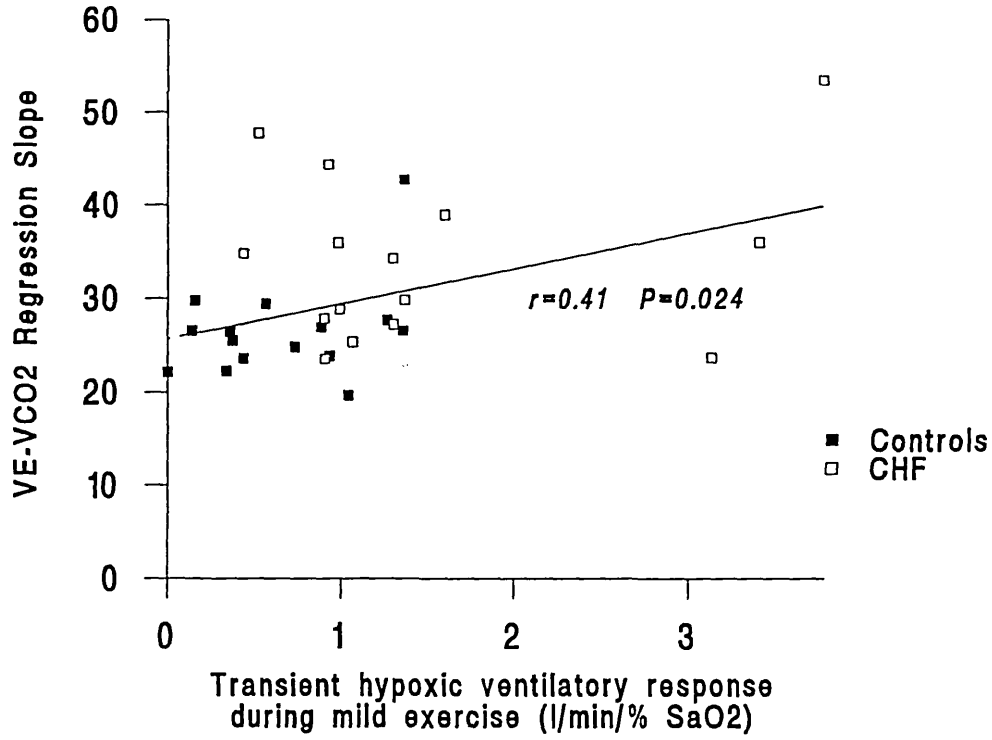

Figure 3.16 Relationship between hypoxic chemosensitivity measured during mild exercise and the ventilatory response to exercise ($\dot{V}_E$-$\dot{V}CO_2$ regression slope).

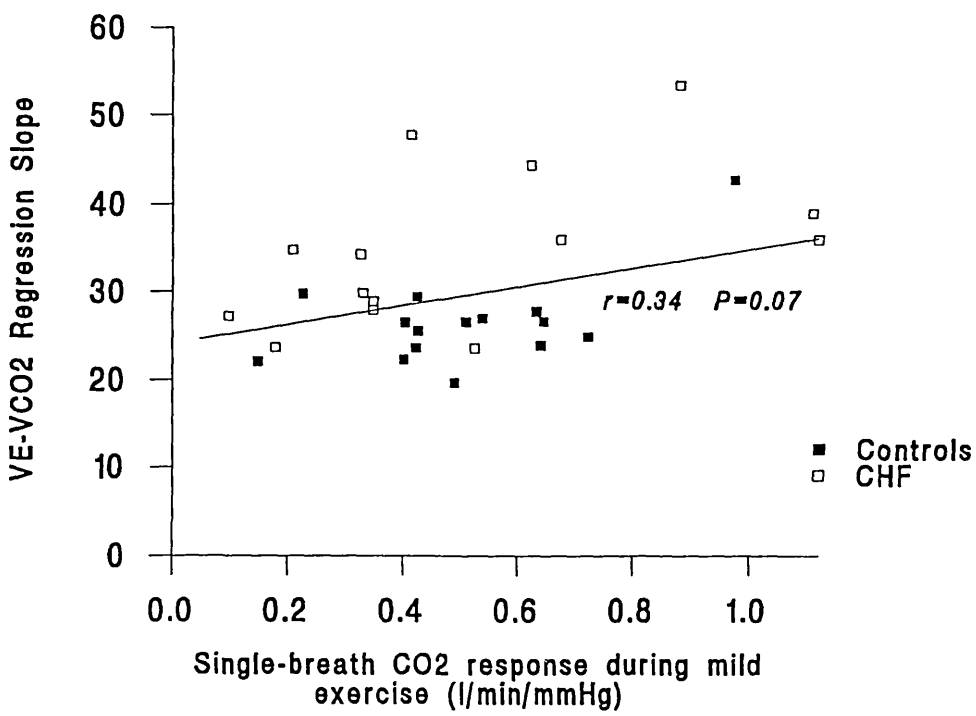

Figure 3.17 A strong trend is seen between peripheral hypercapnic chemosensitivity measured during mild exercise and the ventilatory response to exercise ($\dot{V}_E$-$\dot{V}CO_2$ regression slope).

Discussion

Comparability of the Transient Hypoxic and Single-breath Carbon Dioxide Ventilatory Response Tests

It was shown in the first part of this study that the transient hypoxic ventilatory responses correlated with height but not with age, compatible with the findings of Hirshman et al [1975] using the progressive hypoxic method. However, a significant correlation with weight or spirometric results was not demonstrated. There was no significant correlation between single-breath carbon dioxide responses and age, height, weight, body surface area or spirometric results. The significance of this observation is not known but may point towards the divergence of the two responses.

If the transient hypoxic and single-breath carbon dioxide ventilatory response tests are assessments of the peripheral chemoreflex, it is plausible that there should be a significant correlation between the two tests. This study however indicates that there is no correlation between the transient hypoxic and the single-breath carbon dioxide ventilatory response tests. It has been previously shown that there is a positive correlation between progressive hypoxic and *rebreathing* hypercapnic ventilatory response [Hirshman *et al*, 1975] but it must be borne in mind that the latter is a test of the central chemoreceptors [Read, 1966; Rebuck *et al*, 1973]. Furthermore, there appears to be no correlation between the single-breath carbon dioxide ventilatory response and rebreathing carbon dioxide response [McClean *et al*, 1988]. It has also been demonstrated that nitrendipine, a dihydropyridine Ca^{2+}-channel blocker, inhibited the release of dopamine, a neurotransmitter in the carotid body chemoreceptors, by hypoxia but not by hypercapnia [Gonzalez *et al*, 1994]. This suggests that although hypoxic and peripheral hypercapnic responses are mediated by the carotid body, the pathways are

partially separate, and this fact may account for our observations. When oxygen tension decreases, Ca^{2+}-channels are activated with Ca^{2+} entry, causing the release of neurotransmitter. On the other hand, hypercapnia acts indirectly by altering intracellular pH [Donnelly *et al*, 1982; Gonzalez *et al*, 1994]. Consequent to this, there is active H^+ extrusion from the chemoreceptor cells in exchange for Na^+. The rise in the intracellular Na^+ concentration triggers the Na^+-Ca^{2+} exchanger so that Na^+ is in turn extruded in exchange for entry of Ca^{2+}, causing the release of neurotransmitter.

The other possibility which may explain the lack of correlation between the two tests lies in the methodology of the single-breath carbon dioxide ventilatory response test. The single breath of 13% carbon dioxide may not have provided an adequate stimulus for the complete transduction of a ventilatory response. Carbon dioxide is thought to activate the carotid body chemoreceptors by its intracellular acidifying capacity as discussed above. The peripheral chemoreceptor response to carbon dioxide is therefore to a large extent indirectly dependent on the effects of hypercapnia on intracellular pH. Thus, fundamental differences in the methodology of the two tests may also explain the observation in this study. As the ventilatory responses 20 seconds after the stimulus breath of carbon dioxide were excluded, it is unlikely that the responses were influenced by the central chemoreflex. In studies which involve inactivation of peripheral chemoreceptors, there may be lag of up to 60 seconds before a ventilatory response is seen following a hypercapnic stimulus [Edelman *et al*, 1973; Gelfand *et al*, 1973; McClean *et al*, 1988]. Typical responses to hypoxia and single-breath carbon dioxide were seen within 20 seconds after the stimulus in this study as shown in Figures 3.1 and 3.2.

In summary, both the transient hypoxic and the single-breath carbon dioxide

ventilatory response tests are reproducible. In view of the lack of correlation between the two tests, however, both should ideally be undertaken in the assessment of the peripheral chemoreflex since the presence of a given hypoxic response does not imply a similar peripheral hypercapnic response and vice-versa. The single-breath carbon dioxide test on its own is not an adequate test of the peripheral chemoreflex and cannot be used to predict hypoxic chemosensitivity.

Chemosensitivity and the Ventilatory Response to Exercise in Chronic Heart Failure Patients

General findings

Little is known about chemosensitivity in chronic heart failure. It has been documented that central hypercapnic chemosensitivity is enhanced in chronic heart failure patients with central sleep apnoea but hypoxic chemosensitivity was not studied [Wilcox *et al*, 1993]. It was shown earlier in this chapter that there is increased hypoxic and central hypercapnic chemosensitivity in chronic heart failure patients. Patients in New York Heart Association functional class III had a higher chemosensitivity than those in class II although this was not statistically significant with respect to hypoxic chemosensitivity. The lack of differentiation may be because there is much overlap in hypoxic chemosensitivity between class II and III patients or perhaps hypoxic chemosensitivity is less associated with the functional capacity of patients. It has to be acknowledged that even in normal subjects both hypoxic and hypercapnic chemosensitivity may vary considerably between subjects [Hirshman *et al*, 1975]. However, the central hypercapnic chemosensitivity was significantly higher in patients with a worse functional class and may therefore relate more to the severity of chronic heart failure.

The absence of a significant increase in single-breath carbon dioxide response in chronic heart failure patients is surprising although not totally unexpected. As discussed earlier, the single-breath carbon dioxide response test measures the peripheral hypercapnic chemosensitivity. Functional hypercapnic chemosensitivity is predominantly mediated by the central chemoreceptors. Some studies have shown that the peripheral hypercapnic chemosensitivity accounts for only about a tenth of overall carbon dioxide chemosensitivity [Gelfand *et al*, 1973]. The single breath of 13% carbon dioxide may also not have provided an adequate stimulus for the complete transduction of a ventilatory response by the peripheral chemoreceptors as mentioned above.

Mechanisms causing increased chemosensitivity in chronic heart failure

There are several possible mechanisms causing increased hypoxic chemosensitivity in chronic heart failure patients. It is recognised that there are neurohormonal changes [Francis *et al*, 1990; Packer, 1992] in chronic heart failure patients and these include raised catecholamines. Catecholamines are known to potentiate chemosensitivity [Cunningham *et al*, 1963; Weil *et al*, 1972]. Peripheral blood flow is also known to be reduced in chronic heart failure [Levine & Levine; 1990] and this may be due to reduced cardiac output or increased vasomotor tone. It has been previously suggested that a fall in chemoreceptor blood flow, causing an ischaemic hypoxia, may also mediate an increase in chemosensitivity [Fidone & Gonzalez, 1986].

Mechanisms causing altered central hypercapnic chemosensitivity are more obscure. Alteration in central neurogenic input or signals from muscle ergoreceptors [Kao, 1963; Coats *et al*, 1994] may induce changes in central hypercapnic chemosensitivity. Alternatively, signals from muscle ergoreceptors may feed directly into

the respiratory control centres causing central augmentation of both medullary and carotid chemoreceptor input. Recent research in our laboratory has shown that the contribution of ergoreceptors to the ventilatory response to exercise is higher in chronic heart failure patients than in controls [Piepoli *et al*, 1995]. Early lactic acidosis during exercise may reduce the buffering ability in chronic heart failure patients with consequent increased chemoreceptor activity but this cannot explain the increased chemosensitivity at rest. Perhaps the interaction of carbon dioxide with other ventilatory control mechanisms may offer clues. It may be that the respiratory control centers are similarly and non-specifically more responsive to various stimuli including carbon dioxide and exercise [Dempsey *et al*, 1984].

Relationship between chemosensitivity and exercise ventilation

The role of chemosensitivity in mediating the ventilatory response to exercise is not known in chronic heart failure. In normal subjects, it has been shown in one study that carbon dioxide chemosensitivity as measured by the rebreathing method is related to the ventilatory response to exercise [Rebuck *et al*, 1972]. In another study, exercise ventilation has been shown to be positively correlated with both hypoxic and hypercapnic chemosensitivity in healthy subjects [Martin *et al*, 1978]. The mechanisms by which chemoreceptors may mediate exercise hyperpnea remain unclear given that there is little fluctuation in arterial blood gases, the putative stimuli, during exercise. Suggested mechanisms include an increased gain in chemosensitivity during exercise [Dejours 1963; Weil & Swanson. 1990]. Augmentation in chemosensitivity during exercise has been well-documented in normal subjects [Weil *et al*, 1972; Pandit & Robbins, 1994]. In other words, for a given partial pressure of arterial blood gases, it represents a higher stimulus

to ventilation than otherwise had the chemosensitivity not been enhanced. Thus the absence of significant hypoxaemia or hypercapnia does not exclude the existence of increased chemoreceptor-dependent ventilatory drive. In this study, there was an increase in hypoxic and central hypercapnic chemosensitivity measured at rest in chronic heart failure patients compared with normals. There was also a significant degree of correlation between the resting chemosensitivity and the ventilatory response to exercise. Hypoxic and hypercapnic (at least the peripheral component) chemosensitivity were shown to be augmented in chronic heart failure patients during exercise. Despite the augmentation, the relationship between hypoxic chemosensitivity and the ventilatory response to exercise remained significant and that between peripheral hypercapnic chemosensitivity and the ventilatory response to exercise became stronger. The latter probably suggests that the peripheral hypercapnic chemosensitivity plays an increasing role in the control of ventilation during exercise in comparison to the situation at rest.

The augmentation in chemosensitivity during exercise may be explained by further increase in catecholamines during exercise [Weil *et al*, 1972], elevation of arterial potassium level [Paterson, 1992], perhaps early lactic acidosis during exercise or other mediators as discussed in Chapter 1. Increased oscillations in arterial carbon dioxide, oxygen and pH caused by exercise and exaggerated in heart failure may also be a possible mechanism of augmentation of chemosensitivity during exercise. The potential importance of such oscillations as a mechanism by which chemoreceptors may affect exercise hyperpnea has been documented previously [Purves, 1966; Saunders, 1980; Cross, 1982]. In chronic heart failure, the increased ventilatory response to exercise is often attributed to the increase in dead space ventilation [Sullivan *et al*, 1988a]. However, it remains to be answered how this dead space is sensed by the body

particularly if arterial blood gases remain little changed in chronic heart failure [Wilson *et al*, 1984; Sullivan *et al*, 1988a; Clark & Coats, 1994]. Increased physiological dead space and ventilation-perfusion mismatch may well increase the amplitude of oscillations in blood gases which is sensed by chemoreceptors. They may therefore also be important in mediating the effects of increased dead space and ventilation-perfusion mismatch in chronic heart failure.

Conclusion

The increase in chemosensitivity may serve as a compensatory mechanism producing an increase in ventilatory response during exercise and thereby preserving blood gas homeostasis including maintaining arterial oxygen concentration. In fact, it has been shown that increasing inspired oxygen concentration during exercise improves breathlessness and reduces minute ventilation in these patients [Moore *et al*, 1992]. Other investigators have reported mechanisms such as increased erythropoiesis which directly improve arterial oxygen content in chronic heart failure patients to compensate for reduced systemic arterial oxygen delivery [Herlin & Sylven, 1991].

In conclusion, there is increased hypoxic and central hypercapnic chemosensitivity in chronic heart failure patients. Both hypoxic and hypercapnic chemosensitivity appear to correlate well with the ventilatory response to exercise. Although this association does not necessarily mean causation, arterial chemoreceptors may mediate the exercise hyperpnoea seen in patients with this condition. The control of ventilation during exercise is complex, probably more so in chronic heart failure. Therefore, whilst increased chemosensitivity may play a role in the exercise hyperpnoea in chronic heart failure, there are likely to be other factors involved. It remains to be seen whether drugs which

suppress chemosensitivity such as mild opiates [Woodcock *et al*, 1981] would be of therapeutic benefit in relieving the debilitating symptoms of breathlessness in chronic heart failure. This will be investigated in the next two chapters.

Limitations of the Study

With the transient hypoxic chemosensitivity test, both the arterial oxygen desaturation and the resultant ventilatory response are fleeting in nature. The measurement of arterial oxygen saturation and the use of a 2-breath period to define maximal minute ventilation in such conditions, although necessary under the constraints of the method, may give rise to errors. However, a pulse oximeter (Nellcor N-200E, U.S.A.) with a fast response time of 2 to 3 seconds was used in our study. Previous studies have demonstrated the accuracy ($< \pm 3$ percent) and reliability of arterial oxygen saturation obtained by pulse oximeter of this particular model in comparison to direct measurement of arterial blood samples [Hannhart *et al*, 1991; Barker *et al*, 1993]. Furthermore, as shown by Shaw et al [1982], the transient method can give as good an index of hypoxic chemosensitivity as the progressive method.

Some subjects felt an acid taste of the 13% carbon dioxide used in the single-breath carbon dioxide test although none developed a cough. The acid taste may have affected ventilation and is a potential drawback of this method. However, the overall results of the single-breath carbon dioxide test in the control population in this study compare favourably with previous data [McClean *et al*, 1988; Sebert *et al*, 1990].

From the results of the first 15 consecutive chronic heart failure patients, the hypoxic chemosensitivity was found to be significantly higher in chronic heart failure patients compared with controls, both at rest and during exercise. The assessment of the

exercise chemosensitivity of the remaining patients was therefore discontinued, primarily because hypoxia during exercise was unpleasant to patients and had a certain risk associated. These 15 patients had similar age, exercise capacity, radionuclide ejection fraction and resting chemosensitivity compared with all the chronic heart failure patients studied as a whole. A randomly chosen subgroup of subjects underwent the carbon dioxide rebreathing test with which it was demonstrated that the central hypercapnic chemosensitivity was increased in chronic heart failure patients. The measurement of central hypercapnic chemosensitivity was not attempted during exercise, for reasons stated, which may have otherwise added more information to the study.

Finally, because of the obvious limitation of using ventilatory changes to quantitate chemosensitivity, it is not possible to distinguish whether the increased ventilatory responses to hypoxia or hypercapnia are solely due to an increased gain in intrinsic chemoreceptor function or whether they reflect the altered kinetics caused by an increased dead space in heart failure. However, as discussed earlier, there are several abnormalities in chronic heart failure which may cause an increased chemosensitivity, thus making it unlikely that the results in this study are largely due to an increased dead space. Furthermore, there is a fundamental difference between the ventilatory response to metabolic changes during exercise and the ventilatory response to hypoxia or hypercapnia as in the tests of chemosensitivity, in relation to dead space. The ventilatory response to exercise represents a response to an endogenous load whereas the ventilatory response to hypoxia or hypercapnia represents that to an external stimulus. An increased dead space may therefore actually diminish the level of the external stimulation reaching the arterial chemoreceptors. That there was an increase in chemosensitivity therefore suggests that there is an inherent change in chemoreceptor function.

Chapter 4

THE CONTRIBUTION OF PERIPHERAL CHEMORECEPTORS TO VENTILATION AND THE EFFECTS OF THEIR SUPPRESSION ON EXERCISE TOLERANCE IN CHRONIC HEART FAILURE

Introduction

Patients with chronic heart failure exhibit reduced exercise tolerance which may be related to dyspnoea and fatigue. They also demonstrate increased ventilation when compared with normal subjects [Sullivan *et al*, 1988a; Buller & Poole-Wilson, 1990]. This increased ventilation may partially contribute to the symptom of dyspnoea [Rubin & Brown, 1984]. The mechanisms underlying the increased ventilation especially during exercise are not fully understood. In Chapter 3, both hypoxic and central hypercapnic chemosensitivity were shown to be enhanced in chronic heart failure patients and they may partly contribute to the increased ventilatory response to exercise.

Hypoxic chemosensitivity is mediated by peripheral chemoreceptors. Hyperoxia is known to suppress the peripheral chemoreceptors and the consequent fall in ventilation therefore reflects their contribution to ventilation [Dejours, 1962]. Although there is an increase in chemosensitivity, the contribution of peripheral chemoreceptors to ventilation in chronic heart failure patients remains unknown. It may be that the contribution of peripheral chemoreceptors to overall control of ventilation remains unchanged considering the latter is likely to be multifactorial as discussed in Chapter 1, possibly involving central neurogenic drive [Eldridge *et al*, 1985], central chemoreceptors [Chua *et al*, 1995], cardiac mechanoreceptors [Uchida 1975 & 1976; Jones *et al*, 1982], and

muscle ergoreceptors [Iaria *et al*, 1959; Kao, 1963], and the input of some, if not all, of these factors may also be increased. On the other hand, if the contribution of the peripheral chemoreceptors is enhanced, its role in the control of ventilation may be more than that of the other factors in chronic heart failure. It has been shown by Dejours and other investigators that the contribution of the peripheral chemoreceptors to ventilation in normal subjects is between 10% to 20% [Dejours, 1962; Wassermann K, 1976; Jeyaranjan *et al*, 1989].

In this chapter, the contribution of the peripheral receptors to ventilation at rest and during mild exercise was investigated by transient hyperoxic suppression. Transient hyperoxia was used in order to prevent other opposing confounding factors such as the accumulation of carbon dioxide consequent to the fall in ventilation [Dejours, 1962]. In the second part of this study, however, the effects of continuous inspired oxygen on incremental treadmill exercise was examined. The study was approved by the local ethics committee and subjects gave written informed consent.

Subjects and Methods

Part 1

Thirteen patients with chronic heart failure (10 men; age 60.5±2.1 years; radionuclide left ventricular ejection fraction 25.5±4.2%) and 8 healthy control subjects (6 men; age 52.0±4.7 years) participated in the first part of this study. All patients had been in heart failure for more than six months and none had a history of acute decompensation within this period. All subjects were well acquainted with the exercise laboratory and had previously participated in cardiopulmonary exercise testing. Subject characteristics are further given in Table 4.1.

	Normal Controls (n=8)	Chronic Heart Failure (n=13)
Age (years)	52.0±4.7	60.5±2.1
Sex (M/F)	6/2	10/3
Height (cm)	170.3±2.8	171.5±2.3
Weight (kg)	71.2±4.8	82.7±2.3
Spirometry		
FEV_1 (% predicted)	104.4±7.6	87.5±4.1
FVC (% predicted)	112.3±7.0	86.5±4.1
Aetiology of CHF		IHD 7 DCM 6
Symptoms (NYHA)		II 7 III 6
Left Ventricular Ejection Fraction (MUGA %)		25.5±4.3
Treatment		
Diuretics		n = 13
(Dose of frusemide or its equivalent*)		(43.08±6.7 mg)
ACE Inhibitors		n = 12

Values expressed as means±SEM.

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NYHA, New York Heart Association classification of symptoms; MUGA, multigated radionuclide ventriculography; IHD, ischaemic heart disease; DCM, idiopathic dilated cardiomyopathy; ACE inhibitors, angiotensin-converting enzyme inhibitors

*1 mg bumetanide is taken as equivalent to 40 mg frusemide.

Table 4.1 Characteristics of normal subjects and chronic heart failure patients who participated in the first part of the study in this chapter looking at the effects of transient hyperoxia on ventilation.

Subjects were told to avoid caffeinated products on the morning of the test. They were seated, wore a noseclip and after a period of quiet breathing through a pneumatic respiratory valve (Innovision, Odense, Denmark), they were given transient inhalations of 100% oxygen for 3 breaths, without them being aware of the timing of these inhalations, from a 4-litre reservoir bag quietly refilled with pure oxygen. Minute ventilation was measured breath-by-breath using a heated pneumotachograph and continuous monitoring of oxygen and carbon dioxide was done at the mouth by mass spectrometry (Amis 2000, Innovision, Odense, Denmark). The pneumotachometer and mass spectrometer were calibrated before each test. The average minute ventilation of the preceding 5 breaths before the inhalation of 100% oxygen was taken as the baseline ventilation. The minute ventilation of ten breaths following the commencement of oxygen inhalation was analysed and that of the smallest breath noted. This was repeated, on average, four times for each subject after the end-tidal oxygen had return to its initial level. The mean baseline ventilation and that of the smallest breath following hyperoxia were calculated from these 4 transients. The magnitude of fall in ventilation, both in absolute values as well as expressed as a percentage of the baseline ventilation, was accordingly analysed.

Following a 20-minute interval, the subjects then had the same procedure repeated as above but this time during mild exercise on a cycle ergometer (Tunturi, Finland) at 25 W. Inhalations of 100% oxygen were not given until 3 minutes after the onset of exercise to allow steady state [Sietsema *et al*, 1994].

On another day, the subjects returned for the assessment of their peripheral chemosensitivity. This was performed using the transient hypoxic ventilatory response test which was described in the last chapter [Shaw *et al*, 1982; Chua & Coats, 1995a].

Part 2

The effects of suppression of peripheral chemoreflex with continuous inspired 100% oxygen on exercise ventilation and exercise tolerance were assessed in a second group of 12 chronic heart failure patients (all men; age 65.5±1.5 years; radionuclide left ventricular ejection fraction 21.3±3.0%). They were stable and did not have a history of acute decompensation for at least 6 months prior to the study. Patient characteristics are given in Table 4.2.

The patients underwent treadmill cardiopulmonary exercise testing on two occasions breathing air or 100% oxygen in a randomised single blind manner using the Bruce protocol [Bruce *et al*, 1963] with the addition of a "Stage 0" at 1.0 mph and 5% gradient. Each patient wore a noseclip and breathed through a pneumatic respiratory valve. The inspirate port was further connected to a T-valve placed away from the patient and depending on the position of the T-valve, the subject breathed either room air or 100% oxygen from a Douglas bag constantly refilled with oxygen. Respiratory gas exchange analysis (oxygen consumption, carbon dioxide output, minute ventilation) was carried out by means of breath-by-breath analysis using respiratory mass spectrometry and a heated pneumotachograph [Beaver *et al*, 1973]. The analysis of oxygen consumption during exercise on continuous inspired 100% oxygen was not performed due to technical difficulties in the use of the mass spectrometry method during oxygen breathing. Heart rate, assessed electrocardiographically, and blood pressure, measured manually using a mercury sphygmomanometer, were recorded before exercise, at the end of each 3-minute exercise stage and at peak exercise. Arterial oxygen saturation was measured with a pulse oximeter (Model N-200E, Nellcor, Hayward, California, USA) and a probe placed on the right supraorbital artery. At the end of each exercise stage and

Age (years)	65.5±1.5
Sex	All male
Height (cm)	172.9±1.8
Weight (kg)	77.4±3.1
Spirometry	
FEV_1 (% predicted)	90.5±4.9
FVC (% predicted)	89.9±4.4
Aetiology of CHF	IHD 8 DCM 4
Symptoms (NYHA)	II 6 III 6
MUGA Left Ventricular Ejection Fraction (%)	21.3±3.0
Treatment	
Diuretics	n = 12
(Dose of frusemide or its equivalent*)	(65±11.8 mg)
ACE Inhibitors	n = 12

Values expressed as mean±SEM.

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NYHA, New York Heart Association classification of symptoms; MUGA, multigated acquisition radionuclide ventriculography; IHD, ischaemic heart disease; DCM, idiopathic dilated cardiomyopathy; ACE inhibitors, angiotensin-converting enzyme inhibitors

*1 mg bumetanide is taken as equivalent to 40 mg frusemide.

Table 4.2 Clinical characteristics of chronic heart failure patients who participated in the second study looking at the effects of continuous inspired oxygen during exercise.

at peak exercise, the patient was also asked to score the level of dyspnoea and fatigue using a modified Borg scale [El-Manshawi *et al*, 1986]. The scale rates the level of perceived symptoms from 0 (none) to 10 (maximum) as shown in Appendix 3. Patients were also asked the major symptom which stopped them from continuing after each exercise testing.

Statistical Analysis

Statistical analysis was performed using paired and unpaired Student's *t* test as appropriate. $P < 0.05$ was considered significant. Results are expressed as mean$\pm$SEM.

Results

Part 1

The results of the hyperoxic suppression of ventilation are summarised in Table 4.3. There was a trend towards a higher baseline ventilation at rest in patients with chronic heart failure (P=0.13). Following the transient inhalation of 100% oxygen, there was a significant fall in ventilation from baseline of 2.0$\pm$0.4 l/min in normals (P=0.001) and 2.7$\pm$0.4 l/min in chronic heart failure patients (P=0.0001) but the fall was not significantly different between the two groups. This fall in ventilation amounted to 18.1% of baseline ventilation in normals and 17.9% in chronic heart failure patients (P=NS). On average, the minute ventilation was smallest at the sixth breath for normals and seventh breath for chronic heart failure patients following inhalation of oxygen (P=NS). During mild exercise at 25 W on the cycle ergometer, there was again a strong trend towards a higher minute ventilation in chronic heart failure patients (P=0.056). In absolute terms, the fall in exercise ventilation with transient oxygen inhalations was

5.5±1.0 in normals (P=0.001) and 6.3±0.6 l/min in chronic heart failure patients (P<0.0001). Expressed as a percentage of the exercise minute ventilation before the inhalation of oxygen, this was 20.4% in normals and 21.0% in chronic heart failure patients (P=NS). On average, the minute ventilation was smallest at the sixth breath for both groups of subjects following inhalation of oxygen during mild exercise.

	Controls (n=8)	**Chronic Heart Failure** (n=13)	***P* value**
Rest			
Baseline Minute Ventilation (l/min)	11.8±0.9	14.5±1.2	0.13
Post-Hyperoxia Minute Ventilation (l/min)	9.8±1.0	11.8±1.2	0.19
Magnitude of Decrease in Ventilation (%)	18.1±2.9	17.9±2.6	NS
Cycle Ergometry (25W)			
Minute Ventilation (l/min)	26.0±1.1	29.7±1.5	0.056
Post-Hyperoxia Minute Ventilation (l/min)	20.5±0.2	23.4±1.1	0.025
Magnitude of Decrease in Ventilation (%)	20.4±2.8	21.0±1.7	NS

Values expressed as mean±SEM.

Table 4.3 Summary of the transient hyperoxic suppression of ventilation at rest and during mild exercise in controls and chronic heart failure patients.

Peripheral chemosensitivity at rest, as measured by the transient hypoxic ventilatory response test, this was higher in patients (0.572±0.082 v 0.232±0.022 l/min/%SaO_2; P=0.002).

Part 2

The results of the treadmill cardiopulmonary exercise test are shown in Table 4.4. Continuous inspired 100% oxygen significantly increased exercise time. There was also a trend towards a reduction in the ventilatory response to exercise, as characterised by a shallower regression slope relating minute ventilation to carbon dioxide output, with inspired oxygen. A reduction in heart rate and systolic blood pressure at peak exercise was seen but this was not statistically significant. The effects of continuous inspired 100% oxygen on minute ventilation, end-tidal carbon dioxide, arterial oxygen saturation and carbon dioxide output are summarised in Table 4.5. There was a trend towards a reduction in minute ventilation at submaximal exercise. End-tidal carbon dioxide concentration also increased steadily during exercise with inspired oxygen in contrast to the fall seen at peak exercise with air. In terms of arterial oxygen saturation, there was a small reduction in the peak value compared with that at rest when patients exercised breathing air. Continuous inspired oxygen minimised this drop in arterial oxygen saturation. The peak arterial oxygen saturation was also higher during oxygen breathing than air breathing. There was a non-statistically significant reduction in carbon dioxide output with inspired oxygen at rest and submaximal exercise. The modified Borg scores for dyspnoea and for fatigue are given in Table 4.6. There was a trend towards an improvement in the symptom of dyspnoea at submaximal exercise with inspired oxygen compared with air (-0.8 at 6 minutes of exercise; $P=0.05$). No significant difference was noted for fatigue. With air breathing, the major limiting symptom at peak exercise was dyspnoea in 10 patients and fatigue in the remaining 2 patients. Of these 10 patients, the predominant limiting remained dyspnoea in eight of them while the other two became limited by fatigue, with oxygen breathing.

	Air	*100% Oxygen*	*P* value
Exercise duration (s)	455±27	517±31	0.003
Peak Oxygen Consumption (ml/kg/min)	18.0±0.6	-	-
$\dot{V}_E$-$\dot{V}CO_2$ regression slope	34.19±2.35	31.27±2.60	0.08
Respiratory exchange ratio (*R*)	1.26	-	-
Heart rate at rest (min^{-1})	73±3	72±3	NS
Heart rate at peak exercise (min^{-1})	132±6	129±5	NS
Systolic blood pressure at rest (mmHg)	118±7	121±7	NS
Systolic blood pressure at peak exercise (mmHg)	144±10	129±5	NS

Values expressed as mean±SEM.

$\dot{V}_E$-$\dot{V}CO_2$ regression slope is the slope of the regression line relating minute ventilation and carbon dioxide output during exercise and is a measure of the ventilatory response to exercise.

Table 4.4 Cardiopulmonary exercise results in 12 chronic heart failure patients breathing air or continuous inspired 100% oxygen.

	Air	*100% Oxygen*	*P* value
Rest			
Minute Ventilation (l/min)	13.9±1.1	14.3±2.0	NS
End-tidal CO_2 (%)	4.95±0.17	4.67±0.26	NS
Arterial oxygen saturation (%)	100.0±0	100.0±0	NS
Carbon dioxide output (ml/min)	332.1±41.5	300.1±40.5	NS
3 minutes			
Minute Ventilation (l/min)	31.9±1.9	30.2±2.3	NS
End-tidal CO_2 (%)	5.05±0.15	5.11±0.22	NS
Arterial oxygen saturation (%)	99.8±0.1	100.0±0	0.17
Carbon dioxide output (ml/min)	838.9±68.3	825.2±69.4	NS
6 minutes			
Minute Ventilation (l/min)	48.0±3.7	43.8±2.8	0.10
End-tidal CO_2 (%)	4.95±0.27	5.18±0.15	NS
Arterial oxygen saturation (%)	99.5±0.3	99.9±0.1	0.04
Carbon dioxide output (ml/min)	1335.7±87.4	1229.9±61.5	0.33
Peak Exercise			
Minute Ventilation (l/min)	57.34±4.7	58.6±5.8	NS
End-tidal CO_2 (%)	4.66±0.22	5.07±0.34	0.19
Arterial oxygen saturation (%)	99.4±0.3	99.9±0.1	0.05
Carbon dioxide output (ml/min)	1765.0±110.0	1896.0±125.0	NS

Values expressed as mean±SEM.

Table 4.5 Summary of the effects of continuous inspired 100% oxygen on minute ventilation, end-tidal carbon dioxide, arterial oxygen saturation and carbon dioxide output in comparison to air during incremental exercise testing in 12 chronic heart failure patients.

	Borg score (*dyspnoea*)			Borg score (*fatigue*)		
	Air	**100% Oxygen**	***P* value**	**Air**	**100% Oxygen**	***P* value**
3 minutes	1.17±0.35	1.33±0.28	NS	1.33±0.36	1.25±0.30	NS
6 minutes	3.60±0.22	2.75±0.37	0.05	3.00±0.49	2.79±0.39	NS
Peak Exercise	5.67±0.74	5.75±0.48	NS	5.71±0.54	5.92±0.63	NS

Values expressed as mean±SEM.

Table 4.6 Modified Borg scores for dyspnoea and for fatigue with air and inspired 100% oxygen showing a trend in the reduction of perception of dyspnoea at submaximal exercise with the latter.

Discussion

Part 1

The contribution of peripheral chemoreceptors to ventilation in chronic heart failure patients is hitherto unknown. We have shown in this study that by suppressing the peripheral chemoreceptor drive with the transient inhalation of 100% oxygen, the percentage reduction in ventilation in chronic heart failure patients was not significantly different from normal subjects despite the fact that these patients have an increased peripheral chemoreceptor sensitivity. There are two possible explanations. The first is that peripheral chemoreceptors are not an important factor in the mediation of ventilatory response to exercise and however increased the chemosensitivity may be, it has little influence on exercise ventilation. This is probably unlikely considering that chemosensitivity correlates well with ventilatory response to exercise in normal individuals [Martin *et al*, 1978]. As shown in the last chapter, there was also a modest but significant correlation between peripheral chemosensitivity and ventilatory response to exercise in chronic heart failure patients. Furthermore, in subjects with bilateral carotid resection for the management of asthma, the exercise ventilatory dynamics are known to be significantly delayed [Lugliani *et al*, 1971]. The second and more plausible explanation is that the input from other modulators of exercise ventilation in chronic heart failure is also increased so that despite an augmented peripheral chemosensitivity, the overall contribution of the peripheral chemoreceptors to ventilation remains similar in percentage terms to controls. Other than the peripheral chemoreflex, modulators such as the central chemoreflex, metaboreflex and cardiac mechanoreflex may also play a role, all interacting to produce the exercise hyperpnoea seen in these patients. The tendency to hyperpnoea was demonstrated even at rest and during mild exercise in

chronic heart failure patients in this study in keeping with previous data [Sullivan *et al*, 1988a].

The increased peripheral chemoreceptor sensitivity in these patients may be due to several factors as previously discussed. There is sympathetic overactivity in chronic heart failure and this is known to potentiate peripheral chemosensitivity [Cunningham *et al*, 1963]. In addition, the arterial baroreflex is known to inhibit chemoreflex activity [Shepherd, 1987] and thus, the impaired baroreflex sensitivity in chronic heart failure patients may also give rise to an augmented chemosensitivity. Another possible factor causing an increased peripheral chemosensitivity is ischaemic hypoxia due to a reduction in chemoreceptor blood flow [Fidone & Gonzalez, 1986] since peripheral blood flow is known to be reduced in chronic heart failure patients [Levine & Levine, 1990].

There are limitations to the first part of this study. It is assumed that there is abolition of the peripheral chemoreceptor drive with inhalation of three breaths of pure oxygen as had been shown previously with a single or two breaths of oxygen [Dejours, 1962]. It is possible that because of the increased chemosensitivity in chronic heart failure patients, there is failure to abolish the chemoreceptor drive completely despite the additional breath of oxygen and hence the percentage reduction may be less than expected. Further prolonging the inhalation of oxygen was not attempted because this will not only suppress the peripheral chemoreceptor drive but may provoke changes in other secondary factors which will affect ventilation such as increased arterial carbon dioxide tension, a lowered arterial pH, a decrease in cerebral blood flow and also other metabolic changes due to variation in tissue oxidation.

Part 2

The second part of this study was to investigate the effects of continuous inspired oxygen on exercise tolerance in chronic heart failure patients. It was shown that inspired oxygen increased exercise duration. This is compatible with previous studies with normals [Bannister & Cunningham, 1954; Asmussen & Nielsen, 1958; Kozlowski *et al*, 1971; Chronos *et al*, 1988] and chronic heart failure patients [Moore *et al*, 1992]. There are several possible ways that oxygen may improve exercise tolerance in these patients. Firstly, that oxygen suppressed the peripheral chemoreceptor drive and consequently reduced ventilation was shown in Part 1 of this study. With reduced ventilation, the work of breathing is conceivably reduced and this may contribute to the increased exercise tolerance. Secondly, a concomitant reduction in the perception of breathlessness was noted, also in keeping with other studies [Bannister & Cunningham, 1954; Chronos *et al*, 1988; Moore *et al*, 1992]. Thus symptom reduction may also have contributed to the increased exercise tolerance.

This study however does not provide any information regarding the nature of the relationship between ventilation and dyspnoea despite their close association. It may be that the afferent signals from the peripheral chemoreceptors not only act on the medullary respiratory centres but are also directly perceived as breathlessness. On the other hand, the effects of oxygen on ventilation and breathlessness may be two separate entities with oxygen having a direct effect on the sensory cortex modifying the perception of dyspnoea [Chronos *et al*, 1988]. The reduced effort of breathing associated with decreased ventilation may also lead to the reduction in the sensation of dyspnoea. Alteration of the "length:tension inappropriateness" may also reduce the perception of dyspnoea [Campbell & Howell, 1963; Manning & Schwartzstein, 1995]. According to

the "length:tension inappropriateness" theory, dyspnoea arises from a disturbance in the relation between the force generated by the respiratory muscles ("tension") and the resulting change in ventilation (which is determined by lung volume and respiratory rate and thus muscle "length").

With continuous inspired oxygen, there was only a trend for a reduction in ventilation during exercise in comparison to the significant hypoventilation with transient hyperoxia. This may be due to the fact that in the former, exercise was maximal and symptom-limited while in the latter, mild exercise was used. More importantly, as alluded to earlier, with continuous inspired oxygen, changes in secondary factors affecting ventilation such as increased arterial carbon dioxide tension and a lowered arterial pH consequent to hyperoxia-induced hypoventilation and also to the Haldane effect [Guyton, 1991a], may increase ventilation by acting on central chemoreceptors. Also with hyperoxia, there may be a decrease in cerebral blood flow causing cerebral acidosis with the consequence of stimulating ventilation [Jeyaranjan *et al*, 1989].

The third possible mechanism whereby oxygen may improve exercise tolerance is by increasing oxygen delivery to the muscles and hence reducing anaerobic metabolism [Kozlowski *et al*, 1971]. Although plasma lactate was not measured, a non-significant reduction in carbon dioxide output during submaximal exercise with oxygen breathing was seen which may have reflected the facilitation of aerobic metabolism of exercising muscles to a small extent. In one previous study with chronic heart failure patients, however, it was shown that oxygen delivery remained unchanged despite increased arterial oxygen saturation with oxygen breathing due to the associated reduction in cardiac output [Moore *et al*, 1992]. Thus, bearing these considerations in mind, it may well be that the predominant mechanism of increased exercise tolerance with oxygen

breathing in chronic heart failure is secondary to its effects on the peripheral chemoreceptors with the associated reduction in ventilation and breathlessness. It is also pertinent to note that the 2 patients who were limited by muscle fatigue when exercising breathing air remained limited by this with inspired oxygen. On the contrary, of the 10 patients who were limited by dyspnoea when exercising breathing air, 8 remained limited by this and 2 by fatigue with inspired oxygen. Thus it appears that inspired oxygen may modify the perception of breathlessness more than it does fatigue.

Conclusion

Transient oxygen reduces ventilation in chronic heart failure patients by suppressing the peripheral chemoreceptor drive. The contribution of peripheral chemoreceptors to ventilation in chronic heart failure appears similar to normals. This suggests that peripheral chemoreceptors are not the main contributory cause to increased ventilation in these patients and that there are other factors involved. Continuous inspired oxygen improved exercise tolerance in these patients and this is probably due to the decrease in ventilation and the improvement in the perception of dyspnoea although the reduction of skeletal muscle anaerobiosis as another contributory factor cannot be fully excluded.

Chapter 5

THE EFFECTS OF DIHYDROCODEINE ON CHEMOSENSITIVITY AND EXERCISE TOLERANCE IN PATIENTS WITH CHRONIC HEART FAILURE

Introduction

Whilst the survival of patients with chronic heart failure has improved with vasodilator therapy especially angiotensin-converting enzyme inhibitors [Cohn *et al*, 1986; CONSENSUS Trial Study Group, 1987; SOLVD Investigators, 1991; Cohn *et al*, 1991], the symptoms remain debilitating. Patients are often limited by exertional dyspnoea. The origin of dyspnoea is multifactorial [Wasserman & Casaburi, 1988; Manning & Schwartzstein, 1995] but the increased ventilation seen during exercise in these patients may play a role [Rubin & Brown, 1984]. Apart from the increased ventilation, these patients also have an abnormal breathing pattern such that at a given minute ventilation, respiratory rate is increased whilst the change in tidal volume is less significant compared with normal subjects [Rubin & Brown, 1984; Sullivan *et al*, 1988a]. The onset of dyspnoea during exercise may indeed be related to the disproportionate increase in respiratory rate relative to tidal volume during exercise [Yokoyama *et al*, 1994]. In Chapter 3, the chemosensitivity to arterial blood gases of chronic heart failure patients has been shown to be augmented which may in part contribute to the increased ventilation of these patients.

Opiate drugs have a respiratory depressant effect and are used to relieve breathlessness, morphine being used in the treatment of acute pulmonary oedema and also in the palliation of breathlessness in malignancies [Cohen *et al*, 1992] and

dihydrocodeine in the palliation of breathlessness in chronic obstructive pulmonary disease [Woodcock *et al*, 1981]. Accordingly, dihydrocodeine has also been shown to increase the exercise tolerance of patients with chronic obstructive pulmonary disease [Woodcock *et al*, 1981]. Respiratory depression may be due to the reduced responsiveness of chemoreceptors to arterial blood gases as was demonstrated with the acute administration of morphine [Weil *et al*, 1975]. Hitherto, the effects of opiates on the exertional dyspnoea and exercise tolerance in chronic heart failure patients have not been studied. The effects of dihydrocodeine, a mild opiate which can be conveniently taken orally, on chemosensitivity and the exercise tolerance in these patients were therefore investigated and the findings presented in this chapter.

Patients and Methods

12 male patients with stable chronic heart failure and in New York Heart Association functional class II and III were studied. The mean age was 65.5±1.5 (SEM) years (range 58-75 years) and all patients had a multigated acquisition radionuclide left ventricular ejection fraction of less than 40% (mean 21.3±3.0%, range 8-39%). The aetiology of chronic heart failure is shown in Table 5.1. All patients were taking diuretics and angiotensin-converting enzyme inhibitors and were non-oedematous. None of them had chest pain or inducible ischaemia during previous exercise testing or a history of pulmonary disease. Hypoxic and central hypercapnic chemosensitivity were assessed in these patients one hour after the patients received placebo or dihydrocodeine (1 mg per kg of body weight) in a randomised double-blind design on two separate days, followed by treadmill exercise testing on each occasion. The assessment of peripheral hypercapnic chemosensitivity was omitted because of the previous finding that this was

not significantly different from normal controls as discussed in Chapter 3. The placebo and dihydrocodeine were given in the form of a drink made up to 200 ml with bitter lemon prepared by the Department of Pharmacy, Royal Brompton National Heart & Lung Hospital. The study had been approved by the local ethics committee and all patients gave informed written consent.

Hypoxic chemosensitivity was assessed using the transient hypoxic ventilatory response method as described earlier. Briefly, after a period of quiet breathing in room air, the patients were given transient inhalations of pure nitrogen, without being aware of the timing of these inhalations, for two to eight breaths. This was repeated ten times so as to provide a wide range of arterial oxygen saturations from 75% to 100%, with appropriate intervals of air breathing between exposures to allow arterial oxygen saturation and end-tidal carbon dioxide concentration to return to baseline. The maximal minute ventilation following each period of nitrogen inhalation was obtained by averaging the largest 2 consecutive breaths using breath by breath analysis with a heated pneumotachograph (Amis 2000, Innovision, Odense, Denmark), calibrated before each test. Continuous monitoring of oxygen and carbon dioxide was done at the mouth by respiratory mass spectrometry (Amis 2000, Innovision, Odense, Denmark), also calibrated before each test. Arterial oxygen saturation was measured using a pulse oximeter (Model N-200E, Nellcor, Hayward, California, USA) set at fast mode with a response time of 2 to 3 seconds and a lightweight probe clipped gently on the patients' right ear lobe. Minute ventilation was plotted against the lowest arterial oxygen saturation reached for each period of nitrogen inhalation. The hypoxic chemosensitivity was obtained as the slope of the regression line relating minute ventilation to arterial oxygen saturation and expressed in terms of litres per minute per percent oxygen

saturation (l/min/%SaO_2).

Central hypercapnic chemosensitivity was assessed using the rebreathing of 7% carbon dioxide in 93% oxygen through a 6-litre bag for 4 minutes. Minute ventilation was measured breath-by-breath using a heated pneumotachograph and continuous monitoring of oxygen and carbon dioxide was done at the mouth by respiratory mass spectrometry. Hypercapnic chemosensitivity was obtained as the slope of the regression line relating minute ventilation to end-tidal carbon dioxide concentration and expressed in terms of litres per minute per mm Hg (l/min/mmHg).

Cardiopulmonary exercise testing was performed using the Bruce protocol [Bruce *et al*, 1963] with the addition of a "Stage 0" at 1.0 mph and 5% gradient. Respiratory gas exchange analysis (oxygen consumption, carbon dioxide output and minute ventilation) was carried out breath-by-breath by means of respiratory mass spectrometry and a heated pneumotachograph, calibrated before each exercise testing [Beaver *et al*, 1973]. Heart rate, assessed electrocardiographically, and blood pressure, measured manually using a mercury sphygmomanometer, were recorded before exercise, at the end of each 3-minute exercise stage and at peak exercise. Arterial oxygen saturation was measured with a pulse oximeter (Model N-200E, Nellcor, Hayward, California, USA) and a probe placed on the right supraorbital artery. At the end of each exercise stage and at peak exercise, the patient was also asked to score the level of dyspnoea and fatigue using a modified Borg scale [El-Manshawi *et al*, 1986]. The scale rates the level of perceived symptoms from 0 (none) to 10 (maximum). Patients were also asked the major symptom which stopped them from continuing after each exercise testing.

Statistical analysis was performed using the paired Student's *t* test. $P < 0.05$ was considered significant. The results are expressed as mean$\pm$SEM.

Age (years)	65.5±1.5
Sex	All male
Height (cm)	172.9±1.8
Weight (kg)	77.4±3.1
Spirometry	
FEV_1 (% predicted)	90.5±4.9
FVC (% predicted)	89.9±4.4
FEV_1/FVC (%)	80.6±3.2
Aetiology of CHF	IHD 8 DCM 4
Symptoms (NYHA)	II 6 III 6
MUGA Left Ventricular Ejection Fraction (%)	21.3±3.0
Treatment	
Diuretics	*n*=12
(Dose of frusemide or its equivalent*)	(65±11.8 mg)
ACE Inhibitors	*n*=12

Values expressed as mean±SEM.

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NYHA, New York Heart Association classification of symptoms; MUGA, multigated acquisition radionuclide ventriculography; IHD, ischaemic heart disease; DCM, idiopathic dilated cardiomyopathy; ACE inhibitors, angiotensin-converting enzyme inhibitors

*1 mg bumetanide is taken as equivalent to 40 mg frusemide.

Table 5.1 Clinical characteristics of chronic heart failure patients in the study.

Results

All patients completed the study. Only one patient felt nauseated after dihydrocodeine but this manifested only after he completed the exercise testing.

Table 5.2 shows the significant reduction in hypoxic and hypercapnic chemosensitivity following the administration of dihydrocodeine. This reduction amounted to 40% for the hypoxic chemosensitivity and 16% for hypercapnic chemosensitivity when compared with placebo. The results of the cardiopulmonary exercise tests are shown in Table 5.3. Peak oxygen consumption increased from 18.0 ml/kg/min to 19.7 ml/kg/min after dihydrocodeine (P=0.002). There was also a significant improvement in exercise time. The ventilatory response to exercise, characterised by the slope of the regression line relating minute ventilation and carbon dioxide output during exercise, reduced by approximately 10% with dihydrocodeine compared with placebo. The respiratory exchange ratio (R) at peak exercise increased with dihydrocodeine but this was not statistically significant. The predominant limiting symptom at peak exercise on placebo was dyspnoea in ten patients and fatigue in two. Of these ten patients, the major limiting symptom at peak exercise on dihydrocodeine remained dyspnoea for eight of them while the remaining two were limited by fatigue.

	Placebo	**Dihydrocodeine**	***P* value**
Hypoxic Chemosensitivity (l/min/%SaO_2)	0.746±0.104	0.447±0.096	0.005
Hypercapnic Chemosensitivity (l/min/mmHg)	2.966±0.283	2.480±0.234	0.01

Values expressed as mean±SEM

Table 5.2 Chemosensitivity of patients after placebo and dihydrocodeine administration.

Footnote for Table 5.2

As seen in Table 5.2, the mean change in hypoxic chemosensitivity comparing dihydrocodeine with placebo was -0.299 l/min/%SaO_2 (95% Confidence Interval -0.488, -0.112) and in central hypercapnic chemosensitivity was -0.487 l/min/mmHg (95% Confidence Interval -0.837, -0.136). Thus although the coefficient of variation is known to be high for tests of chemosensitivity as seen in Chapter 3, it is most probable from the confidence intervals above that both chemosensitivities were suppressed with dihydrocodeine.

	Placebo	Dihydrocodeine	*P* value
Peak oxygen consumption (ml/kg/min)	18.0±0.6	19.7±0.6	0.002
$\dot{V}_E$-$\dot{V}CO_2$ slope	34.19±2.35	30.85±1.91	0.011
Exercise duration (s)	455±27	512±27	0.001
Respiratory exchange ratio (*R*)	1.26	1.31	0.17

Values expressed as mean±SEM.

$\dot{V}_E$-$\dot{V}CO_2$ slope is the slope of the regression line relating minute ventilation and carbon dioxide output during exercise and is taken as an index of the ventilatory response to exercise.

Table 5.3 Cardiopulmonary exercise results after placebo and dihydrocodeine administration.

Table 5.4 shows the haemodynamic data, end-tidal carbon dioxide concentration and arterial oxygen saturation at rest, 3 minutes of exercise, 6 minute of exercise and at peak exercise. There was no difference in heart rate and blood pressure with dihydrocodeine administration and placebo. End-tidal carbon dioxide concentration was significantly higher with dihydrocodeine than placebo at peak exercise. There was also a small but not significant fall in arterial oxygen saturation at peak exercise comparing dihydrocodeine with placebo. Focusing on the end-tidal carbon dioxide concentration when patients were taking placebo, there was a trend towards a decrease at peak exercise compared with the resting value. In contrast, when patients were taking dihydrocodeine, there was a trend towards an increase in the end-tidal carbon dioxide concentration during exercise; there was also a non-significant fall in arterial oxygen saturation during exercise compared with the resting value.

	Placebo	Dihydrocodeine	*P* value
Pre-exercise			
Pulse (min^{-1})	73±2	72±2	0.43
Systolic BP (mmHg)	118±7	116±5	0.70
$\dot{V}O_2$ (ml/min)	414.7±69.2	264.5±34.3	0.13
$\dot{V}CO_2$ (ml/min)	332.1±41.5	260.5±32.2	0.26
End-tidal CO_2 Concentration (%)	4.95±0.17	5.01±0.15	0.73
Arterial O_2 Saturation (%)	100±0	99.3±0.3	0.03
3 minutes			
Pulse (min^{-1})	94±5	95±5	0.74
Systolic BP (mmHg)	129±9	128±7	0.64
$\dot{V}O_2$ (ml/min)	830.6±53.9	894.5±61.6	0.41
$\dot{V}CO_2$ (ml/min)	838.9±68.3	887.1±63.1	0.61
End-tidal CO_2 Concentration (%)	5.05±0.15	5.20±0.18	0.36
Arterial O_2 Saturation (%)	99.8±0.11	99.4±0.26	0.18
6 minutes			
Pulse (min^{-1})	113±5	110±4	0.19
Systolic BP (mmHg)	134±7	140±8	0.80
$\dot{V}O_2$ (ml/min)	1121.7±69.2	1174.0±78.2	0.41
$\dot{V}CO_2$ (ml/min)	1335.7±87.4	1302.5±86.9	0.87
End-tidal CO_2 Concentration (%)	4.95±0.27	5.32±0.25	0.50
Arterial O_2 Saturation (%)	99.5±0.26	98.9±0.40	0.09
Peak exercise			
Pulse (min^{-1})	132±6	132±5	0.9
Systolic BP (mmHg)	144±10	140±9	0.32
$\dot{V}O_2$ (ml/min)	1390.0±87.1	1524.7±87.2	0.002
$\dot{V}CO_2$ (ml/min)	1765.0±110.0	1979.0±120.0	0.017
End-tidal CO_2 Concentration (%)	4.66±0.22	5.12±0.24	0.008
Arterial O_2 Saturation (%)	99.4±0.26	98.9±0.40	0.08

Values expressed as mean±SEM; BP, blood pressure; $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbon dioxide output.

Table 5.4 Haemodynamic, oxygen consumption, carbon dioxide output, end-tidal carbon dioxide concentration and arterial oxygen saturation at rest, 3 minutes of exercise, 6 minutes of exercise and at peak exercise with placebo and dihydrocodeine.

Figure 5.1 compares the minute ventilation, respiratory rate and tidal volume during exercise with dihydrocodeine and placebo, showing a significant reduction in minute ventilation during submaximal exercise with dihydrocodeine which was accounted principally by the reduction in respiratory rate. The minute ventilation at peak exercise was however similar in both. Table 5.5 shows the modified Borg score for dyspnoea and also that for fatigue. It demonstrates a reduction in breathlessness at submaximal exercise with the administration of dihydrocodeine but in contrast, there was no significant change in the perception of fatigue.

	Modified Borg Score *(dyspnoea)*			**Modified Borg Score *(fatigue)***		
	Placebo	**Dihydrocodeine**	***P* value**	**Placebo**	**Dihydrocodeine**	***P* value**
3 minutes	1.17 ±0.35	1.33 ±0.28	0.64	1.33 ±0.36	1.33 ±0.33	1.0
6 minutes	3.60 ±0.22	2.91 ±0.25	0.003	3.00 ±0.49	2.64 ±0.37	0.21
Peak exercise	5.67 ±0.74	5.33 ±0.67	0.52	5.71 ±0.54	5.67 ±0.48	0.91

Values expressed as mean±SEM.

Table 5.5 Modified Borg scores for dyspnoea and for fatigue with placebo and dihydrocodeine.

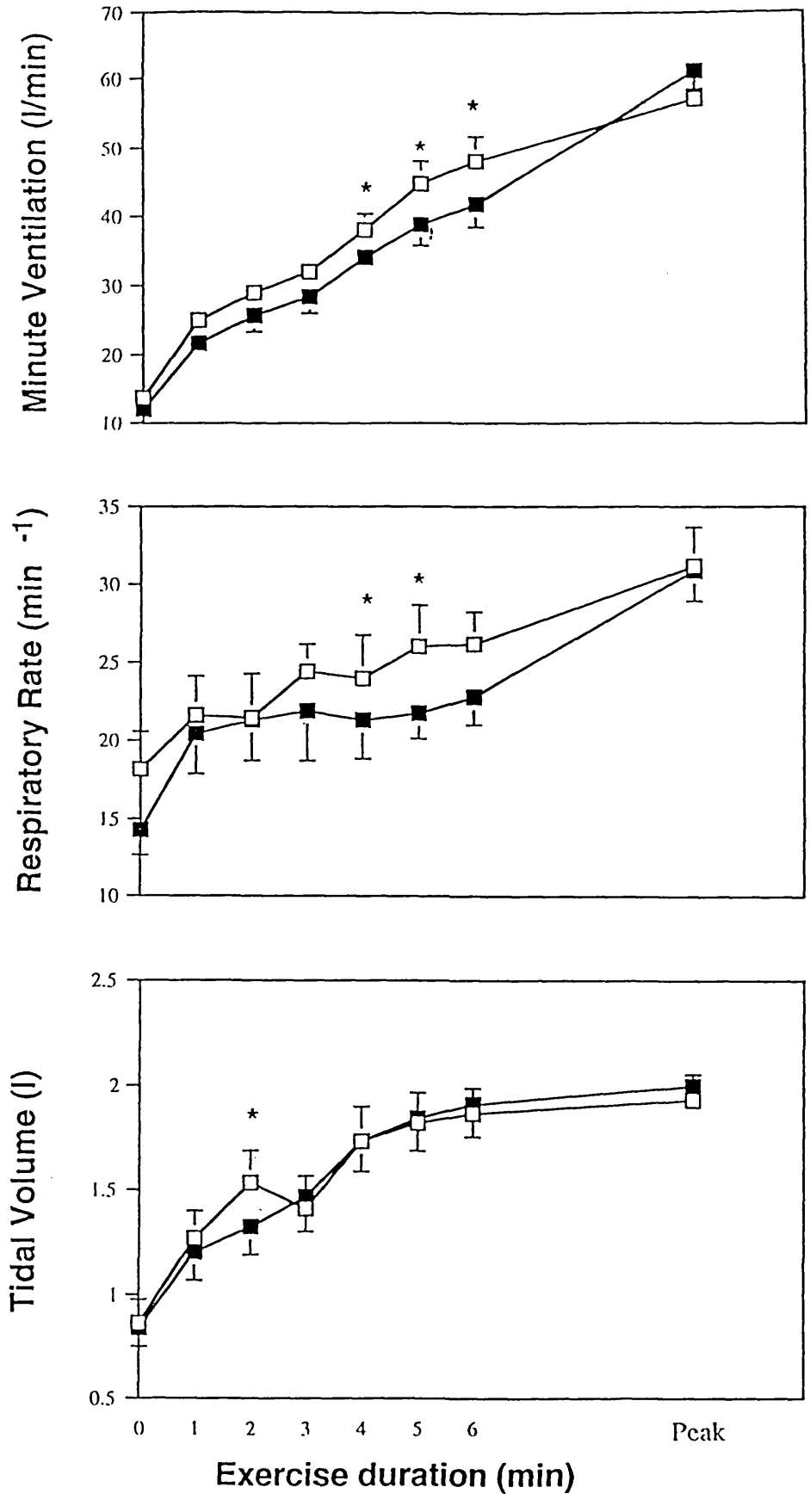

Figure 5.1 Comparison of minute ventilation, respiratory rate and tidal volume with placebo (open symbol) and dihydrocodeine (closed symbol). * indicates a probability value of <0.05.

Discussion

In this study, dihydrocodeine was shown to reduce breathlessness, at least during submaximal exercise, and improve exercise tolerance. There are several possible ways that dihydrocodeine may do this. The first is that it may alter the central perception of discomfort, both dyspnoea and fatigue. It is unlikely that this is the main explanation because there was an absence of significant improvement in the perceived symptom of fatigue. Secondly, there may be some beneficial haemodynamic effects of dihydrocodeine. Morphine has been shown to have both venodilatory [Vismara *et al*, 1976] and systemic arteriolar dilatory effects [Zelis *et al*, 1982] secondary to a reduction in sympathetic activity. However, previous studies showed that improving haemodynamics with vasodilator drugs in chronic heart failure patients did not necessarily improve exercise tolerance or symptoms in the short term [Rubin *et al*, 1980]. Furthermore, the haemodynamic effects of dihydrocodeine are probably less than morphine considering that it is less potent [Marks *et al*, 1978]. Although the central venous pressure or the systemic vascular resistance in these patients was not measured, there were no significant changes seen in blood pressure or heart rate. Thus, although the possible haemodynamic effects of dihydrocodeine cannot be fully discounted, it is unlikely that this is a key factor in improving breathlessness and exercise tolerance.

The third possibility is that dihydrocodeine reduced breathlessness and improved exercise tolerance by blunting of chemosensitivity. It was demonstrated that chemosensitivity was reduced with dihydrocodeine administration. There was a concomitant reduction in minute ventilation at all stages, except at peak exercise, accounted mainly by a decrease in respiratory rate. As expected, there was a significant increase in end-tidal carbon dioxide concentration at peak exercise with dihydrocodeine

compared with placebo. There was also a small fall in arterial oxygen saturation at peak exercise with dihydrocodeine administration compared with placebo. This was also not significant when compared with the pre-exercise dihydrocodeine arterial oxygen saturation value, suggesting that oxygen saturation was maintained and not further compromised during exercise despite dihydrocodeine administration. That minute ventilation was similar at peak exercise in both instances lends credence to the notion that the predominant mechanism of dihydrocodeine causing respiratory depression is by the blunting of chemoreceptor-mediated respiratory reflexes rather than by the generalised depression of the central nervous system.

The genesis of dyspnoea may in part be due to an excessive increase in exercise ventilation and also the disproportionate rise in respiratory rate relative to tidal volume [Yokoyama *et al*, 1994]. A higher respiratory rate may conceivably cause respiratory muscle fatigue, contributing to the sensation of dyspnoea [Mancini *et al*, 1992]. In addition, such a characteristic mode of ventilation is inefficient because the proportion of dead space (hence wasted) ventilation is increased [Rubin & Brown, 1984; Sullivan *et al*, 1988]. Of interest is the recent finding that there is an association between the decreased hypoxic chemosensitivity and the lack of perception of dyspnoea in asthmatics with a history of a near-fatal status asthmaticus [Kikuchi *et al*, 1994]. Other studies have shown a reduction in the perception of dyspnoea in asthmatic patients who had both carotid bodies removed as part of the treatment of asthma, suggesting a close association between hypoxic chemosensitivity and the perception of this symptom [Davidson *et al*, 1974; Chang *et al*, 1978]. Although a greater reduction in hypoxic chemosensitivity was noted with dihydrocodeine administration vis-a-vis hypercapnic chemosensitivity (40% versus 16%), it does not provide further information as regards the specific contribution

of each towards the generation of dyspnoea. The major limiting symptom at peak exercise did not change in the majority of patients indicating dihydrocodeine only reduced breathlessness to a certain extent but not complete enough to render it a non-limiting exertional symptom, perhaps in part because patients were able to exercise longer.

It is surprising to see that there was an improvement in the peak oxygen consumption following dihydrocodeine administration. The most likely reason for this is that with the reduction in the perceived sensation of breathlessness, these patients were able to improve their exercise duration. Because of the delayed oxygen kinetics in chronic heart failure patients [Sietsema *et al*, 1994], the peak oxygen consumption may not reflect maximal oxygen consumption and the slow upward drift with exercise prolongation may account for the improvement in peak exercise consumption with dihydrocodeine. It is also pertinent to note that oxygen consumption at rest was less, albeit non-significantly, with dihydrocodeine administration. However, this was not observed during submaximal exercise in agreement with a previous report with dihydrocodeine administration [Stark *et al*, 1983] but in contrast to another with morphine administration [Santiago *et al*, 1979]. This is probably due to the lesser potency of dihydrocodeine in comparison to morphine. It is thought that morphine may reduce the metabolic rate for as yet unknown physiological reasons [Santiago *et al*, 1979]. The observation that the oxygen consumption during submaximal exercise with dihydrocodeine was similar to placebo is against the reduction of metabolic rate as a factor in causing increased exercise tolerance, as had been suggested in studies with chronic obstructive pulmonary disease [Woodcock *et al*, 1981].

This study has several implications. Dihydrocodeine appears to be beneficial in

the short term under exercise laboratory conditions. The potential benefits of longer term administration of this drug in chronic heart failure patients who are limited by breathlessness despite optimal conventional therapy merits further investigation. This, however, has to be considered against the background of possible drug tolerance and the small risk of dependence. It is also pertinent to bear in mind that with symptomatic severe heart failure patients in whom there is no prospect of surgical intervention or cardiac transplantation, the primary goals of treatment are to reduce symptoms and morbidity; extending a miserable existence by a few months with drugs of proven prognostic value is only of secondary importance [Cleland *et al*, 1994]. Secondly, the role of the chemoreflex in the pathophysiology of chronic heart failure has largely been ignored. It may not only be important in influencing the increased exercise ventilation and the perception of breathlessness but also contribute to the neurohormonal abnormality in chronic heart failure by increasing sympathetic outflow via its excitatory action on the brainstem [Shepherd, 1987; Floras 1993]. Thirdly, it reinforces the probable role of chemosensitivity in mediating the increased ventilatory response to exercise and breathlessness in chronic heart failure patients.

Chapter 6

THE EFFECTS OF CHRONIC HYPOXAEMIA ON CHEMOSENSITIVITY: A STUDY OF CHEMOSENSITIVITY IN CYANOTIC UNIVENTRICULAR PATIENTS

Introduction

In the previous chapters, an increased chemosensitivity in chronic heart failure was demonstrated. It has been previously reported that chronic hypoxia may blunt the hypoxic chemosensitivity in patients with cyanotic heart disease [Edelman *et al*, 1970] but the relationship between chemosensitivity and exercise ventilation in these patients is not known. Patients with univentricular heart are also cyanosed and they have ventricular overload which may lead to heart failure [Sluysmans *et al*, 1992]. These patients, like chronic heart failure patients, also have reduced exercise tolerance and excessive ventilation at rest and during exercise. As there was a cohort of univentricular patients in the author's Institute, these patients offered an opportunity to study the effects of chronic hypoxaemia both on hypoxic and hypercapnic chemosensitivity in the context of the ventilatory response to exercise. This may aid the further understanding of the ventilatory control of exercise in general.

Univentricular hearts by definition have both atrioventricular valves or a common atrioventricular valve open into a single ventricular chamber [Anderson *et al*, 1983]. Patients who have had a paliative operation such as a Blalock-Taussig shunt remain cyanosed and are still ventricular overloaded. Over the last 20 years however, more definitive operations have been developed which are undertaken during childhood or early adult life aiming to reduce ventricular overload and to correct hypoxaemia. In the

Fontan operation [Fontan & Baudet, 1971] or modifications of it [Kawashima *et al*, 1984], the systemic venous return is directed to the pulmonary artery, with a direct connection between the right atrium and the main pulmonary artery or a cavopulmonary connection which bypasses the right atrium. Thus, both ventricular overload and cyanosis are consequently reversed or reduced although myocardial function may not subsequently improve [Sluysmans *et al*, 1992; Fontan *et al*, 1990].

The objective of the study in this chapter was to investigate the chemosensitivity in univentricular patients who were cyanosed and those whose chronic hypoxaemia had been reversed following surgical correction in relation to the ventilatory response to exercise. This may aid the further understanding of the control of exercise ventilation in general.

Subjects and Methods

Ten cyanotic double-inlet univentricular patients were studied (Group A; 5 men; age 29.9±2.5 [SEM] years). The clinical characteristics of these patients are given in Table 6.1. In terms of ventricular function, there was a gradation of ventricular contractility as given by the echocardiographic shortening fraction (23.6±7.9%, range 10-30%). As a comparison, 8 patients with Fontan-type circulation whose hypoxaemia had been relieved (Group B; age 29.4±1.5 years; 4 men) were also studied. Most of these patients had Fontan-type operation performed during early adult life and their clinical characteristics are given in Table 6.2. In addition, 10 healthy controls (Group C; age 30.7±1.9, range 24-39 years; 5 men) were studied.

Patient	Age (y)	Diagnosis	Operation	Resting O_2 Sat (%)	Hb (g/ 100ml)	Arterial Blood Gases at Rest				NYHA Class	Rx	Echo SF (%)	mVO_2 (ml/kg/ min)
						pH	pO_2 (kPa)	pCO_2 (kPa)	HCO_3^- (mmol/l)				
1	38	DILV, TGA	None	95	19.1	7.39	8.46	4.66	21.1	II	Nil	N.A.	20.7
2	30	DILV, TGA, Sub-PS	None	97	14.0	7.45	9.61	2.48	13.0	II	F, ACEI	25	38.9
3	32	DILV, TGA, PS	None	93	15.0	Not done	Not done	Not done	Not done	I	B, ACEI	17	21.7
4	43	DILV, TGA, PS	None	93	18.3	7.40	7.59	3.85	18.0	II	Nil	25	15.5
5	28	DILV, PA	Waterston	90	15.9	7.45	6.92	4.21	22.2	II	Nil	25	15.9
6	25	DILV, PA	Right & Left B-T	82	15.8	Not done	Not done	Not done	Not done	III	B	30	18.0
7	23	DILV, TGA	None	95	14.7	7.39	9.35	4.99	22.6	II	F, Am, ACEI	25	28.4
8	19	DIRV, PA	Right & Left B-T	80	17.7	7.41	5.71	4.69	22.2	III	F, ACEI	10	10.3
9	31	DILV, DOLV, Sub-PS	Left B-T	91	15.8	7.41	8.42	3.23	15.4	II	Digoxin	27	20.9
10	36	DILV, TGA, PS	Left B-T	89	18.0	7.39	6.87	4.28	20.3	I	Nil	28	26.3

ACEI, angiotensin-converting enzyme inhibitor; Am, amiodarone; B, bumetanide; B-T, Blalock-Taussig shunt; DILV, double-inlet left ventricle; DIRV, double-inlet right ventricle; DOLV, double-outlet left ventricle; Echo SF, echocardiographic shortening fraction; F, frusemide; mVO_2, maximal oxygen consumption; PA, pulmonary atresia; PS, pulmonary stenosis; Resting O_2 Sat, arterial oxygen saturation at rest; Rx, medication; TGA, transposition of great arteries.

Table 6.1 Clinical characteristics of cyanotic univentricular patients.

Patient	Age (y)	Diagnosis	Operation	Age at Operation (y)	Resting Oxygen Saturation (%)	NYHA Class	Rx	Echo SF (%)	mVO_2 (ml/kg/min)
11	32	DILV, PS, TGA	Fontan	18	92	I	F	30	31.8
12	28	DILV, PS	TCPC	27	95	II	W	NA	19.1
13	29	DILV, PS	Fontan	23	97	II	ACEI, Digoxin, Am, W	21	24.7
14	24	DIRV, DORV, PS	TCPC	23	90	II	F, Am, W	25	20.4
15	24	DIRV, PA	TCPC	22	93	III	Digoxin, W	15	15.8
16	35	DILV, PS	Fontan	12	98	I	Sotalol, W	27	22.3
17	35	DIRV, PS	Fontan	25	97	II	F, Digoxin, W	25	14.8
18	28	DILV, PS	Fontan	21	96	II	F, ACEI, Am, W	27	19.4

ACEI, angiotensin-converting enzyme inhibitor; Am, amiodarone; DILV, double-inlet left ventricle; DIRV, double-inlet right ventricle; DORV, double-outlet right ventricle; Echo SF, echocardiographic shortening fraction; F, frusemide; mVO_2, maximal oxygen consumption; NA, not available; PA, pulmonary atresia; PS, pulmonary stenosis; Rx, medication; TCPC, total caval-pulmonary connection; TGA, transposition of great arteries; W, warfarin.

Table 6.2 Clinical characteristics of univentricular patients with Fontan-type circulation.

Cardiopulmonary exercise testing was performed in all subjects. They were exercised to exhaustion using the Bruce protocol [Bruce *et al*, 1963], with the addition of a "Stage 0" at 1.0 mph and 5% gradient. Blood pressure was measured manually using a mercury sphygmomanometer before and during exercise. Arterial oxygen saturation was monitored during exercise using a pulse oximeter (Model N200E, Nellcor, Hayward, California, USA) with a probe placed on the right supraorbital artery. Metabolic gas exchange analysis was carried out by means of mass spectrometery (Amis 2000, Innovision, Odense, Denmark) using the inert gas dilution technique [Davies & Denison, 1979].

Peripheral and central chemosensitivity were determined using transient hypoxia and the rebreathing of carbon dioxide respectively in all subjects as described in previous chapters. In brief, after a period of quiet breathing in room air, the patients were given transient inhalations of pure nitrogen, without being aware of the timing of these inhalations, for two to eight breaths. This was repeated ten times so as to provide a wide range of arterial oxygen saturations generally from 75% (lower for some of the cyanotic patients) to 100%, with appropriate intervals of air breathing between exposures to allow arterial oxygen saturation and end-tidal carbon dioxide concentration to return to baseline. The maximal minute ventilation following each period of nitrogen inhalation was obtained by averaging the largest 2 consecutive breaths using breath-by-breath analysis with a heated pneumotachograph (Amis 2000, Innovision, Odense, Denmark), calibrated before each test. Continuous monitoring of oxygen and carbon dioxide was done at the mouth by respiratory mass spectrometry, also calibrated before each test. Arterial oxygen saturation was measured using a pulse oximeter (Model N-200E, Nellcor, Hayward, California, USA) set at fast mode with a response time of 2 to 3

seconds and a lightweight probe clipped gently on the patients' right ear lobe. Minute ventilation was plotted against the lowest arterial oxygen saturation reached for each period of nitrogen inhalation. The hypoxic chemosensitivity was obtained as the slope of the regression line relating minute ventilation to arterial oxygen saturation and expressed in terms of litres per minute per percent oxygen saturation (l/min/%SaO_2).

Central hypercapnic chemosensitivity was assessed using the rebreathing of 7% carbon dioxide in 93% oxygen through a 6-litre bag for 4 minutes. As previously, the test was stopped sooner if patients were too breathless to continue or if end-tidal carbon dioxide concentration exceeded 10%. Minute ventilation was measured breath-by-breath using a heated pneumotachograph and continuous monitoring of oxygen and carbon dioxide was done at the mouth by mass spectrometry. Hypercapnic chemosensitivity was obtained as the slope of the regression line relating minute ventilation to end-tidal carbon dioxide concentration and expressed in terms of litres per minute per mm Hg (l/min/mmHg).

Statistical Analysis

The results are presented as mean$\pm$SEM. One-way analysis of variance (ANOVA) was used for comparison of groups followed by Student's *t-test* where appropriate to assess the significance of results. The relationship between variables was assessed using linear regression analysis. $P < 0.05$ was considered significant.

Results

Cardiopulmonary Exercise Responses

The cardiopulmonary exercise responses of the two groups of univentricular patients in comparison to normal subjects are summarised in Table 6.3. The maximal oxygen consumption in the univentricular patients was reduced compared with normal subjects (22.1±2.8 v 21.0±1.9 v 34.7±1.9 ml/kg/min in groups A, B and C respectively; A v B, P=NS; A v C, P=0.0008; B v C, P=0.007). Exercise duration, as expected, was reduced in the patient groups (548±43 v 631±55 v 919±26 seconds respectively; A v B, P=NS; A v C, $P<0.0001$; B v C, P=0.007). In terms of chronotropic response during exercise, the heart rate at peak exercise in patient groups was reduced compared with normals (154.7±4.8 v 133.4±10.0 v 174.7±2.4 beats/min; A v B, P=NS; A v C, P=0.003; B v C, P=0.01). Systolic blood pressure both at rest and at peak exercise were comparable in both groups of univentricular patients and normals as given in Table 6.3. The ventilatory response to exercise as characterised by the $\dot{V}_E$-$\dot{V}CO_2$ regression slope [Whipp *et al*, 1984; Buller & Poole-Wilson, 1990], was steeper in cyanotic univentricular patients (43.4±4.0) compared with patients with a Fontan-type circulation (31.4±2.7, P=0.03) and normal subjects (23.3±1.1, P=0.001). The $\dot{V}_E$-$\dot{V}CO_2$ slope was also significantly greater in patients with a Fontan-type circulation than normal subjects (P=0.02). There was an inverse trend between maximal oxygen consumption and the $\dot{V}_E$-$\dot{V}CO_2$ slope in both groups of univentricular patients (r=-0.59, P=0.07; r=-0.54, P=0.17 respectively) as shown in Figure 6.1 but not in normals (r=0.34, P=NS).

	Cyanotic Univentricular Patients (Group A)	Univentricular Patients with Fontan-type Circulation (Group B)	Healthy Controls (Group C)	$P < 0.05$
Maximal Oxygen Consumption (ml/kg/min)	21.7±2.5	21.0±1.9	34.7±1.9	A *v* C; B *v* C
$\dot{V}_E$-$\dot{V}CO_2$ **Slope**	43.40±4.00	31.35±2.70	23.28±1.10	A *v* B; A *v* C; B *v* C
Exercise Time (s)	548±43	631±55	919±26	A *v* C; B *v* C
Respiratory Exchange Ratio (*R*)	1.09±0.06	1.16±0.04	1.19±0.04	*NS*
Resting Heart Rate (beats/min)	92.2±4.5	75.0±6.7	74.4±2.6	A *v* B; A *v* C
Peak Heart Rate (beats/min)	154.7±4.8	133.4±10.0	174.7±2.4	A *v* C; B *v* C
Resting Systolic Blood Pressure (mmHg)	115.6±3.5	111.9±4.0	113.2±5.6	*NS*
Peak Exercise Systolic Blood Pressure (mmHg)	147.7±6.9	137.5±4.5	147.1±8.6	*NS*
Resting Arterial Oxygen Saturation (%)	90.6±1.8	95.1±1.1	99.9±0.1	A *v* B; A *v* C; B *v* C
Peak Exercise Arterial Oxygen Saturation (%)	66.2±3.8	90.5±2.1	99.6±0.2	A *v* B; A *v* C; B *v* C

Values are expressed as mean±SEM

Table 6.3 Summary of cardiopulmonary exercise responses in cyanotic univentricular patients with palliative or no surgery, univentricular patients with Fontan-type circulation and healthy controls.

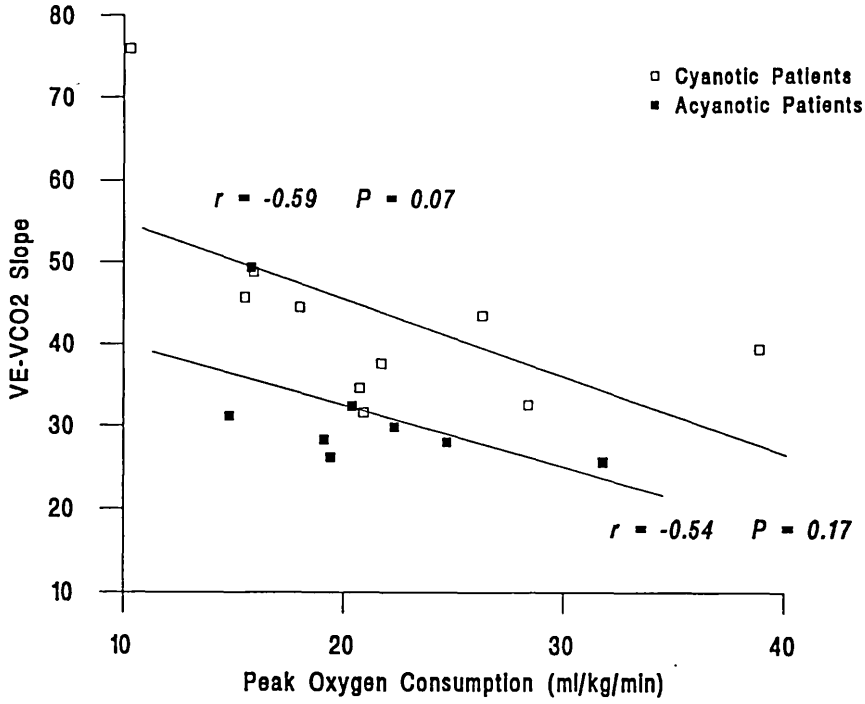

Figure 6.1 Graph shows the inverse relationship between peak oxygen consumption and the ventilatory response to exercise ($\dot{V}_E$-$\dot{V}CO_2$ regression slope) in both groups of univentricular patients.

Also shown in Table 6.3, the mean arterial oxygen saturation at rest was 90.6±1.8% for cyanotic univentricular patients compared with 95.1±1.1% for patients with Fontan-type circulation (P=0.05) and 99.9±0.1% for healthy subjects (P=0.001). At peak exercise, this fell significantly to 66.2±3.8% (P<0.0001) compared with resting values in the cyanotic univentricular patients. In patients with Fontan-type circulation, peak exercise arterial oxygen saturation fell modestly to 90.5±2.1% (P=0.01) and in normals, to 99.6±0.2% (P=NS). Statistically, the peak exercise arterial oxygen saturation values were significantly different among the three groups (A v B, P=0.0001; A v C, P<0.0001; B v C, P=0.003). Arterial oxygen saturation at rest correlated significantly with peak oxygen consumption (r=0.69, P=0.03) in cyanotic univentricular patients but not that at peak exercise (r=0.47, P=0.2) as shown in Table

6.4. In fact, the level of arterial hypoxaemia at which some of these patients continued to exercise was remarkable and was as low as 48%. Similarly, an inverse correlation was seen between the $\dot{V}_E$-$\dot{V}CO_2$ slope and resting arterial oxygen saturation (r=-0.74, P=0.015) in these patients but not arterial oxygen saturation at peak exercise (r=-0.48, P=0.2). Also shown in Table 6.4, neither blood pressure nor heart rate, despite the chronotropic incompetence, appeared to influence exercise tolerance in these patients.

	Cyanotic Univentricular Patients		**Univentricular Patients with Fontan-type Circulation**		**Healthy Controls**	
Correlating Maximal Oxygen Consumption to:	***r***	***P***	***r***	***P***	***r***	***P***
$\dot{V}_E$-$\dot{V}CO_2$	0.59	0.07	0.54	0.17	0.34	*NS*
O_2 Saturation at rest	0.69	0.03	0.28	*NS*	0.52	*NS*
Peak Exercise O_2 Saturation	0.47	*NS*	0.14	*NS*	0.39	*NS*
Heart Rate at rest	0.42	*NS*	0.18	*NS*	0.68	0.03
Peak Exercise Heart Rate	0.01	*NS*	0.21	*NS*	0.03	*NS*
Systolic Blood Pressure at rest	0.15	*NS*	0.21	*NS*	0.31	*NS*
Peak Exercise Systolic Blood Pressure	0.18	*NS*	0.44	*NS*	0.55	0.10

$\dot{V}_E$-$\dot{V}CO_2$ slope, regression slope correlating ventilation to carbon dioxide output; r is the correlation coefficient; P is the probability; *NS*, not significant.

Table 6.4 Summary of the relationship between maximal oxygen consumption and various parameters including heart rate, blood pressure and arterial oxygen saturation.

Chemosensitivity

As shown in Table 6.5, the hypoxic chemosensitivity was significantly reduced in cyanotic univentricular patients compared with patients with Fontan-type circulation (0.148±0.039 v 0.448±0.120 l/min/%SaO2, P=0.04) and normals (0.311±0.037 l/min/%SaO2, P<0.01). Although the hypoxic chemosensitivity of patients with Fontan-type circulation was higher than that of normals, this did not reach statistical significance (P=0.29). In the cyanotic univentricular patients, hypoxic chemosensitivity correlated with arterial oxygen saturation at peak exercise (r=0.73, P=0.02) and was inversely related to the degree of fall in arterial oxygen saturation during exercise (r=-0.63, P=0.05) as shown in Figures 6.2 and 6.3. Interestingly, there was no correlation between hypoxic chemosensitivity and the arterial oxygen saturation at rest (r=0.36, P=NS) in the cyanotic patients.

	Cyanotic Univentricular Patient (Group A)	**Univentricular Patients with Fontan-type Circulation (Group B)**	**Healthy Controls (Group C)**	***P* < 0.05**
Hypoxic Chemosensitivity (l/min/%SaO2)	0.148±0.039	0.448±0.120	0.311±0.037	A *v* B; A *v* C
Rebreathing CO_2 Test Slope of Ventilation/end-tidal CO_2 response line (l/min/mmHg)	1.71±0.26	1.76±0.24	1.70±0.18	*NS*
Extrapolated end-tidal CO_2 for zero ventilation (X-intercept)[mmHg]	31.9±2.3	39.9±1.2	45.2±1.6	A *v* B; A *v* C

Values expressed as mean±SEM

Table 6.5 Summary of the chemosensitivity results in cyanotic univentricular patients, univentricular patients with Fontan-type circulation and healthy controls.

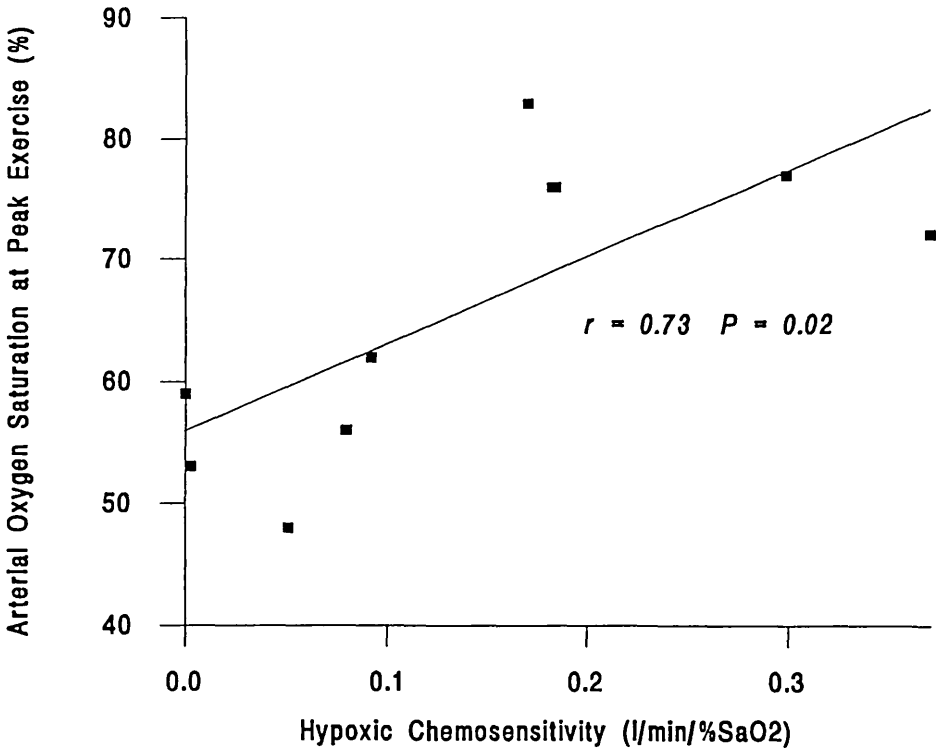

Figure 6.2 Relationship between hypoxic chemosensitivity and arterial oxygen saturation at peak exercise in cyanotic univentricular patients.

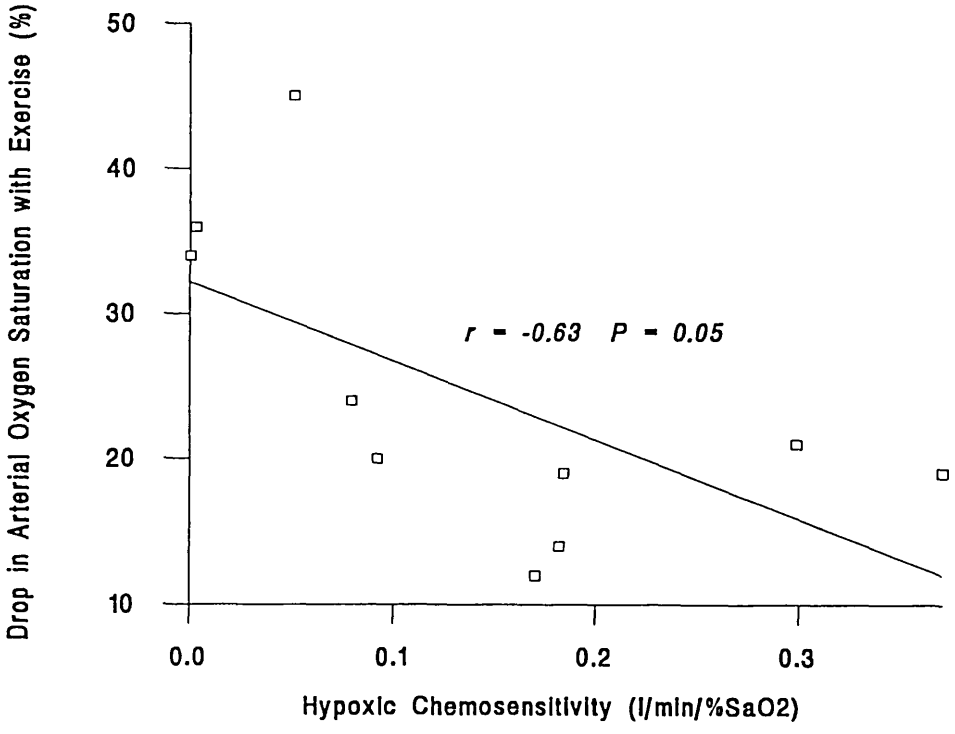

Figure 6.3 Relationship between hypoxic chemosensitivity and the drop in arterial oxygen saturation with exercise in cyanotic univentricular patients.

To see if there was an association with hypoxic chemosensitivity and the ventilatory response to exercise in the two groups of univentricular patients, hypoxic chemosensitivity was not found to correlate with the $\dot{V}_E$-$\dot{V}CO_2$ slope in the cyanotic patients (r=0.21, P=0.28) but a strong trend was evident in patients with Fontan-type circulation in whom hypoxaemia had been relieved (r=0.95, P=0.05), as shown in Figure 6.4. Only a weak trend was seen in normals (r=0.47, P=0.17).

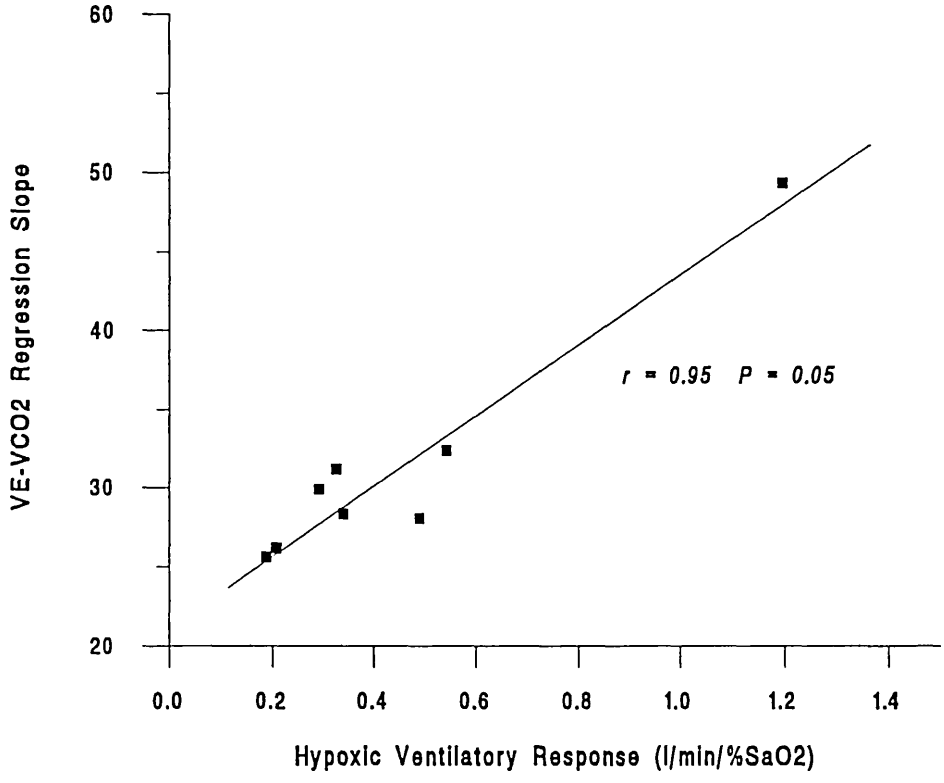

Figure 6.4 Relationship between hypoxic chemosensitivity and the ventilatory response to exercise in patients with Fontan-type circulation.

Hypercapnic chemosensitivity, as judged by the slope of the ventilatory response line to hypercapnia, was similar all 3 groups (1.71 v 1.76 v 1.70 l/min/mmHg; P=NS for all group comparisons). However, on further analysis, the X-intercept of the response line was noted to have shifted to the left in the cyanotic univentricular patients (31.9 v 39.9 v 45.2 mmHg; A v B, P=0.01; A v C, P=0.001; B v C, P=0.10), suggesting that these patients ventilate more for a given level of arterial carbon dioxide. Representative hypercapnic-ventilatory response lines of three subjects are shown in Figure 6.5.

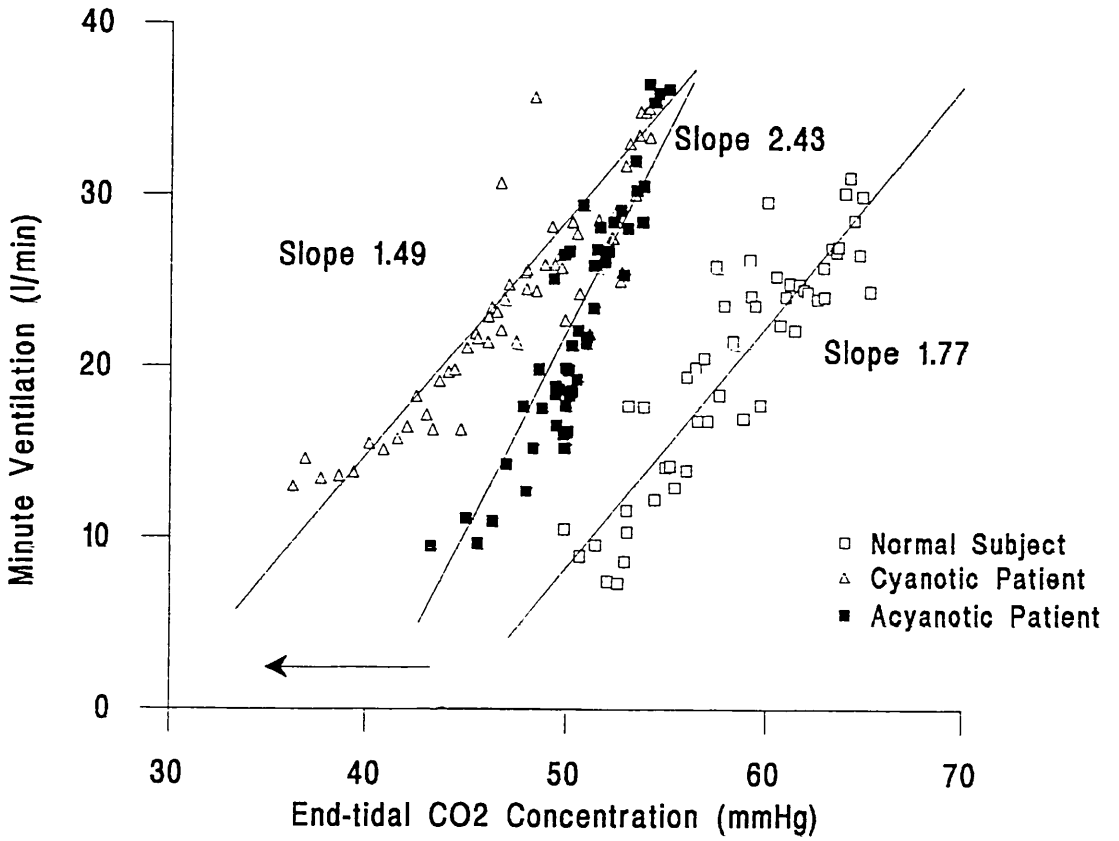

Figure 6.5 This shows the shift of the hypercapnic-ventilatory response line to the left in a cyanotic univentricular patient (as depicted by arrow) compared with a normal subject and a acyanotic patient with Fontan-type circulation. Despite the higher slope of the response line seen in the acyanotic patient in this figure, the mean slope of this group of patients did not differ significantly from the others.

The relationship between hypercapnic chemosensitivity and $\dot{V}_E$-$\dot{V}CO_2$ slope in the two groups of univentricular patients was assessed and a significant correlation between the two parameters was seen in the cyanotic patients (r=0.84, P<0.01) whilst a trend existed for the Fontan patients (r=0.61, P=0.10), as shown in Figure 6.6. A significant correlation between the two parameters was seen in healthy normal controls (r=0.64, P=0.046).

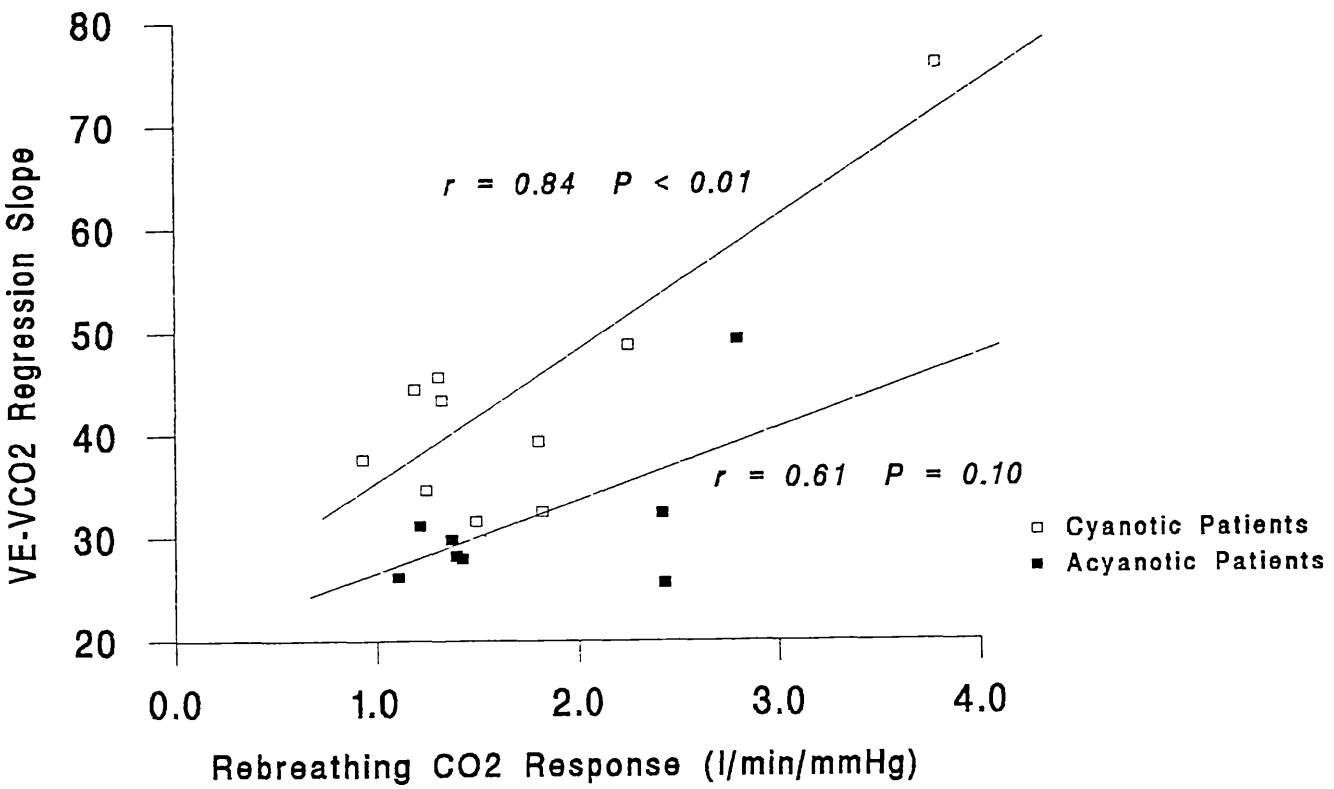

Figure 6.6 Relationship between rebreathing carbon dioxide response and the ventilatory response to exercise in both groups of univentricular patients.

Discussion

Cardiopulmonary Exercise Response

A reduced exercise tolerance and maximal oxygen consumption in univentricular patients compared with normals were demonstrated, in agreement with previous data [Driscoll *et al*, 1984]. It is surprising that the exercise duration and maximal oxygen consumption in the two groups of patients were similar despite patients in the latter group having had a Fontan-type circulation, which reduced ventricular overload and relieved cyanosis. There are several possible explanations for this. Firstly, it may be that most of these patients underwent the operation at a later age, in keeping with the findings that patients who have such definitive surgery after 10 years of age may not subsequently improve their ventricular function [Driscoll *et al*, 1984; Sluysmans *et al*, 1992; Zellers *et al*, 1989]. In one study, a decline in myocardial function was not prevented despite Fontan-type operations being carried out early to avoid age-related decrease in myocardial function [Parikh *et al*, 1991], perhaps suggesting the natural history of these patients is one of gradual decline in heart function despite attempts to reverse this. Secondly, that exercise capacity in patients with the Fontan-type circulation was not better in this study may be related to the number of patients (3 of 8) with the right ventricular morphology in this group. Such morphology, in contrast to left ventricular morphology, is known to have poorer adaptation of ventricular function [Sano *et al*, 1988].

The heart rate response to exercise in both groups of univentricular patients was seen to be lower than normals and may be due to either the down-regulation of myocardial beta-receptors [Kozlik *et al*, 1991], the direct effect of arterial hypoxaemia especially in the cyanotic univentricular patients [Astrand & Astrand, 1958] or the

influence of negative chronotropic agents such as digoxin and amiodarone which some of the patients were receiving for paroxysmal supraventricular arrhythmias. None of the patients, however, developed any arrhythmias during exercise including atrial fibrillation, another cause of chronotropic incompetence [Corbelli *et al*, 1990]. Kozlik *et al* [1991] demonstrated a 50% reduction in myocardial beta-receptor density in cyanotic congenital heart disease patients which is probably related to elevated plasma catecholamine levels found in these patients. Astrand & Astrand [1958] also showed that prolonged hypoxia may itself cause bradycardia. Interestingly, the chronotropic incompetence did not appear to determine exercise performance as seen by the lack of correlation between peak heart rate during exercise and maximal oxygen consumption. It may be that an increased stroke volume during exercise compensated for this or that there were various metabolic adaptations already in place including enhanced tissue oxygen extraction during exercise [Streider *et al*, 1973]. Blood pressure responses with exercise did not differ significantly in the patient groups and normals in keeping with previous data [Driscoll *et al*, 1984; Zellers *et al*, 1989] and did not correlate with maximal oxygen consumption.

In the cyanotic univentricular patients, exercise capacity was influenced by the resting arterial oxygen saturation but not the degree of desaturation during exercise. This may be explained by the fact that resting arterial oxygen saturation is related to the degree of pulmonary flow, which in turn is known to affect exercise capacity [Driscoll *et al*, 1984]. That the level of arterial oxygen desaturation at peak exercise did not affect exercise in the cyanotic univentricular patients may be due to metabolic adaptation such as increased erythropoiesis (Table 6.1), chronic bicarbonate depletion (Table 6.1) which may have caused an increased exercise acidosis and shifted the haemoglobin-oxygen dissociation curve further to the right [Streider *et al*, 1973; Morse & Cassels, 1953], and

possible peripheral changes in these patients including proliferation of muscle capillaries [Valdivia, 1958].

The ventilatory response to exercise was shown to be increased in the univentricular patients as evident by the high $\dot{V}_E$-$\dot{V}CO_2$ slope, with the cyanotic patients having a greater $\dot{V}_E$-$\dot{V}CO_2$ slope than patients with Fontan-type circulation. The higher exercise ventilation suggests reduced efficiency of ventilation in meeting metabolic demands and may relate to the degree of right to left shunt and the amount of dead space ventilation arising from this; the latter is also thought to be applicable in chronic heart failure patients as discussed in Chapters 1,2 and 3 [Buller & Poole-Wilson, 1990]. It also explains the reduced $\dot{V}_E$-$\dot{V}CO_2$ slope in patients with Fontan-type circulation since there is less intracardiac shunting and hence dead space ventilation. As will be discussed later, the $\dot{V}_E$-$\dot{V}CO_2$ slope may also be influenced by the hypoxic chemosensititivity in the case of patients with Fontan-type circulation and the hypercapnic chemosensitivity in the cyanotic patients.

There was an inverse trend between the $\dot{V}_E$-$\dot{V}CO_2$ slope and maximal oxygen consumption in the univentricular patients which resembles that seen in conventional chronic heart failure patients [Buller & Poole-Wilson, 1990; Sullivan *et al*, 1988a]. In chronic heart failure patients, this has traditionally been thought to be due to ventilation-perfusion mismatching, with parts of the lungs being adequately ventilated but receiving little pulmonary blood flow due to heart failure. Such explanation may also hold true in the univentricular patients although it is probably more complex in these patients depending both on the degree of intracardiac shunting and also the ventricular function. The interplay of these two and other factors may also account for the lesser degree of association between the $\dot{V}_E$-$\dot{V}CO_2$ slope and maximal oxygen consumption when

compared with conventional chronic heart failure patients. A larger number of patients may also be required to show the relationship more convincingly. The absence of a significant relationship between the $\dot{V}_E$-$\dot{V}CO_2$ slope and maximal oxygen consumption in normals is consistent with the findings of Davies *et al* [1991] that a critical threshold in maximal oxygen consumption (or exercise capacity) is required, above which such a relationship does not apply.

Other factors affecting the $\dot{V}_E$-$\dot{V}CO_2$ slope in these patients include changes in chemosensitivity as evidenced by the close correlation between chemosensitivity and the $\dot{V}_E$-$\dot{V}CO_2$ slope discussed in previous chapters and possibly the stimulation of pulmonary stretch receptors (J receptors) due to increased pulmonary vascular pressures [Paintal, 1969].

Chemosensitivity

The relationship between chemoreceptor function and exercise ventilatory response in cyanotic patients is generally not known. This study provided an opportunity to investigate the role of chemoreceptors in the control of exercise ventilation in patients who are cyanotic and those who are acyanotic following a Fontan-type operation. Hypoxic chemosensitivity was shown to be blunted in the cyanotic patients compared with patients with Fontan-type circulation and normals. This is in agreement with the previous findings of Edelman [1970]. The hypoxic chemosensitivity in the cyanotic patients also appeared to be inversely related to the degree of drop in oxygen saturation during exercise. There are several explanations to account for the blunting of hypoxic chemosensitivity. First and most importantly, the blunting is probably due to sensory adaptation, characteristic of all sensory receptors, such that the response of

chemoreceptors to a given stimulus decreases with time and intensity of the stimulus [Guyton, 1991b]. This may also explain why there was a lack of correlation between hypoxic chemosensitivity and the arterial oxygen saturation at rest, as the latter might not have been intense enough to cause sensory adaptation. Secondly, the shift of the haemoglobin-oxygen dissociation curve to the right in cyanotic patients due to chronic bicarbonate depletion and increased 2,3-diphosphoglycerate may also increase the oxygen content in blood at any given value of oxygen saturation [Streider *et al*, 1973; Lenfant *et al*, 1968]. In other words, at a given arterial oxygen saturation, there is actually more chemoreceptor oxygenation because of the shift in haemoglobin-oxygen dissocation curve and this may also partly explain the blunting of the hypoxic response. Thirdly, in a similar vein, polycythaemia may also contribute to the blunting although there was no correlation between haemogobin concentration and hypoxic chemosensitivity in these patients (r=0.35, P=NS). The latter may be due to venesections that some of these patients may have had. Fourthly, it has also been proposed that proliferation of capillaries in the carotid bodies may increase tissue oxygenation for a given level of arterial oxygen tension and thus may also contribute to the blunting [Edelman *et al*, 1970]. Finally, the failure of functional maturation of carotid chemoreceptors due to chronic hypoxaemia may also be important; animal studies showed that chronic hypoxaemia from birth impaired the normal maturational increase in hypoxic chemosensitivity occuring during the first few days postnatally [Blanco *et al*, 1988; Eden & Hanson, 1987; Landauer *et al*, 1995], although this last mechanism should also be operative in patients with Fontan-type circulation.

No correlation between hypoxic chemosensitivity and the ventilatory response to exercise was seen in the cyanotic univentricular patients. This supports the notion that

the increase ventilation at rest and during exercise in these patients is not directly due to a response to hypoxaemia. The blunting of hypoxic chemosensitivity, however, appears to be reversible as suggested by the return of the hypoxic chemosensitivity to marginally higher than normal values, albeit not statistically significant, in the patients with Fontan-type circulation. Although these patients demonstrate a small decrease in resting and exercise arterial oxygen saturation, this does not appear to be large enough to cause any blunting of chemoreception, rather a trend to increased chemosensitivity. In contrast to the cyanotic patients, there was also a highly significant correlation between hypoxic chemosensitivity and the $\dot{V}_E$-$\dot{V}CO_2$ slope in these patients, suggesting that changes in hypoxic chemosensitivity may in part mediate the increase in exercise ventilation in them. The mechanisms that may increase hypoxic chemosensitivity, like those in chronic heart failure patients, include increased plasma catecholamines which are known to augment chemosensitivity [Cunningham *et al*, 1963] or the reduced blood flow to the chemoreceptors due to reduced myocardial function or increased vascular resistance [Fidone & Gonzalez, 1986].

Hypercapnic chemosensitivity, as judged by the slope of the ventilatory response line to hypercapnia, was similar in both groups of univentricular patients and also when compared with normals. However, it is interesting to note the shift of the hypercapnic-ventilatory response line to the left in the cyanotic patients, suggesting that these patients ventilate more for a given level of arterial carbon dioxide tension. This may also explain the increased ventilatory response to exercise, as characterised by the steeper the $\dot{V}_E$-$\dot{V}CO_2$ slope. Indeed, the hypercapnic chemosensitivity correlated significantly with the $\dot{V}_E$-$\dot{V}CO_2$ slope, suggesting carbon dioxide elimination is more important in the control of ventilation than chronic hypoxaemia itself in these patients. As evident from the

resting arterial blood gases as shown in Table 6.1, there is chronic bicarbonate depletion (mean plasma bicarbonate concentration 19.4 mmol/l) and a tendency towards metabolic acidosis compatible with other studies [Shepard, 1955]. The cause of the shift hypercapnic-ventilatory response line to the left may therefore, in part, be due to the compensatory metabolic acidosis seen in these patients. Metabolic acidosis is known to cause such a shift [Levitzky, 1995]. With the correction of chronic hypoxaemia, as in patients with Fontan-type circulation, the hypercapnic-ventilatory response line is noted to shift right towards normal. This may in part also explain the intermediate ventilatory response to exercise in these patients.

Conclusions

The exercise capacity of univentricular patients is reduced compared with normals regardless of surgical correction or the degree of arterial oxygen desaturation. There is increased ventilatory response to exercise especially in the cyanotic patients. Arterial oxygen desaturation during exercise did not appear to limit exercise in the cyanotic patients probably because of metabolic adaptations. However, the degree of arterial oxygen desaturation during exercise did appear to affect the level of blunting of hypoxic chemosensitivity in these patients, reflecting sensory adaptation, whereas prevention of desaturation, as in patients with Fontan-type circulation, allowed a normal or even augmented hypoxic chemosensitivity to be maintained. The elimination of carbon dioxide appeared more important in the control of ventilation than chronic hypoxaemia in cyanotic patients as suggested by the significant correlation between the ventilatory response to exercise and hypercapnic chemosensitivity and also the shift of the hypercapnic-ventilatory response line to the left. Hypoxic chemosensitivity may

subsequently assume a role in mediating the exercise ventilatory response in patients with Fontan-type circulation as shown by the significant correlation between hypoxic chemosensitivity and the $\dot{V}_E$-$\dot{V}CO_2$ slope in this group of patients.

This study also shows that the increased ventilatory response to carbon dioxide can be caused not only by the increase in the slope, as demonstrated in chronic heart failure patients* in previous chapters, but also by the shift to the left of the hypercapnic-ventilatory response line.

Limitations of the Study

The number of univentricular patients in this study was small because of the nature of the disease and thus is a potential limitation of study. Arterial blood gases were not measured directly during exercise because of possible complications in inserting indwelling arterial cannulae in patients who have had previous shunt operations, and consequently weak forearm pulses, and because most patients with Fontan-type circulation were anticoagulated.

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* The mean X-intercept of the hypercapnic-ventilatory response line of chronic heart failure patients and that of normal controls studied in Chapter 3 were not significantly different (40.0 v 42.8 mmHg respectively, P=NS).

Chapter 7

RESPIRATORY MUSCLE STRENGTH IN CHRONIC HEART FAILURE: ITS RELATIONSHIP WITH PEAK OXYGEN CONSUMPTION, THE VENTILATORY RESPONSE TO EXERCISE AND LOCOMOTOR MUSCLE STRENGTH

Introduction

As discussed in Chapter 1, respiratory muscle weakness has been reported in patients with chronic heart failure [Hammond *et al*, 1990; McParland *et al*, 1992; Mancini *et al*, 1992a]. It has also been proposed that respiratory muscles may play an important role in the genesis of breathlessness in this condition [Mancini *et al*, 1992c; Weiser & Henson, 1992]. There is significant correlation between respiratory muscle weakness and the ratings of dyspnoea during daily activities [McParland *et al*, 1992] as well as during exercise testing [Mancini *et al*, 1992a] in these patients. Histological changes in the diaphragm have also been demonstrated [Lindsay *et al*, 1992]. The exact cause of respiratory muscle weakness is not known but it may be related to muscle underperfusion [Mancini *et al*, 1991] or may have a similar pathogenetic basis to that of the skeletal muscle abnormalities often seen in these patients [Massie *et al*, 1988; Minotti *et al*, 1991; Wilson *et al*, 1993]. Measurements of locomotor muscle function have indeed shown a reduction in maximal quadriceps strength and its increased tendency to fatigue in chronic heart failure [Buller *et al*, 1991].

Respiratory muscle function has not been widely studied in chronic heart failure. The objective of the study in this chapter was, therefore, to investigate respiratory

muscle strength in chronic heart failure and to examine its correlation with maximal oxygen consumption, an objective measurement of exercise capacity, and the ventilatory response to exercise. The relationship between respiratory muscle strength and locomotor muscle strength is also unknown and this was accordingly assessed using right quadriceps muscle strength for the latter.

Subjects and Methods

Twenty male chronic heart failure patients between 46 to 74 years of age (mean age 61.4±1.6 [SEM] years) participated in this study. Patients with known pulmonary disease were excluded since abnormal skeletal muscle metabolism may also be seen in patients with chronic lung disease [Tada *et al*, 1992]. All patients had suffered from heart failure for more than six months and were adequately treated with diuretics. Mean multigated acquisition (MUGA) radionuclide left ventricular ejection fraction was 25.4±3.0%. Heart failure was caused by ischaemic heart disease in 13 patients, idiopathic dilated cardiomyopathy in 6 patients and valvular heart disease in 1 patient. None of the patients was limited by angina. A control group of 7 healthy men (mean age 54.9±4.3 years, range 41-73 years, P=0.20) was also studied. None had respiratory symptoms. Subject characteristics including the results of lung function tests are summarised in Table 7.1. The study had been approved by the local ethics committee and all subjects gave informed consent.

Respiratory Muscle Strength

Mouth pressures during maximal static inspiratory effort (P_{Imax}) at functional residual capacity (FRC) and residual volume (RV) and during maximal static expiratory

	Normal Controls (n=7)	Chronic Heart Failure (n=20)
Age (years)	54.9±4.3	61.4±1.6
Sex	All male	All male
Height (cm)	172.6±2.7	174.0±1.7
Weight (kg)	74.9±3.8	75.6±3.1
Spirometry		
FEV_1 (% predicted)	110.6±6.3	86.3±4.5
FVC (% predicted)	111.9±6.3	93.2±5.2
Aetiology of CHF		IHD 13 DCM 6 Valvular Disease 1
Symptoms (NYHA)		I 1 II 14 III 4 IV 1
Left Ventricular Ejection Fraction (%)		25.4±3.0
Treatment		
Diuretics		n = 20
(Dose of frusemide or its equivalent*)		(69.0±6.7 mg)
ACE Inhibitors		n = 19
Digoxin		n = 6

Values expressed as mean±SEM.
FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; NYHA, New York Heart Association classification of symptoms; IHD, ischaemic heart disease; DCM, idiopathic dilated cardiomyopathy; ACE inhibitors, angiotensin-converting enzyme inhibitors

*1 mg bumetanide is taken as equivalent to 40 mg frusemide.

Table 7.1 Clinical characteristics of normal subjects and chronic heart failure patients.

effort (P_{Emax}) at FRC and total lung capacity (TLC) were measured. These were taken as indices of inspiratory and expiratory muscle strength respectively [Black & Hyatt, 1969]. All measurements were made with the subject standing and wearing a nose-clip. Mouth pressures were measured in cm H_2O with a manufacturer-calibrated pressure monitor (Druck, Leceister, United Kingdom) and were visually displayed on a liquid crystal display screen on the monitor. Subjects breathed through a pneumotachograph calibrated for spirometry (Innovision, Odense, Denmark) with a scuba-type mouthpiece and coupled to a T-valve. At the selected lung volume (FRC, RV or TLC), the valve was turned to obstruct the airway so that the subject's mouth pressure during maximal inspiratory or expiratory effort could be measured with the pressure monitor. A small leak using a 22-gauge needle was incorporated to the airway to prevent glottic closure and light pressure was applied to the cheeks during expiratory manoeuvres to minimise the contribution of facial muscles. Subjects were urged to perform maximally and repeated efforts were made until the two highest values agreed within ± 5 cm H_2O. An average of 4 efforts were usually required for each lung volume. Subjects were allowed to rest for a few minutes when necessary between the manoeuvres.

Quadriceps Muscle Strength

All controls and 15 CHF patients also had their right quadriceps muscle strength assessed [Buller *et al*, 1991]. They were seated within a rigid framework and were asked to produce a maximal right knee extension against a stirrup attached to a strain gauge. This was accepted as the maximal isometric force produced when a superadded stimulus applied through saline pad electrodes to the right quadriceps of duration 1 ms at 1 Hz failed to demonstrate an additional twitch at the plateau of the contraction. The strain

gauge had previously been calibrated against known masses. The maximal isometric force was expressed in N (Newton).

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing was performed in all subjects to assess exercise capacity. All were exercised to exhaustion (peak respiratory exchange ratio, $R > 1.1$) using the Bruce protocol [Bruce *et al*, 1963], with the addition of a "Stage 0" at 1.0 mph and 5% gradient for the chronic heart failure patients. Metabolic gas exchange analysis was carried out by means of mass spectrometry as described before (Amis 2000, Innovision, Odense, Denmark) using the inert gas dilution technique [Davies & Denison, 1979]. The ventilatory response to exercise was taken as the slope of the regression line relating minute ventilation and carbon dioxide output ($\dot{V}_E$-$\dot{V}CO_2$ slope) as described in previous chapters [Whipp *et al*, 1984; Buller & Poole-Wilson, 1990].

Studies of Reproducibility

Repeat measurements of maximal inspiratory and expiratory mouth pressures were made in 3 controls and 3 chronic heart failure patients on a separate day to evaluate the reproducibility of the test.

Statistical Analysis

The results are presented as means$\pm$SEM. Student's *t-test* was used to assess the significance of results. The relationship between variables was assessed using linear regression analysis. $P < 0.05$ was considered significant.

Results

As shown in Table 7.1, the mean age, height and weight of controls and chronic heart failure patients did not differ significantly. The correlation between repeated measurements of P_{Imax} and P_{Emax} in 6 subjects is shown in Figure 7.1 with $r > 0.9$ for both maximal inspiratory and expiratory mouth pressures. The coefficients of variation for P_{Imax} at FRC and RV were 8.1% and 6.4% respectively. For P_{Emax} at FRC and TLC, these were 6.5% and 6.9%. These were compatible with previous data [Black & Hyatt, 1969].

Results of the maximal oxygen consumption, $\dot{V}_E$-$\dot{V}CO_2$ slope, respiratory and right quadriceps muscle strength in the chronic heart failure patients and healthy controls are presented in Table 7.2. P_{Imax} at FRC was significantly reduced in chronic heart failure patients as was P_{Imax} at RV although the latter did not reach statistical significance. There was also significant reduction in both P_{Emax} at FRC and TLC as presented graphically in Figure 7.2. The quadriceps muscle was also weaker in the chronic heart failure patients.

When maximal oxygen consumption was correlated with maximal mouth pressures in the chronic heart failure patients, P_{Imax} at both FRC and RV correlated significantly as shown in Figure 7.3 (r=0.59, P=0.006 and r=0.45, P=0.048 respectively). On the contrary, P_{Emax} at FRC and TLC failed to correlate significantly with maximal oxygen consumption as shown in Figure 7.4.

When the ventilatory response to exercise characterised by the $\dot{V}_E$-$\dot{V}CO_2$ slope was correlated with maximal mouth pressures in the chronic heart failure patients, there was a strong inverse trend between P_{Imax} at FRC and the $\dot{V}_E$-$\dot{V}CO_2$ slope as shown in Figure 7.5 (r=-0.43, P=0.059). P_{Imax} at RV and P_{Emax} at both FRC and TLC, however,

did not correlate significantly with the $\dot{V}_E$-$\dot{V}CO_2$ slope (Figures 7.5 and 7.6).

As seen in Figures 7.7 and 7.8, there was no significant correlation between P_{Imax} or P_{Emax} with right quadriceps strength.

	Controls (n=7)	**Chronic Heart Failure** (n=20)	***P value***
Maximal Oxygen Consumption (ml/kg/min)	36.2±3.5	17.3±1.5	0.001
$\dot{V}_E$-$\dot{V}CO_2$ regression slope	28.9±2.4	37.0±2.0	0.02
P_{Imax} (cm H_2O)			
FRC	85.6±9.6	59.7±6.3	0.045
RV	89.3±13.0	77.3±6.6	0.44
P_{Emax} (cm H_2O)			
FRC	134.6±9.1	94.8±6.2	0.004
TLC	160.7±13.0	121.7±8.5	0.028
Right Quadriceps Strength (N)	446.2±28	308.5±22	0.001

Values expressed as mean±SEM.

Table 7.2 Results of maximal oxygen consumption, the ventilatory response to exercise, respiratory muscle and right quadriceps strength.

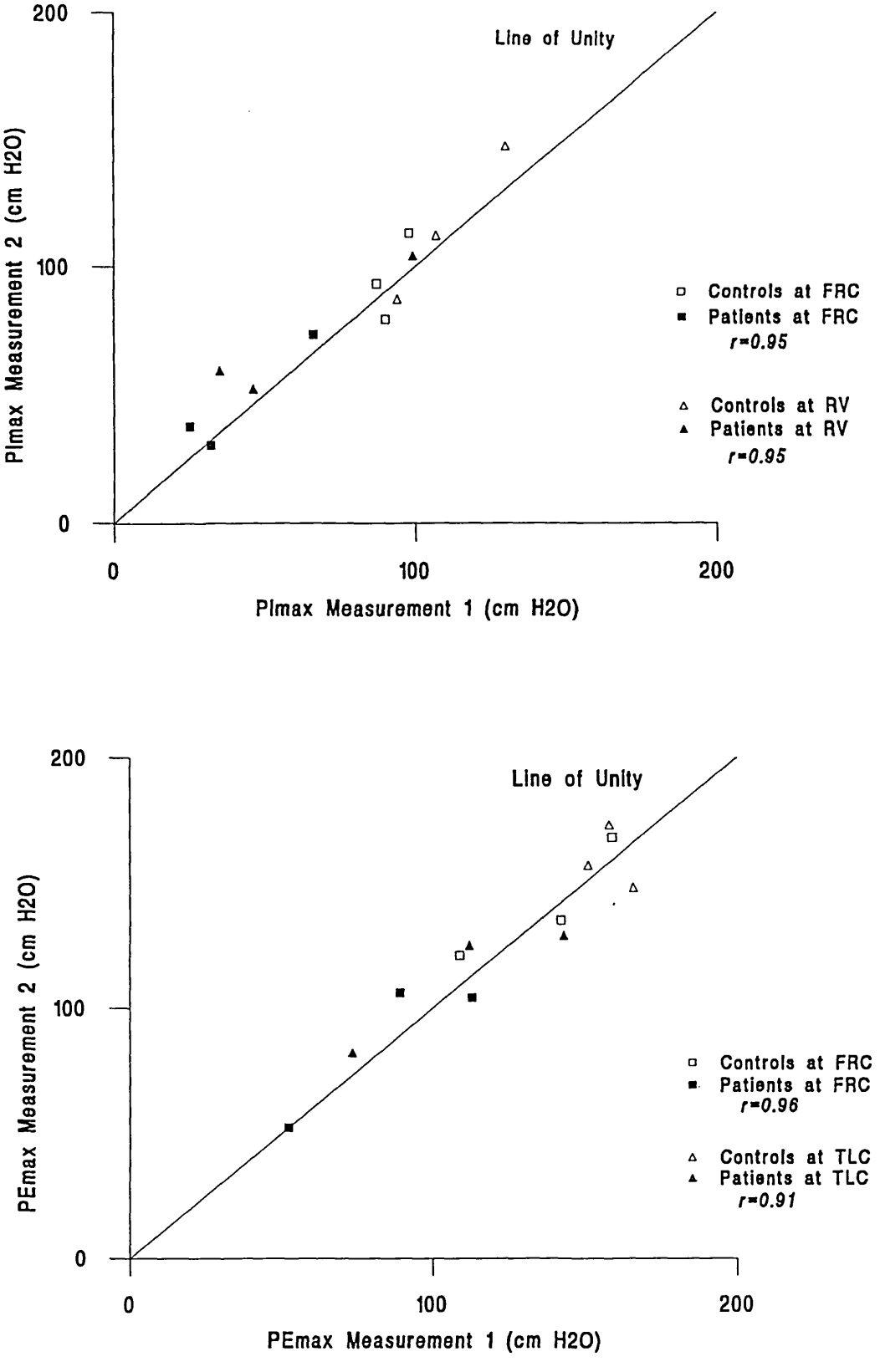


Figure 7.1 Reproducibility studies of maximal mouth pressures during inspiration (top graph) and expiration (bottom graph).

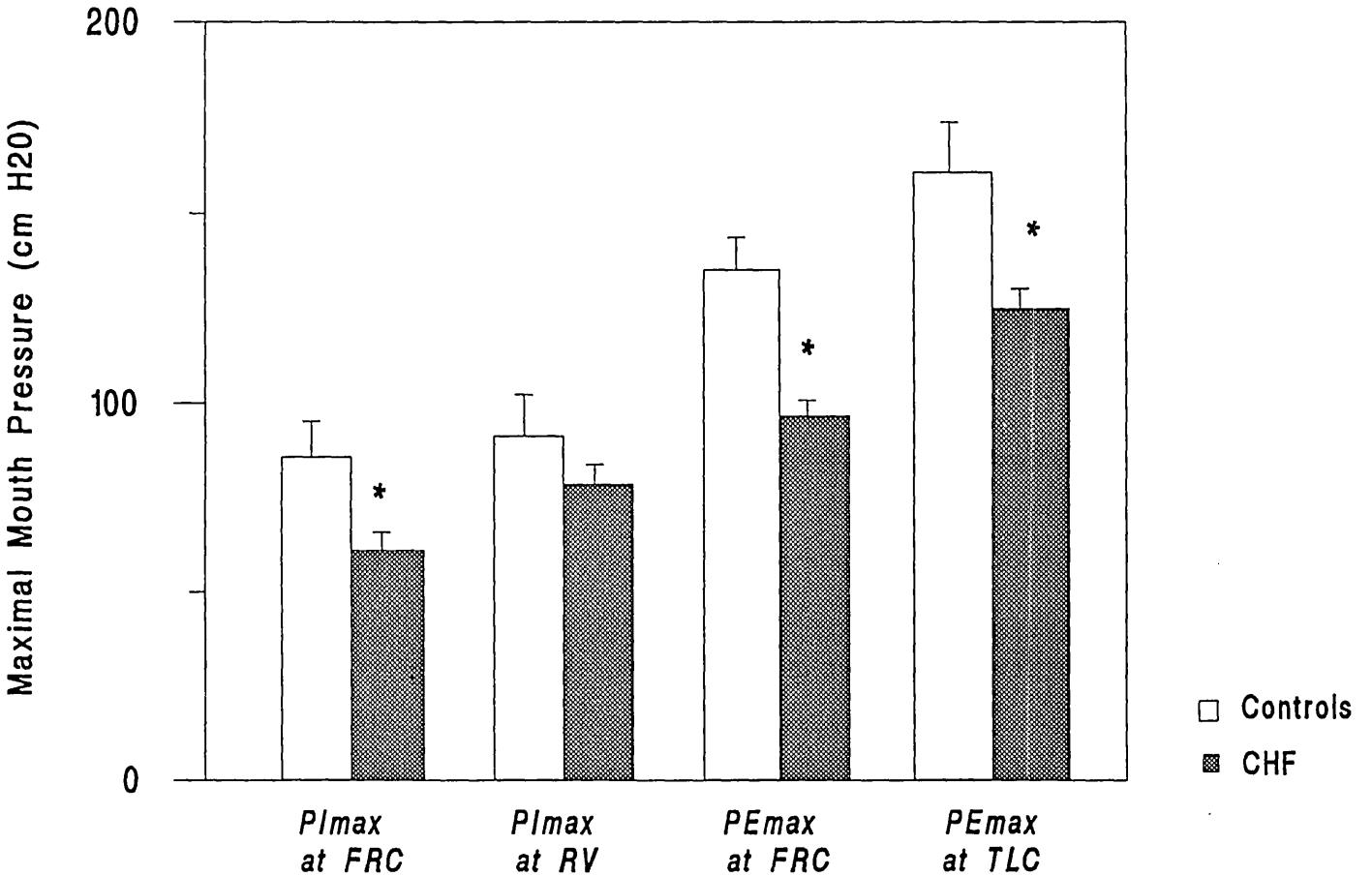
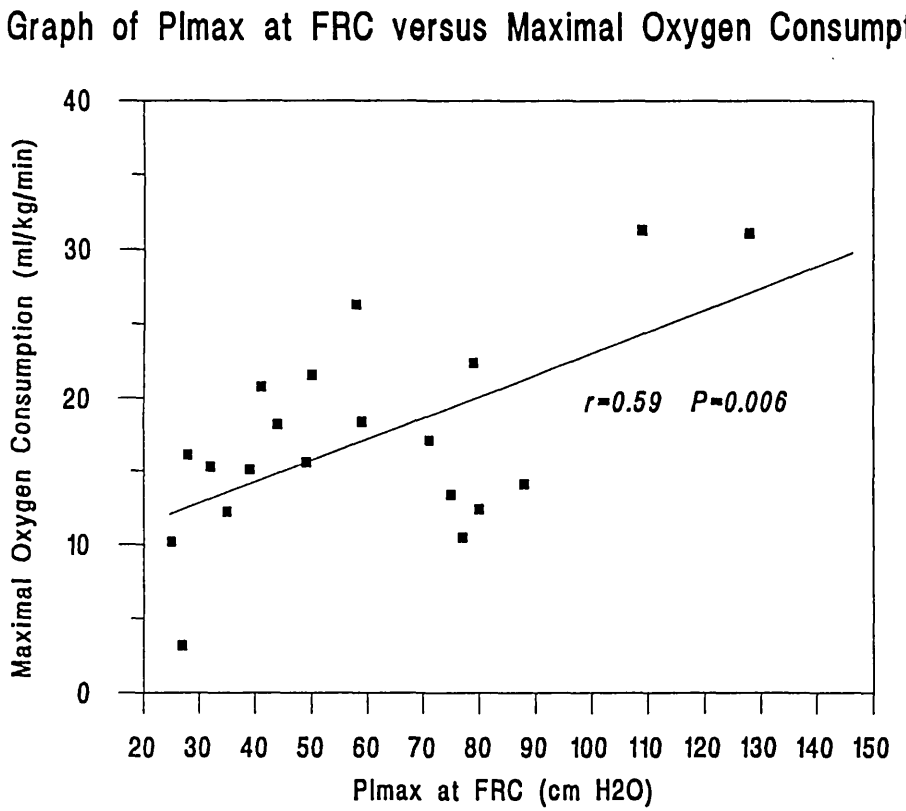


Figure 7.2 The histogram above shows the reduced mouth pressures in chronic heart failure (CHF) patients reflecting respiratory muscle weakness. * denotes $P < 0.05$.



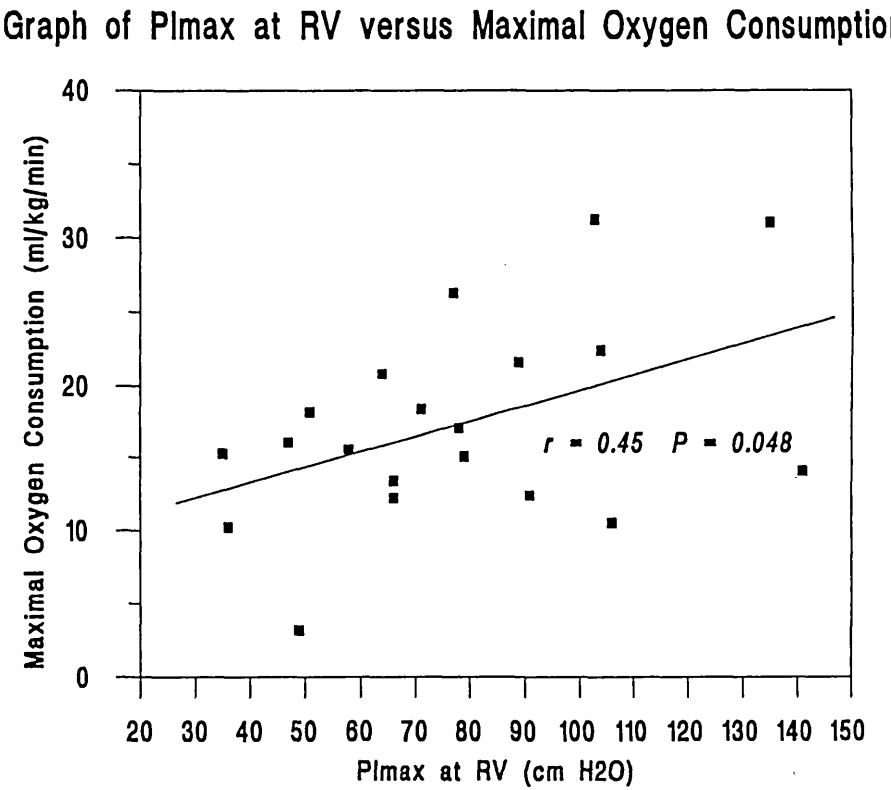
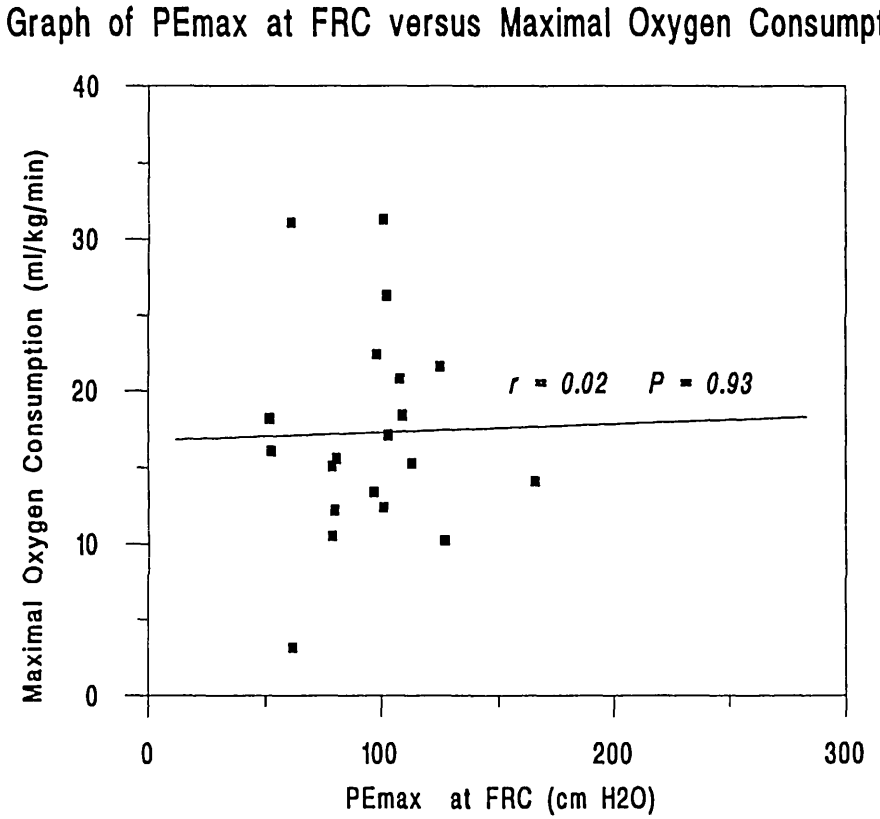


Figure 7.3 The correlation between maximal oxygen consumption and P_{Imax}, reflecting inspiratory muscle strength, is shown above.



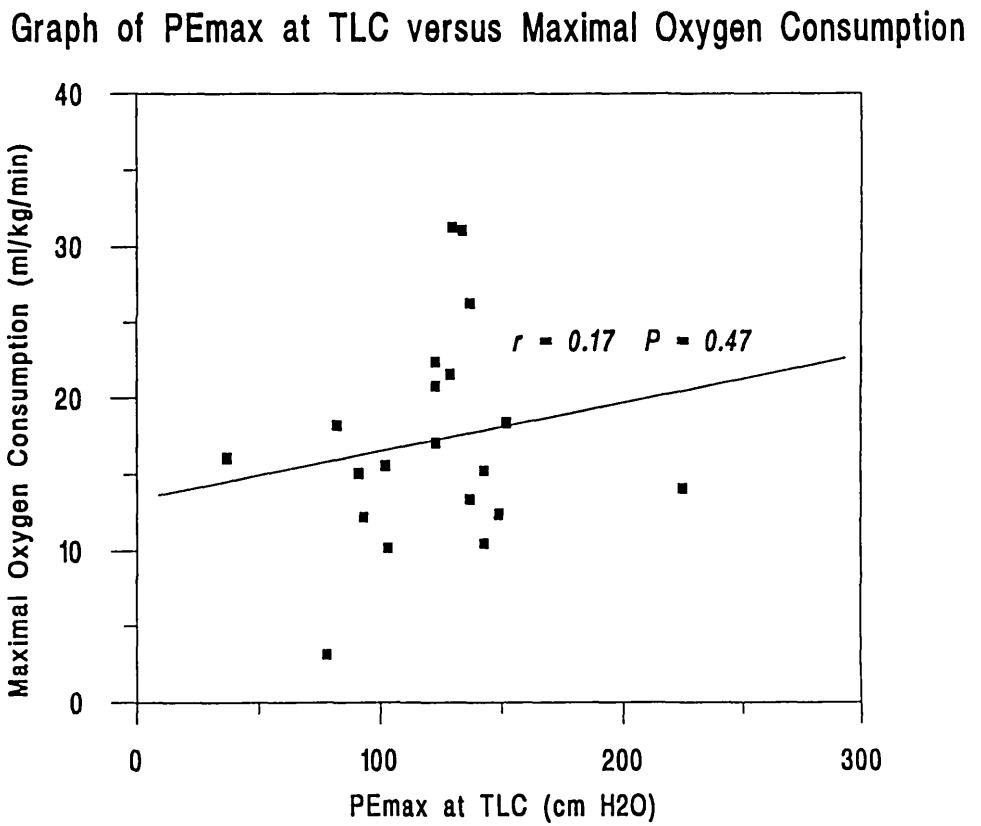
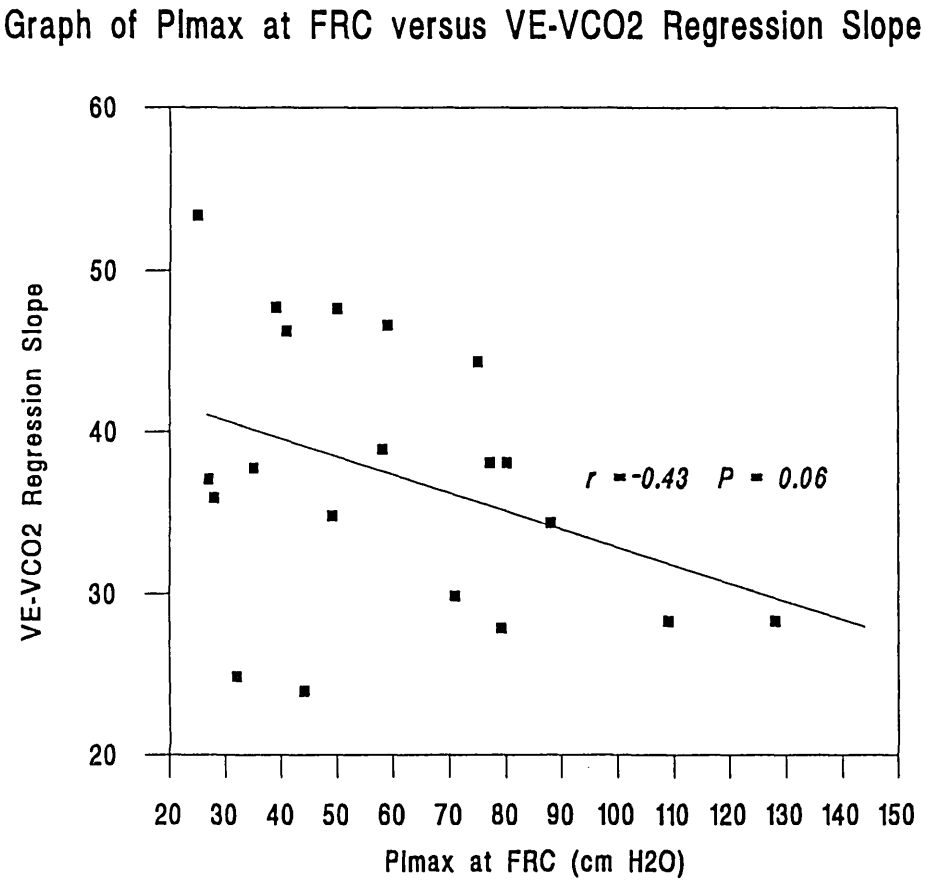


Figure 7.4 The correlation between maximal oxygen consumption and P_{Emax}, reflecting expiratory muscle strength, is shown above.



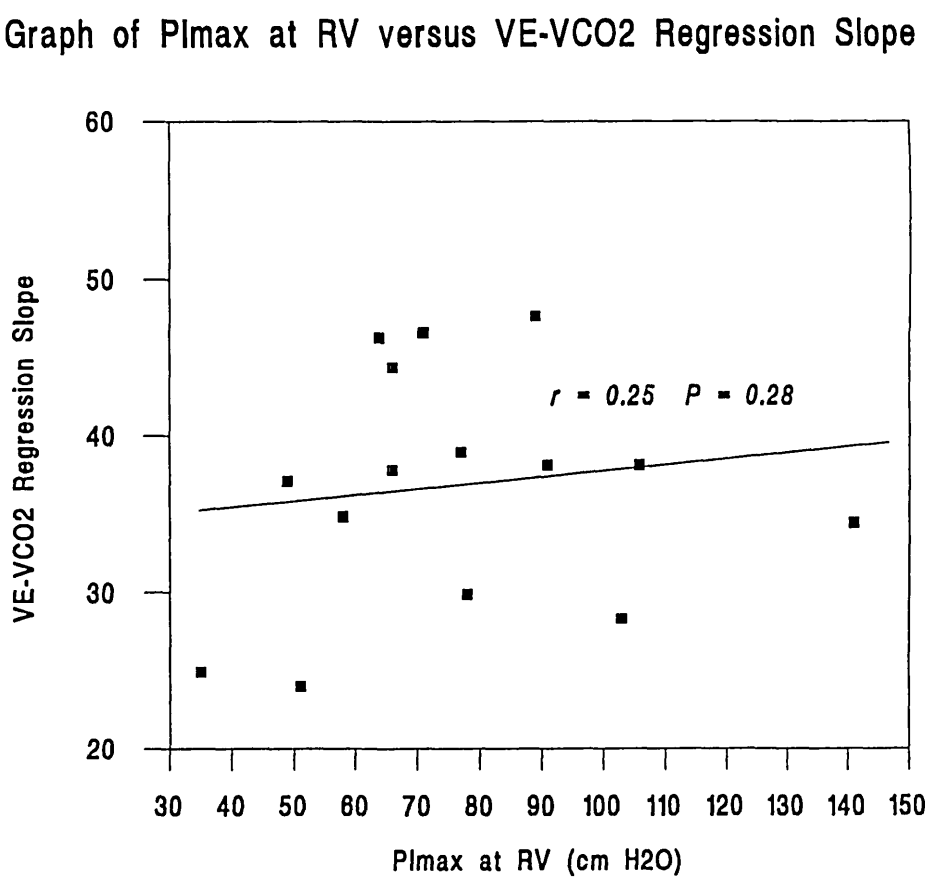
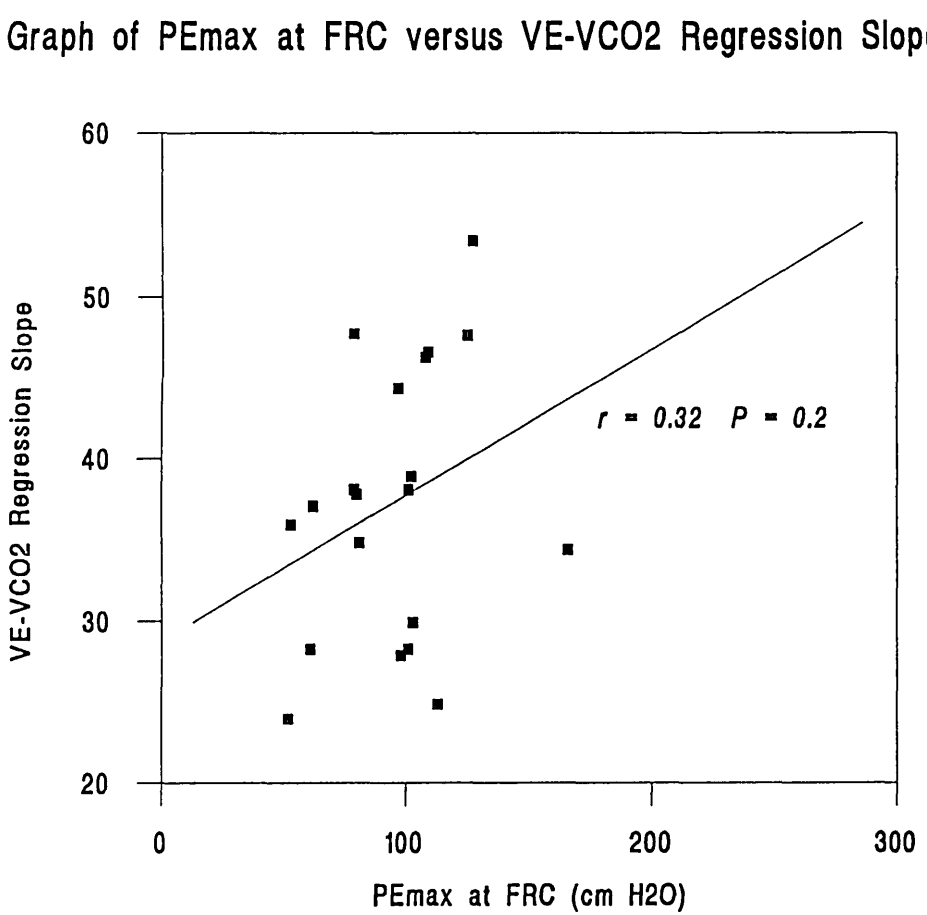


Figure 7.5 The correlation between the ventilatory response to exercise as characterised by the $\dot{V}_E$-$\dot{V}CO_2$ regression slope and P_{Imax} is shown above.



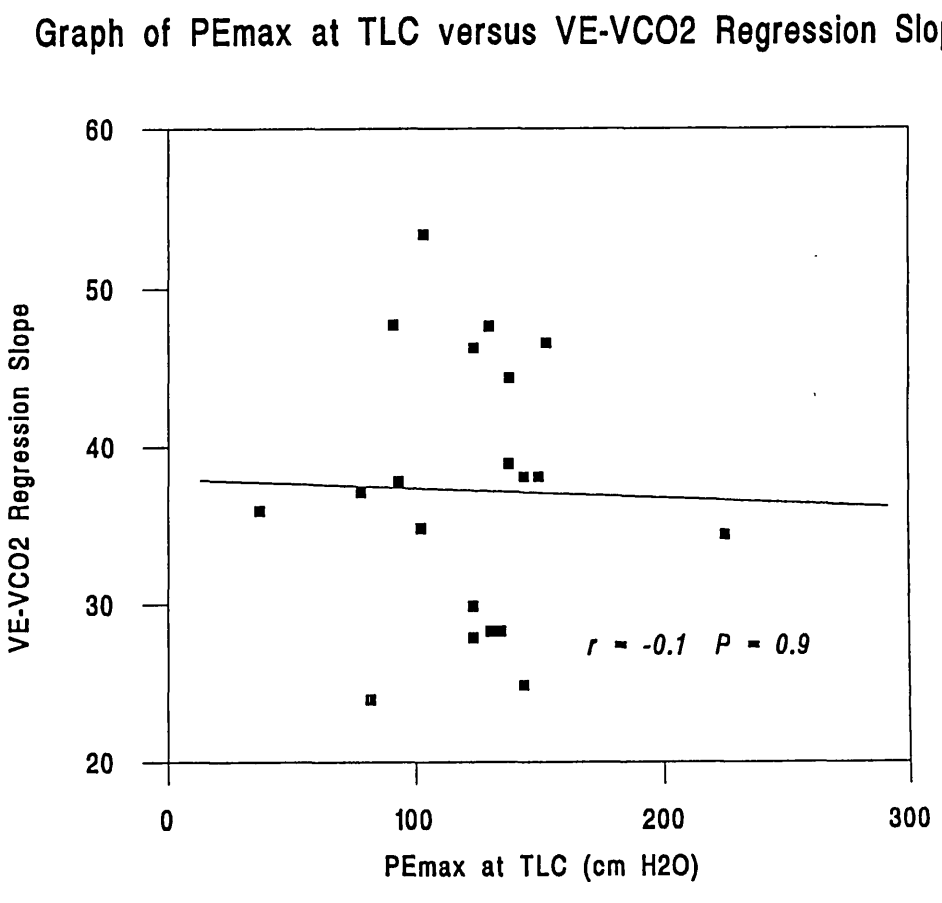


Figure 7.6 The correlation between the ventilatory response to exercise as characterised by the $\dot{V}_E$-$\dot{V}CO_2$ regression slope and P_{Emax} is shown above.

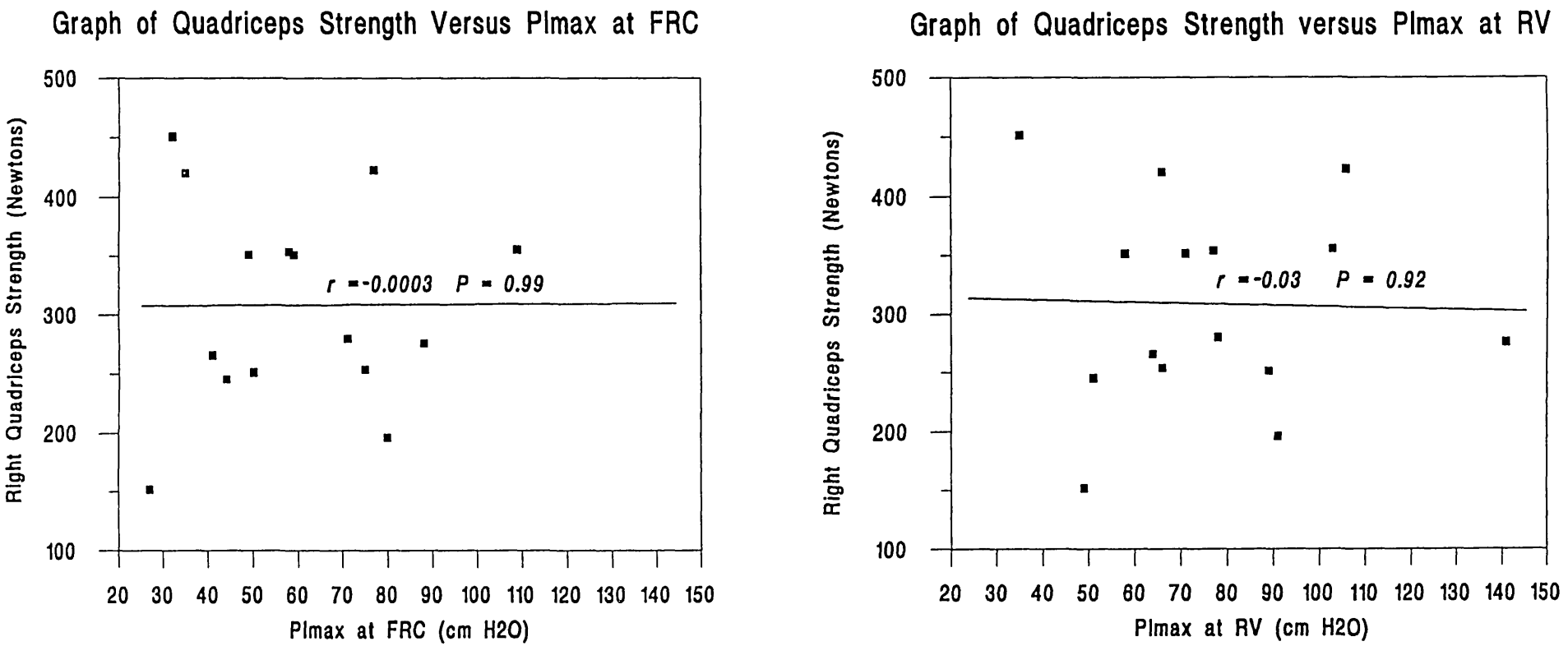
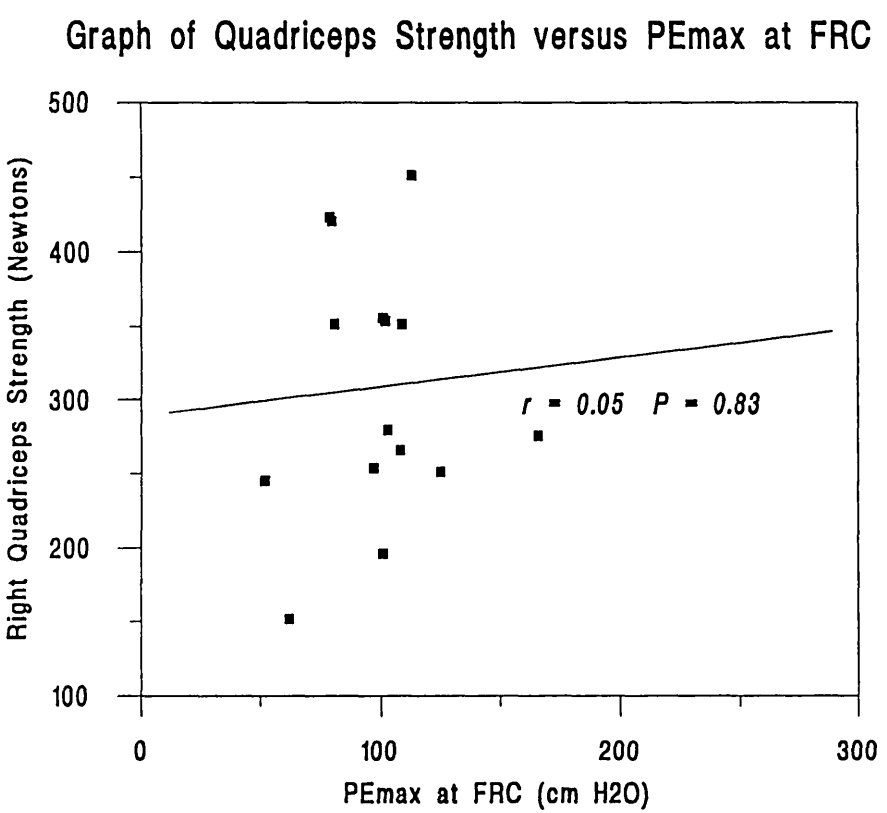


Figure 7.7 The graphs above show that there is no correlation between P_{Imax} and quadriceps muscle strength.



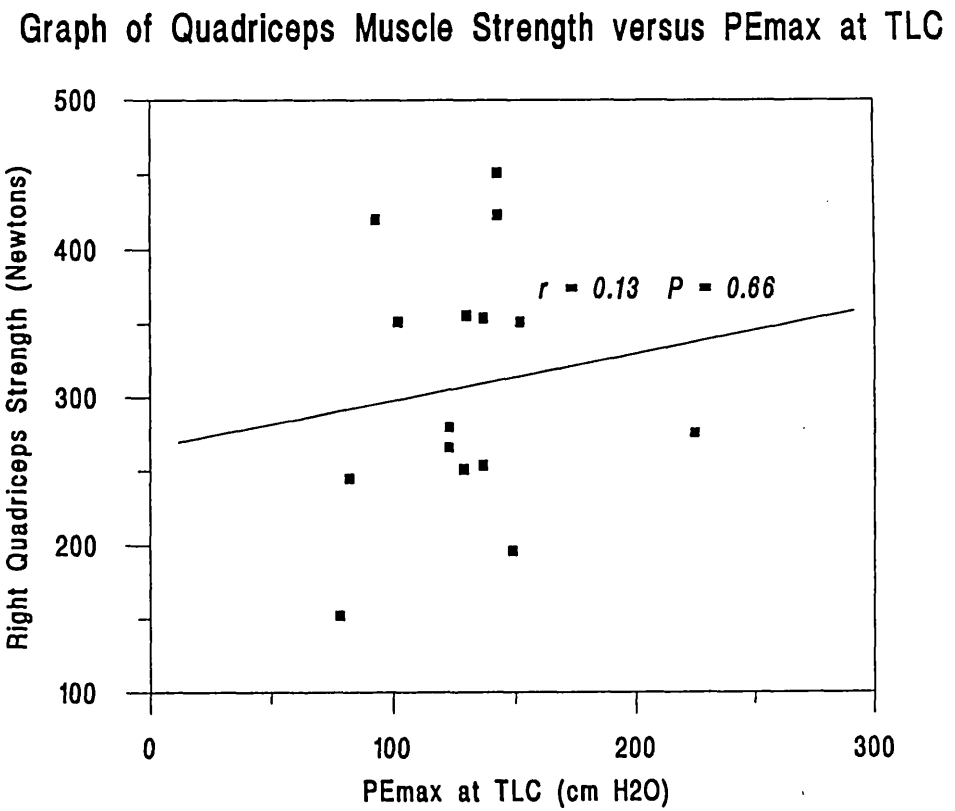


Figure 7.8 The graphs above show that there is no correlation between P_{Emax} and quadriceps muscle strength.

Discussion

This study shows that there is respiratory muscle weakness in chronic heart failure patients. The significant reduction in P_{Imax} at FRC and P_{Emax} at FRC and TLC in chronic heart failure patients is compatible with the findings of some investigators [Hammond *et al*, 1990; Mancini *et al*, 1992a] although others [McParland *et al*, 1992; Nishimura *et al*, 1994] could not demonstrate a significant reduction in P_{Emax}. This may be because of the smaller size of their study population. Although not statistically significant, a reduction in P_{Imax} at RV was also seen in chronic heart failure patients in this study. It may be that a larger more severely affected group of chronic heart failure patients may be needed to demonstrate this reduction in P_{Imax} at RV more convincingly. Respiratory muscle fatigue is, among others, dependent on the amount of energy expended during breathing [Roussos *et al*, 1982]. Even if the work of breathing is the same in chronic heart failure patients compared with normal individuals, a greater fraction of a relatively reduced maximal strength is needed in order to breathe. This increases the energy demands and hence the tendency to fatigue [Roussos *et al*, 1982]. The work of breathing in chronic heart failure is, in fact, not the same as in normal subjects considering that these patients may have an obstructive, restrictive or mixed airway abnormality as discussed in Chapter 1 [Ries *et al*, 1986; Petermann *et al*, 1987; Hosenpud *et al*, 1990; Wright *et al*, 1990; Naum *et al*, 1992; Ravenscraft *et al*, 1993; Faggiano *et al*, 1993] and indeed they breathe excessively for a given workload or rate of carbon dioxide production. This was shown by the increased $\dot{V}_E$-$\dot{V}CO_2$ slope in the patients in this study. They also demonstrated a reduction in both FEV_1 and FVC. Furthermore, some patients may have interstitial lung changes due to chronic pulmonary venous hypertension [Parker & Weiss, 1936; Heath & Edwards, 1959; Kay & Edwards,

1973]. Normally, there is an optimal frequency of breathing and tidal volume, resulting in minimal work [Otis *et al*, 1950]. In chronic heart failure patients, it has been shown that during exercise, the onset of dyspnoea is characterised by a sudden increase in the frequency of breathing with little change in tidal volume, as mentioned in Chapter 4 and 5 [Yokoyama *et al*, 1994]. All these observed abnormalities in chronic heart failure serve only to increase the work of breathing and make respiratory muscle strength even more important as a contributory cause of breathlessness and exercise intolerance. In fact, in addition to demonstrating underperfusion of the respiratory muscles during exercise, Mancini *et al* [1991, 1992a] have shown that there is increased diaphragmatic work in chronic heart failure patients. Interestingly, they could not establish respiratory muscle fatigue in these patients after maximal bicycle exercise although the 3- to 5-minute time delay in recording the measurements after exercise may have made muscle fatigue less detectable.

In this study, inspiratory muscle strength was seen to be a determinant of maximal oxygen consumption in chronic heart failure patients. This is in agreement with the findings of Nishimura *et al* [1994]. The inspiratory muscles consist of the diaphragm, external intercostal and accessory muscles. The diaphragm is the most important of these since breathing with intercostal or accessory muscles does not normally occur [Roussos *et al*, 1982]. Expiration, by contrast, is predominantly due to the passive relaxation of the diaphragm although during heavy breathing, the abdominal recti and internal intercostals are involved in producing rapid expiration [Guyton, 1991c]. Despite the reduced maximal expiratory mouth pressures seen in chronic heart failure patients, it is therefore not surprising to see that only inspiratory muscle strength measurements correlated significantly with maximal oxygen consumption. That there was a significant

correlation further suggests that the inspiratory muscles, in particular the diaphragm, are probably important in determining the exercise tolerance in these patients.

The relationship between respiratory muscle strength and the ventilatory response to exercise has not been established previously. There appeared to be an inverse relationship between inspiratory muscle strength and the ventilatory response to exercise as suggested by the strong inverse trend between P_{Imax} at FRC and the $\dot{V}_E$-$\dot{V}CO_2$ slope. However, the reasons for the lack of a similar correlation between P_{Imax} at RV and $\dot{V}_E$-$\dot{V}CO_2$ slope remains unclear. It may be that a larger group of more severely affected chronic heart failure patients is needed to demonstrate this. The precise nature of the inverse relationship between inspiratory muscle strength and the ventilatory response to exercise remains one of conjecture. It may well mean that inspiratory muscle weakness contributes in part to the increased ventilatory response to exercise in these patients. Muscles have the capacity to sense effort, fatigue and also local metabolic changes, the latter constituting the metaboreflex [Campbell & Howell, 1963; Kao, 1963]. Afferent signals from the inspiratory muscles may therefore act not only on the respiratory centres in the medulla augmenting the ventilatory response to exercise but may also be perceived directly as breathlessness.

The cause of respiratory muscle weakness is not known. It may be due to underperfusion and a reduced flow of nutrients to the muscles consequent upon lower cardiac output or peripheral vasoconstriction [Levine & Levine, 1990], or it may be related to the neuroendocrine abnormalities seen in chronic heart failure such as increased catecholamine level [Packer, 1992] and insulin resistance [Coats *et al*, 1994; Swan *et al*, 1994] leading to changes in diaphragmatic muscle structure or function. Inactivity and subsequent deconditioning are considered important causes of skeletal

myopathy in chronic heart failure, but whether this is applicable to muscles responsible for such constant work and rhythmicity as breathing is open to debate. Part of the process of inspiration also involves the downward displacement of the abdominal viscera. Fluid engorged viscera such as the liver may act as a mechanical impediment to this and cause a reduction in the efficiency of inspiratory muscle activity. None of our patients, however, had obvious peripheral oedema during the study.

It is interesting to see that there was lack of correlation between respiratory muscle strength and locomotor muscle strength. This suggests that the magnitude and time course of muscle weakness involving the respiratory and locomotor muscles may differ in individual patients. It has been shown that physical training is beneficial in chronic heart failure and improves exercise capacity as well as the ventilatory response to exercise [Coats *et al*, 1992]. If respiratory and skeletal myopathy do not follow the same time course of the disease process and if they are not affected equally, then the implication is that treatments, such as training may need to include inspiratory muscle endurance exercises [Leith & Bradley, 1976; Mancini *et al*, 1995]. It may be necessary to "rehabilitate" each particular muscle group including respiratory muscles to improve exercise tolerance and relieve the symptoms of both breathlessness and muscle fatigue.

In conclusion, respiratory muscle weakness is seen in patients with chronic heart failure. Inspiratory muscle strength is a determinant of exercise tolerance and also appears to influence the ventilatory response to exercise. Respiratory and skeletal muscles seem to be discordantly affected. Further research is required to investigate the reasons for this discordance and to test the hypothesis that treatments specifically to improve respiratory muscle function may be beneficial to those in whom respiratory muscle weakness is demonstrated as being a factor in symptomatic limitation to exercise.

Chapter 8

AIRWAY RESPONSIVENESS IN CHRONIC HEART FAILURE

Introduction

Exertional dyspnoea is a limiting symptom in chronic heart failure. Cough and wheeze, features associated with hyper-responsive airways, are not uncommon especially in decompensated chronic heart failure. Classically, non-specific bronchial hyperresponsiveness is seen in bronchial asthma [Britton & Tattersfield, 1986] and is assessed using aerosols of histamine, acetylcholine or its analogue, methacholine with monitoring of the bronchochoconstrictor response in terms of the reduction in forced expiratory volume [Chai *et al*, 1975]. Several studies have described bronchial hyperresponsiveness in chronic heart failure [Cabanes *et al*, 1989; Pison *et al*, 1989, Sasaki *et al*, 1990; Brunee *et al*, 1993] but this is not a unanimous finding [Eihacker *et al*, 1988; Seibert *et al*, 1989]. The number of patients in these studies are small and the findings are often confounded by acute decompensation of chronic heart failure, current smoking of patients or the stopping of treatment including diuretics prior to assessment. Pison *et al* [1989] found that bronchial hyperresponsiveness in decompensated chronic heart failure patients did not improve 5 to 15 days after increased diuretic therapy, confirming that a recent history of acute pulmonary oedema may affect bronchial responsiveness. Cabanes *et al* [1989, 1991] showed that inhalation of the vasoconstrictor methoxamine, an alpha-receptor agonist, attenuated the methacholine-induced bronchial hyperresponsiveness and suggested that bronchial hyperresponsiveness was in part due

to the vasodilatory effect of methacholine causing further oedema and narrowing of the airways even without an increased smooth muscle tone. In addition to airway oedema, a neural reflex has also been postulated by some investigators to mediate bronchial hyperresponsiveness [Sasaki *et al*, 1990; Chung *et al*, 1983]. This may be secondary to the stimulation of pulmonary stretch receptors (J receptors) by raised pulmonary venous pressure although a significant correlation between pulmonary haemodynamics and bronchial hyperresponsiveness could not be demonstrated [Sasaki *et al*, 1990]. Local airway inflammation has also been suggested as a cause of bronchial hyperresponsiveness but the presence of inflammatory cells and mediators has yet to be explored [Pison *et al*, 1989].

To investigate the role of bronchial hyperresponsiveness in the generation of dyspnoea and the increased ventilatory response to exercise, several aspects of airway responsiveness were studied in chronic heart failure patients who were stable and non-smoking so as to avoid the possible confounding factors mentioned above. Specifically, the responsiveness of the airways to the following were examined: (i) methacholine, a direct airway smooth muscle stimulant [Chai *et al*, 1975], (ii) sodium metabisulphite, a putative stimulant of airway sensory nerves [Nichol *et al*, 1989], and (iii) exercise, a known stimulus of the hyperresponsive airways [Cherniack, 1992]. In addition, the cough responses to low-concentration chloride solutions and capsaicin were studied [Fuller & Choudry, 1987]. Afferent fibres of the cough reflex are known to arise in the pulmonary stretch receptors (J receptors) via c fibres [Hanacek *et al*, 1984], in receptors in the upper airways [Widdicombe, 1954; Sant'Ambrogio *et al*, 1978] and also in c fibre endings in the mucosa of the larynx, trachea and bronchi [Coleridge & Coleridge, 1984; Sant'Ambrogio, 1987]. Since the c fibres are stimulated by capsaicin [Coleridge *et al*,

1965], it would be expected that the cough reflex is enhanced if airway hyperresponsiveness is present and mediated by the J receptors and c fibres. Finally, exhaled nitric oxide concentration was also measured to see if this was increased as it is in patients with inflammatory airway disease, such as asthma, due to the action of proinflammatory cytokines [Kharitonov *et al*, 1994, 1995].

Patients and Methods

Ten patients (mean age 56.5±3.2[SEM], range 40-68 years; 7 men and 3 women) with stable chronic heart failure and no history of acute decompensation within 6 months of the study were recruited. Patients were non-smokers or had stopped smoking for at least 5 years prior to the study. Patients with a history of asthma, chronic obstructive airways disease or other airway disease were excluded. All had a radionuclide left ventricular ejection fraction of less than 35% (mean 20.8±2.9%, range 9-33%) and were receiving stable therapy with both diuretic (mean daily frusemide dose 80 mg, range 40-200 mg) and angiotensin-converting enzyme inhibitor medication. None was limited by angina although 3 patients were taking calcium antagonists and 4 patients nitrates. All patients had cardiac catheterisation investigation prior to the study (8 with right and left heart studies, 2 with left heart only). Standard lung function tests and chest radiographs (mean radiographic cardiothoracic ratio 0.56±0.02) were also performed in these patients. Because all patients were receiving angiotensin-converting enzyme inhibitors which may influence airway responsiveness and cough, eight asymptomatic non-smoking controls taking angiotensin-converting enzyme inhibitors for essential hypertension were also studied (mean age 54.3±2.8 years, range 42-65 years; 6 men and 2 women; radiographic cardiothoracic ratio 0.46±0.01, $P<0.001$). None of the subjects in this

study was troubled by cough during treatment with angiotensin-converting enzyme inhibitors. Clinical characteristics of the chronic heart failure patients are given in Table 8.1. This study was approved by the local ethics committee and all subjects gave written informed consent.

Bronchial Provocation Tests

Airway responsiveness was assessed following the inhalation of two pharmacological agents, methacholine and sodium metabisulphite, and following maximal cardiopulmonary exercise testing. Increasing doubling concentrations of methacholine and sodium metabisulphite, ranging from 1 mg/ml to 64 mg/ml and from 5 mg/ml to 160 mg/ml respectively, with preceding saline solution as baseline were used. The preparation of these solutions are given in Appendix 4. Each provocation test was done separately on 2 different occasions using a nebuliser attached to a dosimeter (Model MB3, MEFAR Electromedical, Brescia, Italy; output 0.14 ml per solution). Forced expiratory volume in 1 second (FEV_1) was measured 2 minutes after each test with a spirometer (Vitalograph, USA). Doubling concentrations were used every 5 minutes until a $\geq 20\%$ fall in FEV_1 from the baseline was noted, or until the maximal concentration for each agent was reached if the fall in FEV_1 remained $<20\%$ from baseline. The provocation concentration causing a 20% fall in FEV_1 (PC20) was then calculated by linear interpolation, as given in Appendix 5. If the fall in FEV_1 remained $<20\%$ at a methacholine concentration of 64 mg/ml and a sodium metabisulphite concentration of 160 mg/ml, the PC20 was arbitrarily taken as the next doubling concentration of 128 mg/ml and 320 mg/ml respectively, for the purposes of statistical analysis. Although this may underestimate the PC20 of some patients, such concentrations are relatively high

considering the PC20 of asthmatics is generally <8 mg/ml and <40 mg/ml for methacholine and sodium metabisulphite respectively and can therefore be regarded as values consistent with a negative provocation test.

Cardiopulmonary Exercise Testing

FEV_1 was assessed using a spirometer (Vitalograph, USA) before and after maximal treadmill exercise testing on a separate day to examine if the the airways were hyper-responsive to exercise. Metabolic gas exchange analysis was also done during exercise testing using mass spectrometry (Amis 2000, Innovision, Odense, Denmark) by means of the inert gas dilution technique [Davies & Denison, 1979]. All subjects exercised to exhaustion using the Bruce protocol [Bruce *et al*, 1963], with the addition of "Stage 0" at 1.0 mph and a 5% gradient.

Cough Response

The cough response was assessed using low-concentration chloride solutions and capsaicin respectively, the preparation of which are given in Appendix 4. Four iso-osmolar solutions with decreasing chloride concentrations (150, 75, 37.5 and 0 mM) were used. Inhalations of 4 ml of each chloride solutions were taken for a minute each, between intervals of 5 minutes, from an ultrasonic nebuliser (Ultra-Neb 2000, DeVilbiss, Somerset, Pennsylvania, USA) through the mouth with the subject wearing a noseclip. The number of coughs induced during and 1 minute after nebulisation for each solution was counted. For the capsaicin test, 10 doubling concentrations of capsaicin ranging from 0.975 to 500 μM were used. Single-breath inhalations of 0.02 ml solution of each concentration were administered through the mouth from a breath-activated dosimeter

(PK Morgan, Gillingham, UK). The concentration of capsaicin which produced 2 or more coughs was taken as the threshold concentration. For the purpose of statistical analysis, subjects who had <2 coughs at 500 μM capsaicin were assumed to have a threshold of the next doubling concentration (i.e. 1000 μM).

Nitric Oxide Measurement

Exhaled nitric oxide concentration was measured using a modified chemiluminescence analyser (Model LR2000, Logan Research, Rochester, UK) designed for on-line recording of exhaled nitric oxide and sensitive to concentrations of 2 to 4000 parts per billion (ppb) by volume [Kharitonov *et al*, 1994]. Measurements were made by slow exhalation from the mouth for 30-45 seconds from total lung capacity via a wide-bore Teflon tubing. Subjects wore a nose-clip and the rate of expiration was kept constant using a visual display of expiratory flow measured by flow sensors in the analyser. The average of two readings measured at end-exhalation were taken. The coefficient of variation as a means of assessing the reproducibility of exhaled nitric oxide using this method in our asthma laboratory is 7.4%, with most healthy non-smoking individuals having a recording of <20 ppb.

Statistical Analysis

Paired and unpaired Student's *t*-test were used where appropriate to assess the significance of results. Logarithmic transformation of PC20 and of capsaicin concentration causing 2 or more coughs were used. For the cough response to low-concentration chloride solutions, median cough counts were used and the significance of results assessed by Mann-Whitney *U* test.

Patient	Age (y)	Sex	Aetiology	NYHA Class	Smoking History (pack years)*	LV Ejection Fraction (%)	PCWP (mmHg)	LVEDP (mmHg)	CXR CTR	Maximal O_2 Consumption (ml/kg/min)
1	64	F	DCM	III	1.2	13	5	11	0.50	13.9
2	52	F	DCM	III	6	27	12	16	0.56	13.6
3	66	M	DCM	II	88	33	Not done	19	0.51	22.4
4	40	M	DCM	IV	Nil	8	26	40	0.66	17.8
5	46	M	IHD	II	26	28	14	21	0.50	19.1
6	47	M	IHD	II	Nil	18	Not done	26	0.57	24.8
7	66	M	IHD	III	Nil	9	24	22	0.58	13.9
8	68	M	IHD	III	Nil	15	17	24	0.64	17.3
9	63	F	DCM	III	11	29	16	18	0.55	12.0
10	53	M	IHD	III	1.5	28	25	27	0.50	13.7

DCM, idiopathic dilated cardiomyopathy; IHD, ischaemic heart disease; NYHA, New York Heart Association Functionl Class; LV, Left Ventricle; PCWP, Pulmonary Capillary Wedge Pressure; LVEDP, Left Ventricular End-diastolic Pressure; CXR CTR, Radiographic cardiothoracic ratio.

*All patients with a smoking history had stopped smoking for at least 5 years.
Pack year = (Number of cigarettes smoked per day X Number of years smoking) / 20.

Table 8.1 Clinical characteristics of chronic heart failure patients.

Results

From Table 8.1, chronic heart failure patients had New York Heart Association functional class II to IV symptoms. The aetiology of chronic heart failure was idiopathic dilated cardiomyopathy in 5 patients and ischaemic heart disease in the others. They had a reduced peak oxygen consumption compared with controls (16.9±1.3 v 26.5±2.3 ml/kg/min, $P<0.01$) consistent with moderately to severely impaired exercise tolerance. These patients also had an increased ventilatory response to exercise ($\dot{V}_E$-$\dot{V}CO_2$ regression slope: 38.8±3.4 v 28.4±1.4 in controls, $P=0.02$). The results of the PC20 for methacholine and sodium metabisulphite are summarised in Table 8.2 with the results of individual heart failure patients and controls given in Tables 8.3 and 8.4 respectively. The geometric mean PC20 for methacholine was 67.6±1.3 mg/ml in chronic heart failure patients and 79.8±1.3 mg/ml in controls ($P=0.71$) and for sodium metabisulphite, 276.7±1.2 and 290.4±1.1 mg/ml ($P=0.79$) respectively. As noted in Tables 8.3 and 8.4, the fall in FEV_1 remained <20% in many subjects at the maximum methacholine and sodium metabisulphite concentrations used in this study (64 mg/ml and 160 mg/ml respectively). To ensure that the mean PC20 for chronic heart failure patients and controls, obtained by arbitrarily assuming the PC20 in this subset of subjects to be the next doubling concentration of 128 mg/ml and 320 mg/ml for methacholine and sodium metabisulphite respectively, did not mislead the interpretation of results, the percentage decrease in FEV_1 from baseline at the provocation concentration of 32 mg/ml for methacholine and 160 mg/ml for sodium metabisulphite was also analysed. The methacholine concentration of 32 mg/ml was used because nine of the ten chronic heart failure patients completed the bronchial provocation test at this concentration compared with only eight at 64 mg/ml. The decrease in FEV_1 was 13.7% v 13.4% ($P=0.97$) for

methacholine and 5.5% v 9.9% (P=0.2) for sodium metabisulphite in chronic heart failure patients and controls respectively, thus confirming there was no significant difference bewteen the two groups of subjects.

As shown in Table 8.2, the change in FEV_1 after maximal cardiopulmonary exercise testing was +1.44% in chronic heart failure patients and +2.53% in controls (P=0.47), indicating an absence of exercise-induced bronchospasm in both groups. Exhaled nitric oxide concentration was not elevated in the chronic heart failure patients (12.3±1.7 v 16.2±3.3 ppb, P=0.32).

The results of the cough response to low-concentration chloride solutions and capsaicin are given in Table 8.5. As shown, the median cough counts in chronic heart failure patients were not different from controls for the various chloride-deficient solutions. The capsaicin concentration causing 2 or more coughs in chronic heart failure patients was also not significantly different from controls.

Parameter	CHF Patients	Controls	*P* value
Peak O_2 Consumption (ml/kg/min)	16.9±1.3	26.5±2.3	<0.01
Radiographic CTR	0.56±0.02	0.46±0.01	<0.001
FEV_1 (% predicted)	97.2±4.5	110.0±2.5	0.03
FVC (% predicted)	102.2±5.1	112.6±2.9	NS
PC20 MCh (mg/ml)	67.6±1.3	79.8±1.3	NS
PC20 MBS (mg/ml)	276.7±1.2	290.4±1.1	NS
% Change in FEV_1 with exercise	1.44±0.98	2.53±1.1	NS
Exhaled Nitric Oxide (ppb)	12.3±1.7	16.2±3.3	NS

Values expressed as mean±SEM
FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PC20, provocation concentration which caused a 20% drop in FEV_1.

Table 8.2 Summary of results of peak oxygen consumption, radiographic cardiothoracic ratio (CTR), pulmonary function, airway responsiveness to methacholine (MCh), sodium metabisulphite (MBS) and exercise and exhaled nitric oxide concentration in chronic heart failure (CHF) and controls.

CHF Patient	FEV_1 (% Predicted)	FVC (% Predicted)	PC20 MCh (mg/ml)	PC20 MBS (mg/ml)	Pre-Exercise FEV_1 (l)	Post-Exercise FEV_1 (l)	% Change in FEV_1	Nitric Oxide (ppb)
1	93.9	103	>64	>160	1.63	1.63	0	13
2	111	124	55.71	>160	2.66	2.72	2.26	10
3	102	99	8.00	74.64	2.90	3.08	6.21	20.5
4	76.3	74.6	>64	>160	2.39	2.44	2.09	19.5
5	111	111	>64	>160	3.16	3.15	-0.32	8
6	90	92	>64	>160	3.87	3.97	2.58	8
7	121	125	>64	>160	1.92	1.94	1.04	Not done
8	82	83.3	>64	>160	1.62	1.53	-5.56	11
9	100	121	23.42	>160	1.72	1.76	2.33	15
10	96.5	104	43.63	>160	2.35	2.44	3.83	5.5

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PC20, provocation concentration which caused a 20% drop in FEV_1; MCh, methacholine; MBS, sodium metabisulphite.

Table 8.3 Results of pulmonary function, bronchial responsiveness and exhaled nitric oxide concentration of individual chronic heart failure (CHF) patients.

Controls*	Age(y)/ Sex	CXR CTR	FEV_1 (% Predicted)	FVC (% Predicted)	PC20 MCh (mg/ml)	PC20 MBS (mg/ml)	Pre-Exercise FEV_1 (l)	Post-Exercise FEV_1 (l)	% Change in FEV_1	Nitric Oxide (ppb)
1	42 M	0.45	102	101	>64	>160	2.82	2.82	0	33
2	65 M	0.43	114	127	>64	>160	2.83	2.91	2.83	27
3	46 M	0.48	109	112	17.08	>160	3.17	3.31	4.42	13.5
4	55 F	0.48	122	121	>64	>160	2.56	2.62	2.34	6.5
5	63 M	0.49	114	107	22.01	148.33	2.35	2.44	3.82	8.5
6	52 M	0.45	102	110	>64	>160	2.44	2.64	8.20	18
7	58 F	0.45	113	114	>64	>160	2.23	2.20	-1.35	13.5
8	53 M	0.48	104	109	>64	>160	3.49	3.49	0	8.5

CXR CTR, radiographic cardiothoracic ratio; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PC20, provocation concentration which caused a 20% drop in FEV_1; MCh, methacholine; MBS, sodium metabisulphite.

* None had a smoking history.

Table 8.4 Results of pulmonary function, bronchial responsiveness and nitric oxide concentration of individual controls. The age, sex and radiographic cardiothoracic ratio are also given.

	CHF Patients	Controls	*P* value
Mean Capsaicin Concentration causing >2 coughs (μM)	13.5±2.0 (SEM)	6.5±2.1 (SEM)	0.5
Median Cough Counts with low Cl^- inhalation:			
0 mM	2.5	1	0.6
37.5 mM	5.5	5.5	0.9
75 mM	0	0	0.4
150 mM	0	0	0.7

Table 8.5 Results of cough response to capsaicin and low-concentration chloride (Cl^-) solutions in chronic heart failure (CHF) patients and controls.

Discussion

It is shown in this study that significant airway hyperresponsiveness was not present in stable chronic heart failure patients. Compared with previous studies, the recruitment criteria had been more selective in that patients with a history of acute pulmonary oedema within 6 months and of smoking within 5 years were excluded to avoid possible confounding factors. Airway responsiveness to a wider range of stimuli was also assessed. Airway responsiveness is not only affected by bronchial smooth muscle tone but also by the bronchial vascular tone [Cabanes *et al*, 1989] and the activity

of autonomic fibres innervating the airways [Barnes, 1986]. In view of this, 2 different pharmacological agents, methacholine and sodium metabisulphite, with different modes of action were chosen to assess airway responsiveness. Methacholine, a commonly used agent and an analogue of acetylcholine, acts directly on airway smooth muscle and is a dilator of bronchial vessels [Laitinen *et al*, 1987]. On the other hand, sodium metabisulphite is a putative stimulant of airway sensory nerves. The observation that the chronic heart failure patients did not show an excessive narrowing of airways with either agent suggests that neither the airway smooth muscle is hyperresponsive nor its neural activity upregulated.

Similarly, airway hyper-reactivity in response to exercise was not demonstrated. All the patients were subjected to a maximal treadmill exercise test with a respiratory exchange ratio of >1.1 at peak exercise and all breathed through the mouth which should accentuate exercise-induced bronchospasm had this been present [Cherniack, 1992]. This observation must be differentiated from the finding that inhaled salbutamol and iprotropium bromide caused an increase in FEV_1 following exercise as discussed previously in Chapter 2 [Uren *et al*, 1993]. Similar to our findings, these investigators were unable to detect any decrease in FEV_1 following exercise with the use of a placebo inhaler but with the inhaled bronchodilators, FEV_1 increased. This is not surprising because of the direct bronchodilator action of these drugs which is bound to increase the FEV_1 and this should not be misconstrued as being synonymous with the presence of airway hyperresponsiveness.

The findings that airways are not hyperresponsive in stable chronic heart failure parallel those of Eihacker *et al* [1988]. Several subsequent studies have suggested otherwise [Cabanes *et al*, 1989; Pison *et al*, 1989; Sasaki *et al*, 1990]. There are several

possible reasons for the discrepancy. Patients with a recent history of acute decompensation and pulmonary congestion were included in some studies [Cabanes *et al*, 1989; Pison *et al*, 1989] whilst in another, diuretics were stopped before the tests [Sasaki *et al*, 1990], also perhaps inducing airway oedema. Although tests were performed when patients had clinically recovered from the acute event, airways may remain hyperresponsive as shown by Pison and colleagues [1989]. It may be that a reduction in airway hyperresponsiveness lags behind the clinical recovery of pulmonary congestion. Studies on airway function in patients with acute heart failure generally confirm an obstructive airway pattern [Light & George, 1983; Petermann *et al*, 1987; Faggiano *et al*, 1993; Chua & Coats, 1995b]. This is probably related to peribronchial oedema and vascular congestion [Hogg *et al*, 1972]. Indeed, Light and George [1983] showed that this obstructive pattern persisted for a long time even in non-smokers despite some initial improvement; the mean follow-up duration was 310 days.

How then does acute decompensation and the resultant obstructive airways explain airway hyperresponsiveness? There are several possibilities. Firstly, it is well known that there is an inverse relationship between airway calibre, of which obstructive lung function is an index, and bronchial hyperresponsiveness [Sparrow *et al*, 1984; Paoletti *et al*, 1995]. The resistance to flow in a tube is inversely proportional to the radius of the tube to the fourth power and thus the effect of spasm on airway narrowing in an already narrowed airway is greatly amplified, even if the tone of smooth muscle contraction is no more than normal [Moreno *et al*, 1986]. Secondly, narrowed airways facilitate central deposition of aerosol, thus enhancing airway constriction [Dolovich *et al*, 1976]. Thirdly, the additional vasodilatory effects of methacholine on bronchial vessels may also aggravate any peribronchial vascular congestion and oedema already present.

Another confounding factor which may explain the discrepancy in the results is smoking. Smoking leads to different degrees of airway obstruction [Niewoehner *et al*, 1974] and as discussed earlier, an altered baseline lung function will affect bronchial responsiveness on the basis of simple geometric considerations. In addition, smoking may have direct effects on airway responsiveness [Gerrard *et al*, 1980; Sparrow *et al*, 1984; Cerveri *et al*, 1989; Paoletti *et al*, 1995].

It has been suggested that local inflammation may explain the increased airway responsiveness in some patients [Pison *et al*, 1989]. This was indirectly assessed by measuring the exhaled nitric oxide concentration in this study. Endogenous nitric oxide is synthesised from the amino acid L-arginine by the action of nitric oxide synthase, of which three main isoforms have been described [Moncada & Higgs, 1993]. Constitutive forms of the enzyme are found in endothelial cells which produce nitric oxide (endothelium-derived relaxing factor) responsible for endothelium-dependent vasodilatation, and in neurons, where nitric oxide acts as a neurotransmitter. The other form of the enzyme is the inducible enzyme due to the action of endotoxin and proinflammatory cytokines in a variety of cell types including leucocytes. Exhaled nitric oxide concentration is increased as a result of the latter form of enzyme in inflammatory airway diseases such as asthma [Persson *et al*, 1994; Kharitonov *et al*, 1994] and bronchiectasis [Kharitonov *et al*, 1995]. The finding that exhaled nitric oxide concentration was not increased suggests that local inflammation is not present in patients with stable chronic heart failure. This finding is also compatible with the other results in our study. However, this study does not provide any information as whether the exhaled nitric oxide concentration may be affected by the possible increase in systemic nitric oxide production in the heart failure patients as had been previously reported

[Habib *et al*, 1994; Winlaw *et al*, 1994]. That the exhaled nitric oxide concentration was not higher than that of controls suggests that it probably is not affected.

The cough response to low-concentration chloride solutions and to capsaicin in chronic heart failure patients was not significantly different from controls. As mentioned, it is known that afferent fibres of the cough reflex arise in the pulmonary stretch (J) receptors via c fibres [Hanacek *et al*, 1984], in receptors in the upper airways [Widdicombe, 1954; Sant'Ambrogio *et al*, 1978] and also in c fibre endings in the mucosa of the larynx, trachea and bronchi [Coleridge & Coleridge, 1984; Sant'Ambrogio, 1987]. Since the c fibres are stimulated by capsaicin [Coleridge *et al*, 1965], it would be expected that the cough reflex is enhanced if airway hyperresponsiveness is mediated by the stimulation of J receptors and c fibres by increased pulmonary venous pressures. That the cough response is not different from controls is consistent with the general finding that the airways are not hyper-responsive.

In summary, significant airway hyperresponsiveness, either to pharmacological agents or to exercise, was not demonstrated in non-smoking patients with stable non-oedematous chronic heart failure. Exhaled nitric oxide concentration and the cough response were also not enhanced suggesting the absence of local inflammation and hyper-reflexic neural mechanisms. It is therefore unlikely that airway hyperresponsiveness contributes significantly to the exertional dyspnoea or the increased ventilatory response to exercise in chronic heart failure patients in a stable condition. However, the findings in this study do not exclude the presence of airway hyperresponsiveness in patients with acute pulmonary oedema or during the recovery period.

Limitations of the study

Because of the selective recruitment criteria, the number of patients in this study was small and may be a potential study limitation, although the absence of even of a trend for any airway abnormality makes it unlikely to be an important factor in general in the non-oedematous chronic heart failure population. Another potential limitation is that all the chronic heart failure patients were receiving angiotensin-enzyme inhibitors which may have altered airway responsiveness and the cough reflex. A control group of asymptomatic hypertensive patients also taking angiotensin-converting enzyme inhibitors was chosen to circumvent this possible confounding factor. In any case, no subjects had a history of intolerance of the medication or of developing a cough during treatment. Had angiotensin converting enzyme inhibitors affected the results, an abnormal cough response [Fuller & Choudry, 1987; McEwan *et al*, 1989] and an increased airway responsiveness should have been present but neither was seen. It is also of interest to point out that a previous study had shown that patients who coughed during treatment with angiotensin-converting enzyme inhibitors also had bronchial hyperreactivity while not receiving the treatment [Bucknall *et al*, 1988]. It is thus possible that the patients in this study had already been "pre-selected" by virtue of their tolerance to angiotensin converting enzyme inhibitors i.e. patients intolerant of this class of drug may indeed have latent bronchial hyperresponsiveness despite the absence of a history of asthma or asthmatic symptoms, an observation which is recognised [Rijcken *et al*, 1987; Wollcock *et al*, 1987; Burney *et al*, 1987; Cerveri *et al*, 1988; Bakke *et al*, 1991]. The development of airway hyperresponsiveness may thus be complex and multifactorial in origin depending on genetic characteristics, pathophysiological mechanisms and environmental factors (such as smoking, pollution and concomitant respiratory tract infection).

Chapter 9

CONCLUSION

The main objectives of this thesis were to investigate the mechanisms of increased ventilatory response to exercise in patients with chronic heart failure, the basis of which remains far from clear. As discussed in Chapter 1, the control of ventilation during exercise is complex and several feedforward and feedback mechanisms are involved. The latter are generally reflex mechanisms, some of which may be affected in chronic heart failure. It is no accident that the control of ventilation is complex given the importance of respiration and probably because of this, there is much inbuilt redundancy such that if a particular reflex is removed, another reflex takes over to preserve homeostasis. On the other hand, in disease, the fine balance between all these reflexes may be upset in an effort to re-impose homeostatic control.

In Chapter 2, the objective method of assessing exercise tolerance and ventilatory response using cardiopulmonary exercise testing was discussed. Although it is not always synonymous with patients' usual activities, it is a method which yields reproducible results and one which can be used to compare chronic heart failure and normality, and to assess the outcome of various interventions.

In Chapter 3, the methods for the assessment of the chemoreflex were studied. The hypothesis that the chemoreflex may be increased in chronic heart failure was put forward on the basis that chemoreceptors have a central role in the control of respiration and that the ventilatory response to exercise has been shown to correlate with chemosensitivity in normal individuals. Indeed, in this chapter, chronic heart failure

patients were found to have an increased hypoxic and central hypercapnic chemosensitivity. Peripheral hypercapnic chemosensitivity was not found to be augmented probably because the central arm accounts for the majority of hypercapnic chemosensitivity (approximately 90%). There was also a modest correlation between chemosensitivity and the ventilatory response to exercise.

In Chapter 4, the contribution of the peripheral chemoreceptors to ventilation was specifically investigated using hyperoxic suppression. It was found that the relative contribution of these chemoreceptors to ventilation was not significantly different from normal subjects, reaffirming the views that the ventilatory control system is complex and that in chronic heart failure, several reflex systems may simultaneously contribute to the increased ventilation. These may reflect the compensatory needs of the failing body related to ventricular dysfunction, probably in order to maintain tissue oxygenation. On the other hand, the increased ventilation especially during exercise may also contribute to the genesis of dyspnoea. This may be brought about by the increased work of breathing, by respiratory muscle fatigue and perhaps because afferent signals from chemoreceptors not only feed on the medullary respiratory centres to cause increased ventilation but are also sensed centrally as breathlessness.

In both Chapter 4 and Chapter 5, the hypothesis that suppressing chemosensitivity may lead to the decrease in ventilation during exercise, with an associated reduction in breathlessness, was tested. Continuous oxygen was given during treadmill exercise testing and this was shown to improve exercise tolerance, reduce ventilation and modestly improve the symptom of breathlessness during exercise. In Chapter 5, dihydrocodeine proved to be even more effective in the suppression of chemosensitivity, the reduction of ventilation during exercise and the improvement of breathlessness

probably because both peripheral and central chemosensitivity were suppressed. Whether mild opiates may be of significant benefit in the longer term in end-stage chronic heart failure patients merits further investigation.

Chapter 6 was a more complex undertaking. A cohort of univentricular patients was studied to investigate the effect of chronic hypoxaemia on chemosensitivity and the relationship of the latter with the ventilatory response to exercise in these patients. Despite the limited number of patients due to the nature of their disease, the hypoxic chemosensitivity of cyanotic univentricular patients subjected to chronic hypoxaemia was shown to be blunted. Central hypercapnic chemosensitivity was also "altered" in the sense that a shift of the hypercapnic-ventilatory response line to the left was noted and this may in part account for the increased ventilatory response to exercise in these patients. Such a mechanism is different from that in chronic heart failure patients in whom the augmented chemosensitivity manifested as an increase in the slope of the hypercapnic-ventilatory response line. It was also shown that the blunting of hypoxic chemosensitivity may be reversed as seen in the univentricular patients with Fontan-type circulation whose chronic hypoxaemia had been relieved.

In Chapter 7, the respiratory muscle strength of chronic heart failure patients was assessed and found to be reduced. There was also a significant correlation between inspiratory muscle strength and exercise capacity and the ventilatory response to exercise. That inspiratory muscles were more important than expiratory muscles was explained by the fact that expiration is normally due to the passive relaxation of the diaphragm, the dominant inspiratory muscle, and that expiratory muscles are not usually used. An enhanced muscle metaboreflex in the weakened respiratory muscles may offer a mechanism by which the increased ventilatory response to exercise, and perhaps

dyspnoea, is mediated, in a fashion similar to increased chemosensitivity. Such a reflex is sensitive to the metabolic changes related to the work of muscles and the augmentation may be due to increased acidification (due to lactic acid production), inorganic phosphate accumulation (due to anaerobic metabolism) and abnormal local potassium release. It is beyond the scope of this thesis to investigate the metaboreflex in chronic heart failure but it suffices to say that it may be an important link between muscle weakness and the increased ventilatory response to exercise. In this chapter, a discordance between respiratory muscle and locomotor muscle weakness was also noted, the mechanisms of which were not clear but may indicate that the selective "rehabilitation" of the respective affected muscle group is beneficial to these patients.

In Chapter 8, airway responsiveness did not appear to be an important mechanism in influencing exercise tolerance or the ventilatory control of exercise in stable, well compensated and non-smoking chronic heart failure patients. It may be that the hyperresponsive airways only become significant in the genesis of dyspnoea during the acute stage of heart failure. Exhaled nitric oxide concentration was not found to be increased in these patients suggesting that local airway inflammation is not important in the pathophysiology of this condition.

In summary, the contribution of the findings in this thesis to the understanding of the pathophysiology of chronic heart failure can be seen as additional features appended to the original diagram by Coats *et al* [1994] in the British Heart Journal shown in Figure 9.1 below.

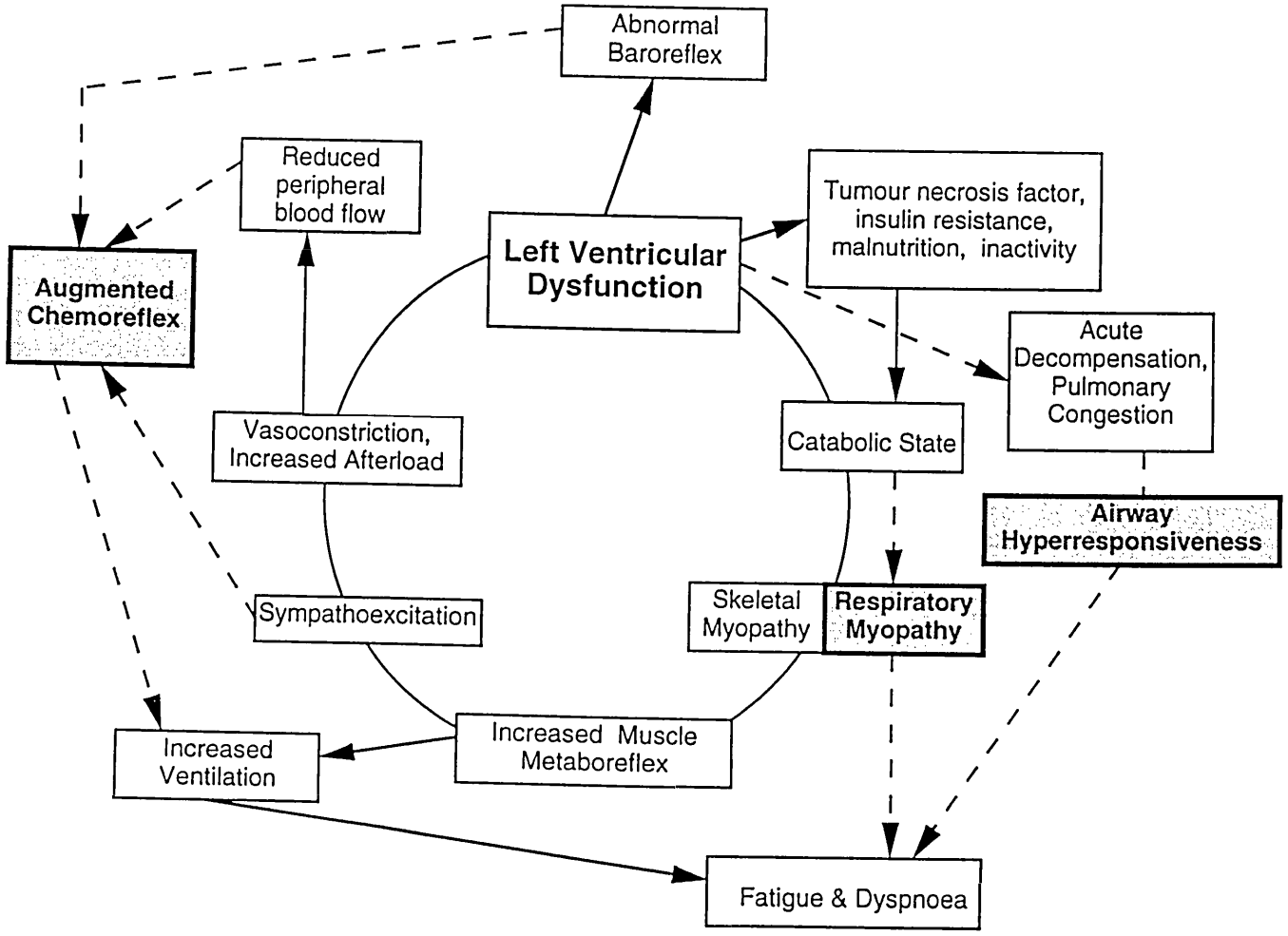


Figure 9.1 The symptoms and increased ventilation in chronic heart failure are initially brought about by a reduction in left ventricular function. A cascade of events are triggered, some of which are novel and described in this thesis. This diagram is adapted from Coats *et al* [1994] and the findings of this thesis can be seen as the additional features appended to the original diagram printed here in bold.

Appendix 1

a. Calculation of $\dot{V}_E$ by inert indicator gas dilution method.

Notations:

$\dot{V}_I$ = Rate of inspired volume per minute

$\dot{V}_E$ = Rate of expired volume per minute (minute ventilation)

F_IN_2 = Fractional concentration of nitrogen in inspirate

F_EN_2 = Fractional concentration of nitrogen in expirate

F_IHe = Fractional concentration of helium in inspirate

F_EHe = Fractional concentration of helium in expirate

$F_{Box}He$ = Fractional concentration of helium in mixing box

fHe = Rate of flow of helium into mixing box

In steady state, nitrogen in neither gained nor lost in the lungs. Thus,

$$\dot{V}_I.F_IN_2 = \dot{V}_E.F_EN_2$$

$$==> \quad \dot{V}_I = \dot{V}_E.F_EN_2 / F_IN_2 \qquad \ldots\ldots \quad (1)$$

$$==> \quad \dot{V}_I / \dot{V}_E = F_EN_2 / F_IN_2 \qquad \ldots\ldots \quad (2)$$

Similarly, helium is neither lost nor gained in the lungs in the steady state. Thus,

$$\dot{V}_I.F_IHe = \dot{V}_E.F_EHe$$

$$==> \quad F_EHe = \dot{V}_I / \dot{V}_E \; . \; F_IHe \qquad \ldots\ldots \quad (3)$$

Sustituting (2) into (3),

$$F_EHe = (F_EN_2 / F_IN_2).F_IHe$$

The quantity of helium entering and leaving the box is the same. Thus,

$$fHe + \dot{V}_E.F_EHe = (fHe + \dot{V}_E).F_{Box}He$$

$$==> \quad fHe + \dot{V}_E.F_EHe = fHe.F_{Box}He + \dot{V}_E.F_{Box}He$$

$$==> \quad \dot{V}_E.(F_{Box}He-F_EHe) = fHe.(1-F_{Box}He) \quad \ldots\ldots (4)$$

Substituting (3) into (4),

$$\dot{V}_E.(F_{Box}He - (F_EN_2 / F_IN_2).F_IHe) = fHe.(1-F_{Box}He) \quad \ldots\ldots (5)$$

The quantity of nitrogen entering and leaving the mixing box is also the same, so

$$\dot{V}_E.F_EN_2 = (fHe + \dot{V}_E).F_{Box}N_2$$

$$==> \quad F_EN_2 = (fHe/\dot{V}_E + 1).F_{Box}N_2 \quad \ldots\ldots (6)$$

Substituting (6) into (5),

$$\dot{V}_E.[F_{Box}He - (fHe/\dot{V}_E + 1).F_{Box}N_2.F_IHe / F_IN_2] = fHe.(1-F_{Box}He)$$

$$==> \dot{V}_E.[F_{Box}He - (fHe/\dot{V}_E.F_{Box}N_2.F_IHe / F_IN_2 + F_{Box}N_2.F_IHe / F_IN_2)] = fHe.(1-F_{Box}He)$$

$$==> \dot{V}_E.[F_{Box}He - (fHe/\dot{V}_E.F_{Box}N_2.F_IHe / F_IN_2) - (F_{Box}N_2.F_IHe / F_IN_2)] = fHe.(1-F_{Box}He)$$

$$==> \dot{V}_E.F_{Box}He - fHe.F_{Box}N_2.F_IHe / F_IN_2 - \dot{V}_E.F_{Box}N_2.F_IHe / F_IN_2 = fHe.(1-F_{Box}He)$$

$$==> \dot{V}_E.F_{Box}He - \dot{V}_E.F_{Box}N_2.F_IHe / F_IN_2 = fHe.(1-F_{Box}He) + fHe.F_{Box}N_2.F_IHe / F_IN_2$$

$$==> \dot{V}_E(F_{Box}He - F_{Box}N_2.F_IHe / F_IN_2) = fHe\,[(1-F_{Box}He) + F_{Box}N_2.F_IHe / F_IN_2]$$

$$==> \quad \dot{V}_E = \frac{fHe\,[(1-F_{Box}He) + F_{Box}N_2.F_IHe / F_IN_2]}{(F_{Box}He - F_{Box}N_2.F_IHe / F_IN_2)} \quad \ldots\ldots (7)$$

b. Calculation of Oxygen Consumption ($\dot{V}O_2$)

If nitrogen is not gained or lost in the lungs,

$$\dot{V}_I.F_IN_2 = (fHe + \dot{V}_E).F_{Box}N_2$$

$$==> \quad \dot{V}_I = \frac{(fHe + \dot{V}_E).F_{Box}N_2}{F_IN_2} \qquad \ldots\ldots (8)$$

The rate of oxygen consumed is equal to the amount of oxygen in the mixing box subtracted from the amount of oxygen inspired, that is,

$$\dot{V}O_2 = \dot{V}_I.F_IO_2 - (fHe + \dot{V}_E).F_{Box}O_2 \qquad \ldots\ldots (9)$$

Substituting (8) into (9),

$$\dot{V}O_2 = F_IO_2\,[(fHe + \dot{V}_E).F_{Box}N_2/F_IN_2] - (fHe + \dot{V}_E).F_{Box}O_2$$

$$= (fHe + \dot{V}_E)\,[F_IO_2.F_{Box}N_2/F_IN_2] - F_{Box}O_2] \qquad \ldots\ldots (10)$$

From equation (7),

$$\dot{V}_E = \frac{fHe\,[(1-F_{Box}He) + F_{Box}N_2.F_IHe / F_IN_2]}{(F_{Box}He - F_{Box}N_2.F_IHe / F_IN_2)}$$

$$==> \dot{V}_E + fHe = \frac{fHe\,[(1-F_{Box}He) + F_{Box}N_2.F_IHe / F_IN_2]}{(F_{Box}He - F_{Box}N_2.F_IHe / F_IN_2)} + fHe$$

$$= fHe \frac{[(1-F_{Box}He) + F_{Box}N_2.F_IHe / F_IN_2]}{(F_{Box}He - F_{Box}N_2.F_IHe / F_IN_2)} + 1$$

$$= fHe \frac{[(1-F_{Box}He) + F_{Box}N_2.F_IHe / F_IN_2]}{(F_{Box}He - F_{Box}N_2.F_IHe / F_IN_2)} + \frac{(F_{Box}He - F_{Box}N_2.F_IHe / F_IN_2)}{(F_{Box}He - F_{Box}N_2.F_IHe / F_IN_2)}$$

$$= fHe / (F_{Box}He - F_{Box}N_2.F_IHe / F_IN_2) \quad \ldots\ldots \quad (10)$$

Substituting (10) into (9),

$$\dot{V}O_2 = [fHe / (F_{Box}He - F_{Box}N_2.F_IHe / F_IN_2)] \cdot [F_IO_2.F_{Box}N_2/F_IN_2 - F_{Box}O_2]$$

$$= \frac{fHe\,[F_IO_2.F_{Box}N_2/F_IN_2 - F_{Box}O_2]}{F_{Box}He - F_{Box}N_2.F_IHe / F_IN_2}$$

The calculation of carbon dioxide output ($\dot{V}CO_2$) is based on the same steps.

Appendix 2

New York Heart Association Functional Classes as used in this thesis:
(Adapted from *The Criteria Committee of the New York Heart Association, 1994*)

Class I

Patients with cardiac disease but without resulting limitation of physical activity.

Class II

Patients with cardiac disease resulting in slight limitation of physical activity. Ordinary physical activity causes some fatigue or dyspnoea but patients can still lead a normal social life.

Class III

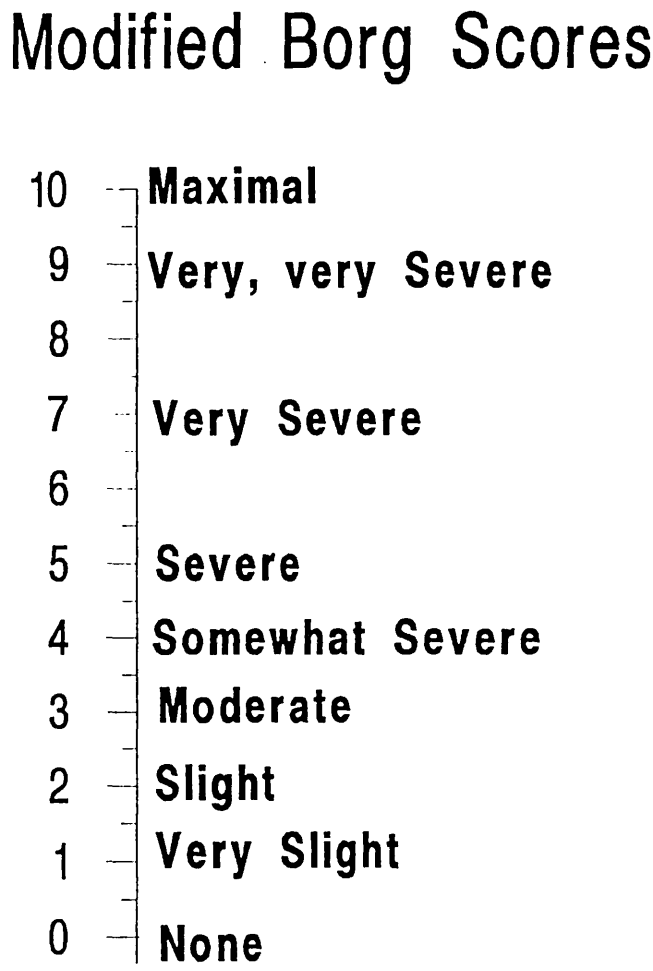
Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest but mild physical activity causes fatigue or dyspnoea. Patients cannot lead a normal social life.

Class IV

Patients with cardiac disease who are incapacitated and symptomatic even at rest.

Appendix 3

The diagram below shows the modified Borg scores used in this thesis.



Appendix 4

Preparation of methacholine, sodium metabisulphite, low-concentration chloride and capsaicin solutions.

i. Preparation of methacholine and sodium metabisulphite (Sigma, UK) solutions.

These were prepared using serial dilutions with an equal amount of normal saline giving concentrations of 64 mg/ml to 1 mg/ml of methacholine and 160 mg/ml to 5 mg/ml of sodium metabisulphite respectively.

ii. Preparation of iso-osmolar low-concentration chloride solutions.

Solutions were made from 150 mM sodium chloride (normal 0.9% saline; 150mM sodium, 150 mM chloride; osmolarity 300 mOsm in total) and 150 mM sodium bicarbonate (1.26% sodium bicarbonate; 150 mM sodium, 150 mM bicarbonate; osmolarity 300 mOsm in total). Four iso-osmolar solutions with decreasing chloride concentrations containing 150, 75, 37.5 and 0 mM chloride were prepared, called solutions A, B, C and D respectively for simplicity, as follows:-

Solution A: Sodium chloride only (i.e. 150mM sodium, 150 mM chloride; osmolarity 300 mOsm),

Solution B: 2 parts sodium chloride and 2 parts sodium bicarbonate (i.e. 150 mM sodium, 75 mM chloride, 75 mM bicarbonate; osmolarity 300 mOsm),

Solution C: 1 part sodium chloride and 3 parts sodium bicarbonate (i.e. 150 mM sodium, 37.5 mM chloride, 112.5 mM bicarbonate; osmolarity 300 mOsm) and

Solution D: Sodium bicarbonate only (i.e. 150 mM sodium, 0 mM chloride; 150 mM bicarbonate; osmolarity 300 mOsm).

iii. Preparation of capsaicin solutions.

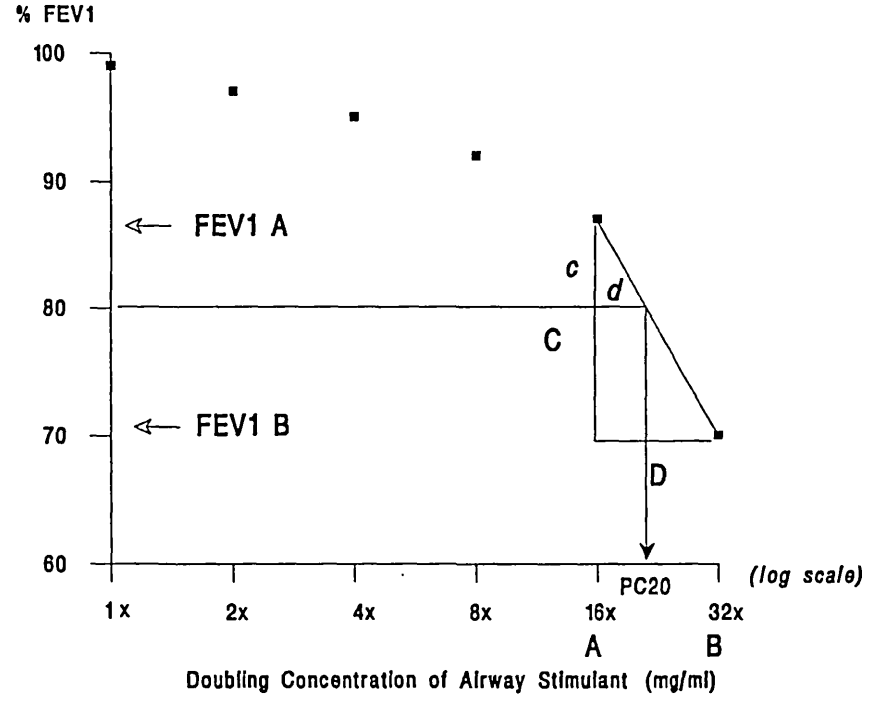
These were prepared from a stock solution of 10^{-2} M of capsaicin (Sigma, UK).

Ten solutions of capsaicin were made by doubling dilutions from 5 X 10^{-4} M to 9.75 X 10^{-7} M capsaicin (i.e. 500 μM to 0.975 μM) using normal saline.

The initial 5 X 10^{-4} M capsaicin solution was made by adding an equal part of normal saline to the stock solution of capsaicin and then further diluted 9:1 with normal saline.

Appendix 5

Calculation of Provocation Concentration causing a 20% fall in FEV_1 (PC20).



The graph above shows a schematic representation of the fall in FEV_1 with doubling concentrations of *x* mg/ml of a given airway spasmogen.

As shown, a 20% fall in FEV_1 corresponds to 80% of the baseline FEV_1 obtained using normal saline. This 80% FEV_1 lies between FEV_1 A and FEV_1 B obtained with the inhalations of 16*x* and 32*x* mg/ml of the spasmogen, henceforth denoted by A mg/ml and B mg/ml respectively. Thus, the PC20, which is the provocation concentration of the spasmogen required to drop the baseline FEV_1 by 20%, lies between A mg/ml and B mg/ml of the spasmogen. The PC20 may be obtained by interpolation as follows:-

From the diagram, $\frac{C}{D} = \frac{c}{d}$

where $C = FEV_1\ A - FEV_1\ B;$

$D = \log B - \log A = \log 2;$

$c = FEV_1\ A - 80\%\ FEV_1\ Saline$

$d = \log PC20 - \log A$

$$\Longrightarrow \quad \frac{FEV_1\ A - FEV_1\ B}{\log 2} = \frac{FEV_1\ A - 0.8\ FEV_1\ Saline}{\log PC20 - \log A}$$

$$\Longrightarrow \quad \frac{\log PC20 - \log A}{\log 2} = \frac{FEV_1\ A - 0.8\ FEV_1\ Saline}{FEV_1\ A - FEV_1\ B}$$

$$\Longrightarrow \quad \log PC20 - \log A = \log 2 \ \frac{FEV_1\ A - 0.8\ FEV_1\ Saline}{FEV_1\ A - FEV_1\ B}$$

$$\Longrightarrow \quad \log PC20 = \log A + \log 2 \ \frac{FEV_1\ A - 0.8\ FEV_1\ Saline}{FEV_1\ A - FEV_1\ B}$$

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