High Intensity Intermittent Exercise Training in Patients with Chronic Heart Failure

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Abstract

High intensity intermittent exercise may provide an alternative means of exercise training with greater health benefits than the lower exercise doses used in current practice, yet definitive guidelines for intermittent exercise are lacking. This thesis examines the methodology for intermittent exercise prescription, and assesses the efficacy of an intermittent exercise training intervention for chronic heart failure patients (CHF), thus providing a novel application in UK cardiac rehabilitation programmes.

Study one was methodological. Ten chronic heart failure (CHF) patients of mixed aetiology (NYHA class II/III; age 75 ± 8 years; LVEF 36 ± 9 %) and 7 healthy controls (age 67 ± 7 years; LVEF 69 ± 7 %) performed two exercise tests: a standard test (10 $W.min^{-1}$) and a steep test (25 $W.10^{-s}$) to determine intermittent training workloads. The tests were repeated one week later. In the standard test, a learning effect on maximal values was demonstrated (VO_{2peak}: test 1: 16.6 ± 1.7 $ml.kg^{-1}.min^{-1}$ vs test 2: 17.9 ± 1.7 $ml.kg^{-1}.min^{-1}$: $P < 0.01$; limits of agreement (LOA) bias ± random error 1.57 ± 1.88 $ml.kg^{-1}.min^{-1}$). Sub-maximal exercise measures were more reproducible than peak measures, but still prone to variability between tests (ventilatory threshold: test 1: 10.8 ± 0.9 $ml.kg^{-1}.min^{-1}$ vs test 2: 10.8 ± 0.9 $ml.kg^{-1}.min^{-1}$: $P > 0.05$; LOA bias ± random error 0.00 ± 1.02 $ml.kg^{-1}.min^{-1}$; respiratory compensation point: test 1: 15.6 ± 1.5 $ml.kg^{-1}.min^{-1}$ vs test 2: 15.6 ± 1.6 $ml.kg^{-1}.min^{-1}$: $P > 0.05$; LOA bias ± random error 0.27 ± 1.33 $ml.kg^{-1}.min^{-1}$). In CHF this variability, combined with the narrow range of work rates between the gas exchange thresholds (27 ± 20 W), makes it difficult to accurately define exercise intensity domains from these thresholds. In controls, intermittent training work rates set by Meyer et al's (1997) protocol (50% steep test peak work rate: 118 ± 13 W), were significantly lower than those set by the traditional method (100% standard test peak work rate: 141 ± 16 W), whereas in CHF there was no difference in work rate between the two methods (96 ± 9 vs 88 ± 10 W).

Study two compared the cardiovascular, respiratory, and metabolic responses to, and perception of effort during, 20 minutes of moderate intensity continuous or intermittent exercise of matched total workload in the same group of CHF and controls as Study 1. There were no differences in oxygen uptake, respiratory exchange ratio, heart rate,

blood pressure, blood lactate concentration (Lac) or rating of perceived exertion between the two modes of exercise.

Study three investigated the effect of adjusting the volatility (the amplitude above and below the mean work rate) of intermittent exercise. Nine CHF (NYHA class II/III; age 75 ± 9 years; LVEF 36 ± 9 %) and 5 healthy controls (63 ± 2 years; LVEF 70 ± 7 %) performed three 20 min exercise bouts of matched total workload: 1) moderate intensity continuous, 2) low volatility (half-way between VT and RCP work rate) and 3) high volatility (110% standard test peak work rate) intermittent exercise. There was no discernable difference in respiratory and cardiovascular variables or in perception of effort between the three modes of exercise. However, Lac was greater when the volatility was high (2.4 ± 0.2 vs 1.9 ± 0.2 and 1.8 ± 0.2 $mmol.L^{-1}$ in low volatility and continuous exercise).

In the fourth and final study 26 CHF (NYHA class II/III; age 73 ± 7 years; LVEF 32 ± 13 %) of mixed aetiology, including patients with implantable devices, were randomly assigned to either traditional circuit training or high intensity intermittent training in a twice-weekly 6 week cardiac rehabilitation programme. After training there was a significant improvement in ventilatory threshold (circuit 11 ± 6%; intermittent 18 ± 5%) and disease-specific quality of life (circuit -8 ± 3 points; intermittent -8 ± 3 points), but there was no difference between the two training methods. Neither intervention resulted in improvements in VO_{2peak}, ventilatory efficiency or B-type natriuretic peptide (BNP). Longer-term and/or more frequent training may be required to achieve improvements in these parameters.

The results of these studies suggest that high intensity intermittent exercise offers an alternative, although no more effective, training method for the management of elderly CHF in UK cardiac rehabilitation programmes.

Declaration

The research contained in this thesis is original work conducted and written by the author. This thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

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The following communications are a direct consequence of this work:

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Symbols, Abbreviations and Definitions

1RM	One repetition maximum
ACE inhibitor	Angiotension-converting enzyme inhibitor
ACPICR	Association of Chartered Physiotherapists in Cardiac Rehabilitation
AF	**Atrial fibrillation**. Abnormal irregular heart rhythm with chaotic generation of electrical signals in the atria
Afterload	Aortic pressure or ventricular wall stress after the onset of systole
AHA	American Heart Association
ANOVA	Analysis of variance
ATP	Adenosine triphosphate
a-vO_2 difference	Aterio-venous oxygen difference
BACR	British Association for Cardiac Rehabiliation
BF	Breathing frequency (breaths.min^{-1})
BNP	**B-type natriuretic peptide.** A hormone released primarily from the left ventricle in response to increased filling pressure
BP	Blood Pressure.
Ca^{2+}	Calcium ions
CHF	Chronic Heart Failure or Chronic Heart Failure patients
CI	Confidence interval
CPET	Cardiopulmonary exercise test(ing)
CR	Cardiac Rehabilitation
CRT-D	Cardiac resynchronisation therapy device with defibrillator
Δ	Change or difference
$\Delta VO_2/\Delta WR$	Change in oxygen uptake for a given change in work rate (ml.min^{-1}.W^{-1})
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram.
EF	Ejection fraction (%)
ESC	European Society of Cardiology
$EqVO_2$	Ventilatory equivalent for oxygen
$EqVCO_2$	Ventilatory equivalent for carbon dioxide
FEV_1	**Forced expiratory volume in one second (L)**. The volume of air expelled from the lungs during the first second of a forced

	expiration from maximal inspiratory volume
FVC	Forced vital capacity
HR	Heart rate (beats.min^{-1})
HR_{max}	**Maximum heart rate (beats.min^{-1}).** The highest heart rate achieved with an exhausting effort in an incremental exercise test.
HRR	**Heart rate reserve (beats.min^{-1}).** The difference between maximum and resting heart rate
ICC	Intraclass correlation coefficient
ICD	Implantable cardioverter defibrillator
Intermittent exercise/training	Short phases of high intensity exercise interspersed with regular rest or recovery periods. Also known as interval training
IL-6	Interleukin-6
Lac	Blood lactate concentration (mmol.L^{-1})
LOA	Limits of agreement
LV	Left ventricular
LVEF	Left ventricular ejection fraction (%)
LVESV	Left ventricular end systolic volume (ml)
LVEDV	Left ventricular end diastolic volume (ml)
MI	Myocardial infarction
MLWHFQ	**Minnesota Living with Heart Failure Questionnaire.** A disease-specific quality of life questionnaire for heart failure patients
mmHg	Millimitres of mercury: a unit of measurement for pressure.
NICE	National Institute for Clinical Excellence
NO	Nitric oxide
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
NYHA Class	New York Heart Association classification of the severity of heart failure based on symptoms and functional capacity
NYHA Class I:	No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea, or palpitations
NYHA Class II:	Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations, or dyspnoea
NYHA Class III:	Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms
NYHA Class IV:	Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity

$PETCO_2$	End tidal gas tension for carbon dioxide (kPa or mmHg)
$PETO_2$	End tidal gas tension for oxygen (kPa or mmHg)
QoL	Quality of life
RCP	**Respiratory compensation point** ($L.min^{-1}$, $ml.min^{-1}$, $ml.kg^{-1}.min^{-1}$). Exercise intensity/work rate during incremental exercise at which the ratio of minute ventilation to carbon dioxide output (VE/VCO_2) starts to increase
rpm	revolutions per minute
RER	Respiratory exchange ratio of carbon dioxide output to oxygen uptake
RPE	Rating of perceived exertion. A subjective evaluation of an applied stimulus, e.g. exercise intensity
RPP	**Rate pressure product** (also known as double product). The product of heart rate and systolic blood pressure that is used as an indication of myocardial workload.
SD	Standard deviation
SEM	Standard error of the mean
SF-36	**Medical Outcomes Survey Short-Form 36**. A generic health-related quality of life questionnaire
SV	**Cardiac stroke volume** (ml). Volume of blood ejected by the ventricle with each systolic contraction
TNF-α	Tumor necrosis factor alpha
UK	United Kingdom
Volatility	Amplitude of the work phases above and below the mean
VCO_2	**Carbon dioxide output** ($L.min^{-1}$, $ml.min^{-1}$, $ml.kg^{-1}.min^{-1}$). Volume of carbon dioxide output exhaled per minute
VO_2	**Oxygen uptake** ($L.min^{-1}$ or $ml.min^{-1}$, $ml.kg^{-1}.min^{-1}$). Volume of oxygen uptake per minute measured from exhaled air
VO_2 kinetics	**Oxygen uptake kinetics**. The rate of change in oxygen uptake during or after exercise
V_E/VCO_2	Ventilatory equivalent for carbon dioxide
V_E/VO_2	Ventilatory equivalent for oxygen
$V_E/VCO_{2\ slope}$	Minute ventilation − carbon dioxide production relationship. A measure of breathing efficiency
$\Delta VO_2/\Delta WR$	Oxygen uptake-work rate relationship

VO_{2max}	**Maximal oxygen uptake** ($L.min^{-1}$ or $ml.min^{-1}$, $ml.kg^{-1}.min^{-1}$). The maximal rate at which an individual can take up and utilise oxygen. Measured during whole body incremental exercise to exhaustion, according to set criteria (plateau in oxygen uptake-work rate relationship, RER ≥ 1.15, final heart rate within ± 10 $beats.min^{-1}$ of age- predicted maximum, post-exercise blood lactate concentration ≥ 8 $mmol.L^{-1}$, subjective fatigue or volitional exhaustion, rating of perceived exertion ≥ 19)
VO_{2peak}	**Peak oxygen uptake** ($L.min^{-1}$ or $ml.min^{-1}$, $ml.kg^{-1}.min^{-1}$). The highest oxygen uptake measured during an incremental exercise test to exhaustion in a given exercise mode or condition when the criteria for VO_{2max} are not met
VO_2R	**Oxygen uptake reserve** ($L.min^{-1}$ or $ml.min^{-1}$, $ml.kg^{-1}.min^{-1}$). The difference between maximum and resting oxygen uptake
V_E	**Minute ventilation** ($L.min^{-1}$). The total volume of air expired per minute from the lungs
V slope method	Method used to detect ventilatory threshold by plotting carbon dioxide output against oxygen uptake. The threshold is the intercept of the two slopes
VT	**Ventilatory threshold** ($L.min^{-1}$ or $ml.min^{-1}$, $ml.kg^{-1}.min^{-1}$). The threshold above which aerobic metabolism is supplemented by anaerobic metabolism with the accumulation of lactic acid. Bicarbonate buffering of lactic acid causes an accelerated rate of carbon dioxide output to oxygen uptake, identifiable by the Vslope method. Also described as the gas exchange threshold
W	Watt
WR	**Work rate** (W, $J.s^{-1}$). The rate of performing work, i.e. power output
WR_{peak}	**Peak work rate** (W). The highest work obtained during an incremental exercise test to exhaustion

CHAPTER 1: INTRODUCTION

Introduction

Chronic heart failure is a complex syndrome that can result from any structural or functional cardiac disorder that impairs the heart's ability to support the physiological circulation (NICE Guideline No. 5) (National Collaborating Centre for Chronic Conditions, 2003). The main causes are myocardial infarction, hypertension and degenerative valve disease, or idiopathic dilated cardiomyopathy (McMurray and Pfeffer, 2005). The disease is characterised by symptoms of breathlessness, fatigue and exercise intolerance. The pathophysiology underlying the reduced exercise tolerance is not yet fully understood, but cannot be explained solely by limitations in central haemodynamics. In response to left ventricular (LV) dysfunction, impairments to peripheral mechanisms, including abnormalities in muscle structure and function, and overactivation of neurohormonal and inflammatory systems, develop in CHF (Lunde et al., 2001; Pina et al., 2003; Clark, 2006). The severity of symptoms may fluctuate, and as they are non-specific to heart failure, diagnosis is made via objective evidence of cardiac dysfunction at rest in addition to symptoms of heart failure at rest or during exercise (Swedberg et al., 2005).

The European Society of Cardiology (ESC) estimates that there are more than 10 million individuals with known CHF, 800,000 of whom are in the UK, for whom the prognosis is poor (Metra et al., 2007). The prevalence of CHF increases with age, and is often exacerbated by the presence of co-morbidies (Braunstein et al., 2003). Six to ten % of people over 65 years old have CHF (McMurray and Pfeffer, 2005), and hospital admission rates for the disorder are increasing, particularly in the elderly (McMurray, 2000). The five-year survival rate is 30-40% (Swedberg et al., 2005), although this may have improved with advances in medical therapy.

Cardiovascular diseases result in substantial disability and a loss of productivity, and contribute considerably to the escalating costs of health care, especially in regard to an ageing population. CHF in particular puts a considerable burden on health services, with an estimated annual cost to the NHS of £625 million, with 70% of that cost being

due to hospitalisation (Health Care Commission 2007). However, there is evidence that physical activity interventions are cost-effective for older people and CHF patients (Georgiou et al., 2001; Hagberg and Lindholm, 2006). The major challenge in preventive cardiology is to prevent subsequent cardiac events, while maintaining adequate physical functioning and independence, and a good quality of life (QoL) (Giannuzzi et al., 2003a). CHF reduces QoL more than other chronic illnesses (Hobbs et al., 2002), therefore therapies that improve functional capacity and QoL are of particular importance in the management of this disease.

There is accumulating evidence that exercise training benefits CHF by reducing mortality and morbidity, and improving functional capacity and QoL (Piepoli et al., 2004; Rees et al., 2004; van Tol et al., 2006). Results recently published from the HF-ACTION trial, the largest randomised controlled, long-term, multi-centre trial, confirm that exercise training is safe and is associated with moderate improvements in mortality and hospitalisation, and in exercise capacity and self-reported health status, in patients receiving contemporary medical management for CHF (Flynn et al., 2009; O'Connor et al., 2009). It is not yet clear if there is an optimal exercise dose, and few studies have compared different methods of exercise training. Traditionally, exercise prescription for CHF has followed the methods used in healthy individuals, where the intensity is based on a percentage of maximal capacity, including maximum oxygen uptake (VO_{2max}), maximum heart rate (HR_{max}), oxygen uptake reserve (VO_2R) or heart rate reserve (HRR). There are various exercise intensity guidelines and prescription methods for cardiac patients (Balady et al., 2000; Fletcher et al., 2001; American College of Sports Medicine, 2006), including suggestions that the exercise intensity for CHF should be at the lower level of these guidelines. However, these methods have been questioned, since percentages of VO_{2max} and HR_{max} correspond to a wide range of intensities and are likely to elicit variable metabolic responses in individuals (Meyer et al., 1999; Wasserman et al., 2005). Consideration of the exercise intensity “domains”, based on the characteristic responses of acid-base status and respiratory gas exchange, are important for accurately predicting the physiological responses to exercise, and provide a better model for prescribing and regulating exercise intensity (Jones et al., 2007) .

Determining the appropriate exercise intensity for CHF is particularly difficult due to a low heart rate (HR) response (Witte et al., 2006), and to the variability in the relationship between VO_2R and HRR, on which the prescription of exercise intensity is traditionally based (Mezzani et al., 2007). It is therefore recommended that cardiopulmonary exercise testing (CPET) should be used to objectively evaluate functional capacity and prescribe subsequent exercise training (Pina et al., 2003). Gas exchange measurements enable the identification of the submaximal "thresholds" that demarcate the exercise intensity domains, thus providing a framework for exercise intensity prescription. In this way, training intensities are aligned to robust physiological parameters (Meyer et al., 2005b). An intensity below the ventilatory threshold (VT), i.e. moderate intensity exercise, has been proposed for CHF (Meyer et al., 2005a).

Intermittent exercise, where short intervals of high intensity work are interspersed with recovery phases, induces a greater training adaptation than continuous exercise of an equal total workload in healthy individuals and cardiac patients (Meyer et al., 1990; Gorostiaga et al., 1991; Daussin et al., 2008). It has been reported that short-term intermittent exercise training can achieve improvements in functional capacity comparable to lower intensity, longer duration training in CHF (Meyer et al., 1997b). Intermittent exercise may therefore offer an alternative and time-efficient means of training for populations who find it difficult to perform continuous exercise, and may permit a higher training stimulus.

The National Institute for Health and Clinical Excellence (NICE) Guidelines advise that patients with CHF should be encouraged to adopt regular aerobic exercise, and that this may be more effective when part of a rehabilitation programme (National Collaborating Centre for Chronic Conditions, 2003) (p. 32). Although cardiac rehabilitation (CR) should be an integral step in the management of cardiac patients, only a minority of patients join these programmes. In particular, CHF patients are less likely to be offered CR even though they may gain even greater benefits than other cardiac patients, through improvements in prognosis as well as QoL (Bethell et al.,

2004). There is a lack of evidence to demonstrate the effectiveness of exercise training in a real-life setting for CHF patients in the UK.

Current exercise training guidelines for CHF recommend intermittent exercise as a training mode (British Association for Cardiac Rehabilitation, 2006; Association of Chartered Physiotherapists in Cardiac Rehabilitation, 2009), but it is not clear if it can be effectively included in current CR practice. The aim of this thesis is to examine the methodology for intermittent exercise prescription, to assess the acute and chronic responses to intermittent exercise and to evaluate its effectiveness for CHF patients in a UK CR programme.

CHAPTER 2: LITERATURE REVIEW

2.1 Chronic heart failure

2.1.1 Definition of chronic heart failure

CHF is a complex syndrome, involving the development of pathopysiological changes in response to LV dysfunction, including over-activation of the neurohormonal (Packer, 1992) and inflammatory systems (Seta et al., 1996), and skeletal muscle myopathy (Williams et al., 2004; Witte and Clark, 2007). Patients experience symptoms of breathlessness and fatigue, and their functional capacity and quality of life are impaired. The ESC definition of heart failure is shown in Table 2.1 (Swedberg et al., 2005).

Table 2.1: Definition of heart failure

I	Symptoms of heart failure at rest or during exercise and
II	Objective evidence (preferably by echocardiography) of cardiac dysfunction (systolic and/or diastolic) at rest and (in cases where the diagnosis is in doubt)
III	Response to treatment directed towards heart failure
	Criteria I and II should be fulfilled in all cases

2.1.2 Diagnosis and classification of chronic heart failure

As indicated in Table 2.1, diagnosis is based on symptoms and objective measures of cardiac dysfunction at rest, including echocardiography, electrocardiography (ECG), haematology and biochemistry (Swedberg et al., 2005). The severity of heart failure is commonly classified by the New York Heart Association (NYHA) Classification, based on subjective assessment of symptoms and functional capacity (Table 2.2).

Table 2.2: New York Heart Association classification of heart failure

Class I:	No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea, or palpitations
Class II:	Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations, or dyspnoea
Class III:	Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms
Class IV:	Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity

The Weber Classification, developed in order to better stratify hemodynamic severity using VO_{2peak} and the anaerobic threshold, may also be used as an objective method of characterising functional status from CPET (Table 2.3) (Weber et al., 1982).

Table 2.3: Weber classification

Weber Classification	**$VO_{2\ peak}$ ($ml.kg^{-1}.min^{-1}$)**	**Anaerobic threshold ($ml.kg^{-1}.min^{-1}$)**
A	> 20	>14
B	16 – 20	11-14
C	10.1 – 15.9	8-11
D	≤ 10	< 8

CHF is usually associated with evidence of LV systolic dysfunction, although diastolic impairment at rest commonly accompanies this. An LV ejection fraction (LVEF) ≥ 50% indicates good LV function, 40-49% indicates moderate LV function and < 40% indicates poor LV function. Diastolic heart failure is often diagnosed when symptoms and signs of heart failure occur in the presence of a normal LVEF at rest (Swedberg et al., 2005). This thesis will focus on CHF with reduced systolic function, which accounts for approximately half of the cases of symptomatic heart failure in the community (McMurray and Pfeffer, 2005).

2.2 Pathophysiology of chronic heart failure

Chronic heart failure is a multifaceted disease involving impairment of central and peripheral mechanisms and increased neurohormonal and inflammatory activity. The pathophysiology has been described in several review papers (Lunde et al., 2001; Tavazzi et al., 2001; Pina et al., 2003; Swedberg et al., 2005; Clark, 2006), and will be summarised below. It is now accepted that CHF is not only a haemodynamic disorder; the "neurohormonal hypothesis" (Packer, 1992), "muscle hypothesis" (Coats et al., 1994) and "cytokine hypothesis" (Seta et al., 1996) combine to explain its progression and symptoms.

2.2.1 Cardiovascular function

A characteristic of CHF is the progressive dilation of the heart chambers and deterioration in cardiac function, termed "left ventricular remodelling" (Haykowsky et al., 2007). Reduced cardiac output, reduced perfusion and decreased oxygen delivery results in the inability of the heart to meet the demands of the tissues. CHF with impaired LV systolic function appear able to use the Frank-Starling mechanism to compensate to some extent for their decreased contractile reserve. However, pericardial constraint may limit diastolic filling and contribute to reduced exercise tolerance (Warburton et al., 2007). The primary symptoms are fatigue and/or breathlessness on exertion, although exercise intolerance is only weakly correlated to resting ventricular function (Pina et al., 2003).

2.2.2 Neurohormonal hypothesis

In order to compensate for reduced cardiac output and organ perfusion, neurohumoral abnormalities occur. The sympathetic nervous system and renin-angiotensin aldosterone systems are activated in order to increase myocardial contractility, HR and vasoconstriction, and to expand extracellular fluid volume. The persistant overactivation of these systems then leads to further myocardial damage, an increased inflammatory response, and skeletal muscle abnormalities (Packer, 1992; Crimi et al., 2009).

2.2.3 Muscle hypothesis

Coats et al's "muscle hypothesis" (1994), described in Figure 2.1, proposes that abnormal skeletal muscle is a central abnormality in CHF that accounts for much of the pathophysiology and symptoms.

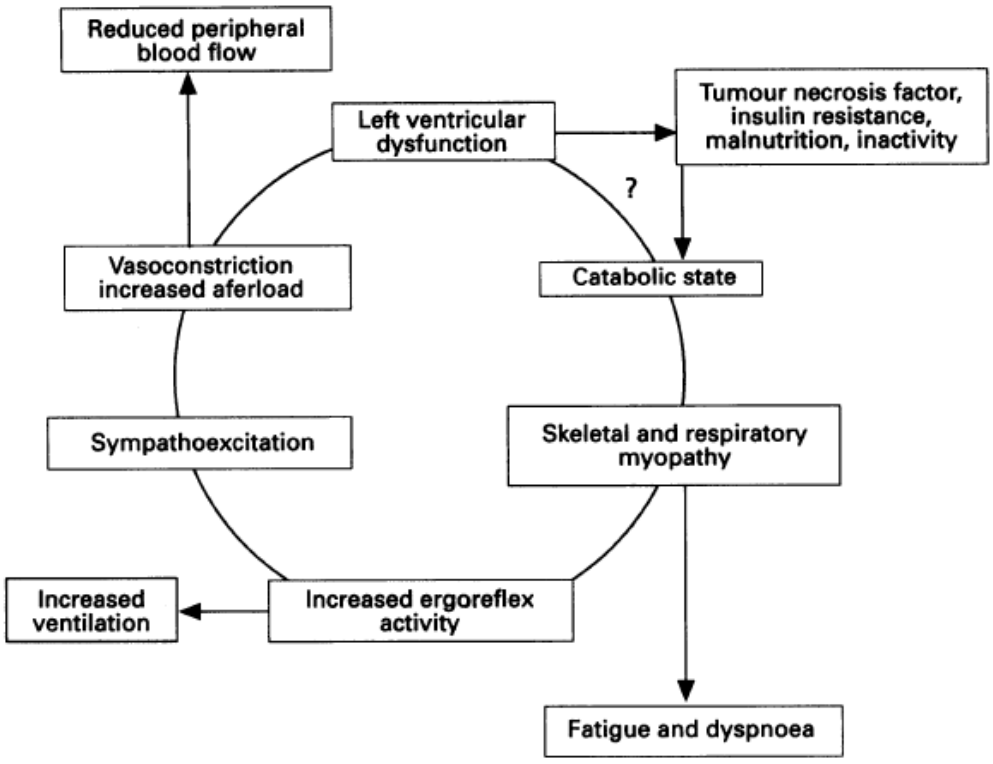

Figure 2.1: The muscle hypothesis of chronic heart failure

A reduction in left ventricular function activates catabolic and reduces anabolic factors that cause skeletal myopathy. This in turn leads to exercise intolerance and sympathoexcitation that, through the combined effects of a persistent catabolic state and of inactivity, further worsen skeletal muscle and function, and may eventually lead to a progressive effect on remodelling of the left ventricle (Coats et al., 1994).

Ultrastructural abnormalities of skeletal muscle in CHF include decreased vascularisation, decreased volume and density of mitochondria, lower oxidative enzyme activity, and increased ratio of type II to type I fibres, resulting in decreased oxidative capacity which is significantly correlated with exercise performance (Drexler et al., 1992). Energy transfer and utilisation is impaired in both cardiac and skeletal muscle, with increased anaerobic metabolism in exercising muscles, delayed recovery of PCr/ATP ratio and a slowing of intracellular calcium cycling (Lunde et al., 2001).

In addition, mechanical efficiency is reduced, thus increasing the energy cost of contraction (Ventura-Clapier et al., 2007). The derangement of energy metabolism and the "energy-depletion hypothesis" accounts for further disease progression (Neubauer, 2007).

Disuse may exacerbate the muscle abnormalities, leading to further muscle atrophy, decreased resistance to fatigue and reduced muscle strength. These are similar to the characteristics of physical deconditioning and the ageing process, and thus many elderly CHF will suffer the additive effect of all three conditions, partially explaining the greater impairment in these elderly patients, and the accelerated progression of the disease process (Gielen et al., 2005). Cycle ergometer exercise performance is directly related to quadriceps muscle area and upper leg muscle function (Senden et al., 2004).

2.2.4 Ergoreflex activation

The ergoreflex is the stimulation of the muscle receptors sensitive to work, leading to increased ventilation and sympathetic activation. These include metaboreceptors which are sensitive to metabolic stimulation, and mechanoreceptors which are sensitive to mechanical changes (Scott et al., 2000). Due to structural muscle abnormalities, during exercise CHF are effectively performing more work per unit of muscle volume than normal muscle, and producing more metabolic products, which in turn stimulate the ergoreceptors to increase ventilation relative to carbon dioxide (CO_2) production (Witte and Clark, 2007).

The role of skeletal muscle ergoreceptors in increasing ventilatory drive, and thus contributing to the symptom of breathlessness in CHF, has been the subject of considerable debate. It is proposed that the impaired skeletal muscle function results in ergoreflex stimulation, causing increased ventilation, thus linking the symptoms of breathlessness and fatigue (Piepoli et al., 1996). The severity of CHF symptoms is related to the ergoreflex activation, thus supporting the theory that this reflex is the neural link between peripheral muscle abnormalities and exercise limitation (Piepoli et al., 2001). Scott et al (2000) demonstrated that symptoms of breathlessness during exercise are mainly due to metabolic stimulation of the muscle metaboreceptors in CHF, a response that was absent in healthy controls. Mechanoreceptors appear to have a limited effect on the ergoreflex response.

2.2.5 Inflammatory cytokine hypothesis

Myocardial damage causes an overexpression of both vasoconstrictor cytokines, such as endothelin, and pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These exacerbate haemodynamic abnormalities and/or exert direct toxic effects on the heart (Seta et al., 1996). Increased free radical production alters the production of nitric oxide, by triggering apoptosis through oxidative stress, and by attenuating mitochondrial energy transfer through increased gene expression of iNOS in skeletal muscle (Adamopoulos et al., 2002). Reduced nitric oxide (NO) bioavailability is linked to abnormal endothelial function (Walther et al., 2004). The adverse effects of the inflammatory cytokine cascade in CHF on cardiac, vascular and skeletal muscle function, and the potential of exercise as an immunomodulatory treatment, is explained in detail by Adamaopoulos (2003).

2.2.6 Excessive ventilatory response

Excessive ventilatory effort and breathlessness are associated with CHF, due to a ventilation-perfusion mismatch arising from haemodynamic dysfunction, augmentation of chemoreflex due to sympathetic overactivity and neurohormonal imbalance, as well as inactivity. The increase in chemosensitivity may serve as a compensatory mechanism to increase ventilatory response during exercise and preserve blood gas homeostasis and maintain arterial oxygen concentration (Chua et al., 1996). As discussed in section 2.2.4, it has been proposed that ergoreflex activation, due to earlier acidosis and the subsequent abnormal muscle signalling in peripheral muscles, including those used for respiration, is the main stimulus for the excessive ventilatory response in CHF (Clark, 2006; Witte and Clark, 2007).

2.3 Determinants of exercise capacity in CHF

In healthy individuals, VO_{2max} is primarily limited by the ability of the cardiorespiratory system to deliver oxygen to the exercising muscle rather than by skeletal muscle oxygen extraction (Bassett and Howley, 2000). Submaximal exercise performance is determined by mitochondrial enzyme activity and capillary density, which influence metabolic factors (fat oxidation and lactic acid accumulation). In CHF, the impairment of central and peripheral mechanisms and the increased

neurohormonal and inflammatory activity described above all contribute to reduced exercise tolerance in CHF. Table 2.4 summarises the determinants of exercise capacity in CHF (Tavazzi et al., 2001).

Patients with a lower functional capacity, in contrast with healthy individuals and CHF patients with a higher functional capacity, do not exhaust their cardiopulmonary reserve during maximal cycle ergometer testing (Jondeau et al., 1992). CHF patients with a VO_{2peak} > 15.ml.kg^{-1}.min^{-1} and age-matched healthy controls reached the same VO_{2max} in cycling alone or cycling plus upper body ergometry combined, whereas patients whose VO_{2peak} was < 15 ml.kg^{-1}.min^{-1} during cycle ergometry increased this value, and their peak heart rate (HR_{peak}), during combined exercise. The authors hypothesised that in healthy individuals and patients with a VO_{2peak} > 15 ml.kg^{-1}.min^{-1}, classified in this study as “moderate” CHF, when 50% or more of the total skeletal muscle mass is activated in exercise VO_{2max} is limited by cardiac output, and is not affected by increasing the active muscle mass. In more severe CHF (classified in this study as VO_{2peak} < 15.ml.kg^{-1}.min^{-1}) VO_{2peak} is also limited by muscle atrophy and/or reduced vasodilatory responses and impaired muscle metabolism.

Table 2.4: Main determinants of exercise capacity in chronic heart failure

Central haemodynamics	Heart rate response to exercise Stroke volume response to exercise Left and right ventricular ejection fraction
Neurohormones	Sympathetic drive during exercise Beta-adrenergic sensitisation Balance between vasoconstrictor and antinatriuretic systems versus vasodilatory and natriuretic systems
Peripheral response	Skeletal muscle perfusion and vasodilatory capacity Muscle vasculature resistance Vascular endothelial function Cytokines, local growth factors and sodium content in the vessel wall Skeletal muscle mass Skeletal muscle function
Pulmonary function	Breathing pattern Bronchial reactivity Gas diffusion Ventilation/perfusion ratio Ventilatory response

2.4 Current medical therapy for CHF

Treatment for CHF is aimed at relieving symptoms, avoiding hospital admission and prolonging life. Drugs form the mainstay therapy for CHF patients with reduced LV systolic function, although modern treatments now include surgery and implantable devices for some patients (McMurray and Pfeffer, 2005)

The NHS NICE guideline algorithm for treatment in illustrated in Figure 2.2. Table 2.5 shows current recommended medications for CHF, their actions, and, where appropriate, the side effects that need to be considered during exercise (National Collaborating Centre for Chronic Conditions, 2003; McMurray and Pfeffer, 2005; British Association for Cardiac Rehabilitation, 2006). Even optimally treated patients

have many unrelieved symptoms which reduce their functional capacity and QoL. Exercise training to improve muscle structure and function may add to the improvements from medical therapy aimed at improving haemodynamic function (Coats et al., 1994).

Figure 2.2: Algorithm for the pharmacological treatment of symptomatic heart failure due to LV systolic dysfunction
NICE Guideline (National Collaborating Centre for Chronic Conditions, 2003)

Table 2.5: Guide to medication used in CHF

Drug Group/Name	Action	Side effects: exercise considerations
Angiotensin Converting Enzyme inhibitor	Reduces production of angiotensin II, thus reducing vasoconstriction, preventing fluid retention and reducing afterload and circulating volume	Hypotension: avoid rapid changes in posture or abrupt cessation of exercise
Angiotensin II receptor blockers	Prevents binding of angiotensin II to its receptor, thus preventing vasoconstrictor action	Fatigue, Hypotension: avoid rapid changes in posture or abrupt cessation of exercise
Anti-arrhythmics Amiodarone Digoxin	Prolongs the refractory period of the heart (i.e. when there is no electrical activity), thus suppressing arrhythmias Increases myocardial contraction and reduces conductivity within the AV node, thereby preventing rapid atrial rates from being transmitted to the ventricles, thus increasing myocardial efficiency	Possible slower heart rate response to exercise, and reduced exercise capacity
Anti-coagulants	Interferes with synthesis of blood clotting proteins in the liver	Haemorrhage: care to avoid injury
Anti-platelets	Decreases platelet aggregation to stop clots forming in the arterial circulation	
β-blocker	Blocks β-receptors to decrease sympathetic activity, resulting in reduced myocardial oxygen demand, reduced heart rate and suppression of arrhythmias Selective β-blockers (e.g. bisoprolol) reduce the effect of noradrenaline and adrenaline on β_1 receptors. Non-selective β-blockers (e.g. carvedilol) block β_1, β_2 and α_1 receptors, as well as having vasodilatory and anti-oxidant properties	Hypotension: avoid rapid changes in posture or abrupt cessation of exercise. Reduced heart rate at rest, and during submaximal and maximal exercise: exercise training heart rates should be adjusted and interpreted with caution
Calcium Channel Blocker Type 2 (Amlodipine)	Reduces calcium influx into smooth muscle in walls of systemic arteries, thus reducing blood pressure	Hypotension: avoid rapid changes in posture or abrupt cessation of exercise
Diuretic (Loop) (Potassium sparing/ aldosterone antagonist)	Interferes with transport of sodium and water across loop of Henle cells in the kidneys, thus increasing the volume of urine excretion, reducing circulating fluid and blood pressure Inhibits the action of aldosterone thereby causing the kidneys to excrete salt and fluid in the urine while retaining potassium.	Dehydration and hypotension: encourage fluid intake during exercise Aching legs and/or fatigue: may affect exercise capacity
Nitrate (Isosorbide dinitrate/ hydralazine)	Vasodilates veins and arteries, thus improving coronary blood flow, and reducing preload and afterload	Hypotension: avoid rapid changes in posture or abrupt cessation of exercise
Statin	Inhibit enzymes involved in cholesterol synthesis, reducing levels of cholesterol and triglycerides in the blood	Possible aching legs: may affect exercise capacity

Pacemakers, cardiac resynchronisation therapy and implantable cardioverter defibrillators are current treatments for the management of CHF (National Collaborating Centre for Chronic Conditions, 2003; Swedberg et al., 2005). There is emerging evidence that exercise training offers additional improvements in functional capacity in patients with these devices, and should be recommended in clinical practice for this population (Conraads et al., 2007; Patwala et al., 2009).

2.5 Exercise training as therapy for CHF

Historically, it was feared that exercise could worsen LV function. In the 1970s and 1980s, studies reported an increase in exercise capacity following exercise training in patients with poor LV function, without any deleterious effect on LV function (Lee et al., 1979; Conn et al., 1982). It was subsequently demonstrated, in a randomised cross-over trial on a small sample of CHF patients with ischaemic aetiology, that 8 weeks of exercise training increased exercise tolerance and peak oxygen uptake (VO_{2peak}) compared with the normal treatment of activity restriction (Coats et al., 1990b). Since this landmark study, numerous studies have confirmed the benefits of exercise training, and investigated the mechanisms for these benefits. Tables A1 (aerobic training) and A2 (combined aerobic and resistance training) (Appendix 1) provide a summary of exercise training studies in CHF, including details of the study design, participants, exercise interventions (including available details of exercise type, frequency, intensity and duration), outcome measures and main results, and their findings are discussed in subsequent paragraphs. The studies were identified by a combined electronic database search of the following databases: Cochrane Library, PubMed, Web of Science and Science Direct. The search terms used were “exercise training” and “heart failure”, and restrictions to humans and English language papers only were applied. All studies dating from 1990 to 2010, for which the full paper could be accessed, and which included a predominantly aerobic exercise training intervention exclusively for CHF patients, were included. The design and methodological quality of these studies was diverse, and includes observational studies and randomised controlled trials (RCTs), studies of short duration and those with long-term follow-up, studies with sample sizes of 8 to ≥ 80 participants, and those assessing clinical outcomes, exercise performance, mechanistic effects, or a combination of these. Analysis of the methodological quality of exercise training studies in CHF has been provided by several authors (Lloyd-

Williams et al., 2002; Rees et al., 2004; van Tol et al., 2006; Davies et al., 2010). The variability in findings from exercise training studies is likely to be due to a combination of the differences in heart failure aetiology and severity, medical therapy and exercise intervention, in addition to different methodological approaches.

2.5.1 Exercise training review papers and meta-analyses

In 1998, data from 134 CHF patients from RCTs was reviewed, and it was concluded that moderate exercise training was safe and beneficial (European Heart Failure Training Group, 1998). In 2002, a systematic review of 22 RCTs and 9 non-RCTs concluded that exercise training had both physiological and psychological benefits for selected sub-groups of CHF patients, but emphasised that the patients enrolled in these studies were not representative of the CHF population as a whole (Lloyd-Williams et al., 2002). In 2004, a meta-analysis by the ExTraMATCH Collaboration reported that there was no evidence that exercise training was dangerous for CHF patients, and that it significantly reduced mortality (hazard ratio 0.65, 95% confidence interval, 0.46 to 0.92). The authors emphasised the need for research examining the optimal exercise therapy and identifying appropriate groups of CHF patients to target (Piepoli et al., 2004). The first Cochrane Review of exercise based rehabilitation for heart failure evaluated 29 randomised controlled trials, including 1126 patients, of exercise-based interventions compared with usual medical care to determine the effect on mortality, morbidity, exercise capacity and health related QoL (Rees et al., 2004). Short-term exercise training was reported to significantly increase VO_{2peak} by 2.16 $ml.kg^{-1}.min^{-1}$ (95% CI 2.82 – 1.49) and work capacity by 15 W (95% CI 18 – 13), with greater improvements in programmes of greater intensity and duration. Health related QoL improved in 7 of the 9 trials that measured this outcome. Further long-term trials were needed to examine the effect on mortality and morbidity. The authors noted that the results were based on patients who were not representative of the total population of CHF, which includes more severe patients, the elderly and females. They recommended that large-scale pragmatic trials of exercise training of longer duration, recruiting a wider spectrum of patients are needed to address these issues. The recent updated Cochrane Review added that exercise does not increase the risk of all-cause mortality, may reduce heart failure-related hospital admissions and offer important improvements in health-related quality of life (Davies et al., 2010). This review

included data from the HF-ACTION trial, the largest RCT of exercise training in CHF, which is discussed below in section 2.5.3.

The effects of exercise training have been reviewed by other authors (Meyer et al., 2004a). Van Tol et al. (2006) were the first to conduct a quantitative analysis on the effects of exercise training compared to usual care on cardiac performance, exercise capacity and QoL in CHF patients (van Tol et al., 2006). They concluded that exercise training has clinically important effects on exercise capacity and health-related QoL, and may have small positive effects on cardiac performance during exercise.

2.5.2 Proposed mechanisms for benefits following exercise training

The improvement in exercise capacity following training is due to a combination of mechanisms, including peripheral vascular, muscular and metabolic function, and possible improvements in cardiac function, or attenuation of the progression of LV dysfunction. A summary of each of these is provided below, and comprehensive reviews are provided by several authors (Piepoli et al., 2001; Adamopoulos et al., 2003; Gademan et al., 2007; Whellan et al., 2007; Crimi et al., 2009). The pathobiological pathways that are favourably influenced by exercise training are illustrated in Figure 2.3 (Crimi et al , 2009).

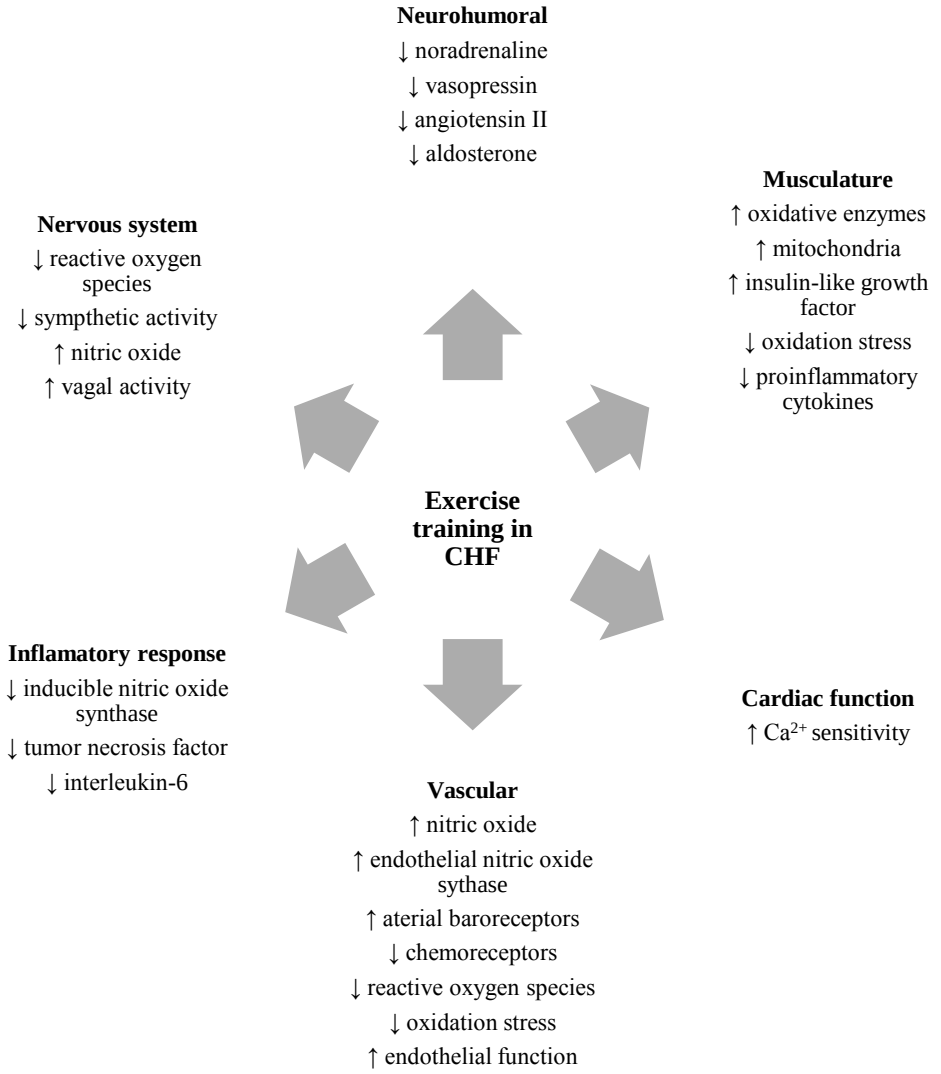

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Figure 2.3: Pathobiological pathways induced by exercise training in CHF patients

2.5.3 Reduction in all cause mortality and hospitalisation: HF-ACTION trial

The HF-ACTION trial is the largest randomised controlled trial to measure the effects of exercise training on clinical outcomes of mortality, hospitalisation and QoL (Whellan et al., 2007). The multi-centre trial took place at 82 centres within the United States, Canada and France and recruited 2,331 medically stable outpatients with heart failure and ejection fraction ≤ 35 %. Patients were randomised to usual care plus aerobic training, consisting of 36 supervised sessions followed by home-based training, or usual care alone. The median follow-up duration was 30 months. There were non-significant reductions in the primary endpoint of all-cause mortality or hospitalisation.

Non-significant reductions were also found in secondary end points (cardiovascular mortality or hospitalisation, and cardiovascular mortality and heart failure hospitalisation). However, after adjustment for highly prognostic predictors of the primary end point, including LVEF and VO_{2peak}, exercise training was associated with modest significant reductions for both all-cause mortality (11%) or hospitalisation, and cardiovascular mortality or heart failure hospitalisation (15%) (O'Connor et al., 2009). Exercise training also resulted in modest but statistically significant improvements in VO_{2peak} (4%), and in self-reported health status, assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) (which measures physical limitation, social limitation, symptoms and QoL), an improvement that was sustained at 3 month intervals during a median follow-up of 2.5 years (Flynn et al., 2009).

The HF-ACTION trial, due to its design, provides the strongest evidence to date on the effects of exercise training on CHF. It is the only single study with an adequate sample size and of a sufficient duration to properly evaluate clinical outcomes (Whellan et al., 2007). The risk of bias is reduced by its multicentre design and blinding of outcome assessors, and complete outcome data was reported non-selectively. Nevertheless, several limitations were identified, including issues of site variation, adherence to exercise, and crossover of patients in the usual care group to exercise training (O'Connor et al., 2009).

Keteyian presented further data from the trial at the 58th Annual Scientific Session of the American College of Cardiology (2009) demonstrating a dose-response effect of exercise training on the 959 patients in the exercise group who were event-free at 90 days. VO_{2peak}, 6-minute walk distance and KCCQ score improved after every 1MET-hour/week increment achieved in exercise intensity. This suggests that patients who comply with an exercise training programme achieve a better outcome, although the ability of patients with a good prognosis to exercise for longer may confound the issue. Furthermore, those who adhered to exercise may have also been more likely to adhere to their medical therapy, thus confounding the issue further.

2.5.4 Effect on exercise capacity

2.5.4.1 Peak oxygen uptake (VO_{2peak})

The reduced exercise capacity in CHF, due to a decline in cardiac function and peripheral abnormalities, is exhibited by a VO_{2peak} in the region of 40-55% of the age-predicted value (Cohen-Solal et al., 1990). A VO_{2peak} < 14 $ml.kg^{-1}.min^{-1}$ was formerly used as the cut-off point for heart transplant evaluation, but improved medical treatment suggests that values < 10 $ml.kg^{-1}.min^{-1}$ is a more appropriate cut-off point. VO_{2peak} values below 11 $ml.kg^{-1}.min^{-1}$ have been associated with a poor prognosis (Myers et al., 1998).

The majority of studies report an increase in VO_{2peak} of 10-30% following exercise training of 1 - 6 months' duration. A systematic quantitative review reports a 13% significant increase in VO_{2peak}, with a pooled effect size of 0.60 and 95% confidence intervals of 0.42 – 0.79 $ml.kg^{-1}.min^{-1}$ (van Tol et al., 2006). Improvements in cardiac output and oxygen extraction may both contribute to the improvement, as discussed in subsequent paragraphs. Not all studies report an increase in VO_{2peak} (Jonsdottir et al., 2006). There is some evidence to suggest that exercise training may be less effective at increasing VO_{2peak} in older CHF patients, with reported average improvements of 1.2 $ml.kg^{-1}.min^{-1}$ in patients under 65 year compared with 0.5 $ml.kg^{-1}.min^{-1}$ in patients over 65 years (Wielenga et al., 1998). As the majority of research to date has focussed on patients < 65 years, this warrants further investigation. The 4% improvement in VO_{2peak} reported in the HF-ACTION trial, where the median age of patients was 59 years, is also lower than improvements previously reported. Possible reasons include the lower volume of exercise performed compared with the prescribed exercise goals, and the reduced additional benefits conferred by exercise on patients treated with contemporary medical therapy.

The shortest duration studies show that improvements can be gained after only 3 weeks (Meyer et al., 1996c), but greater effects appear to be gained from longer duration programmes, with a plateau in improvements at 16-26 weeks (Kavanagh et al., 1996).

2.5.4.2 Sub-maximal exercise capacity

Day-to-day limitations are more likely to be related to sub-maximal exercise tolerance, such as the ventilatory threshold (VT) (Larsen et al., 2001). VT is used alongside VO_{2peak} to characterise functional status in CHF (Weber et al., 1982). It is considerably lower in CHF patients compared with healthy individuals, and decreases according to the severity of the disease. However, the % VO_{2peak} at VT may be high (~72% VO_{2peak} in CHF vs ~60% in healthy individuals), due to an attenuated rise in VO_2 above the VT, and/or the fact that exercise tolerance is very low (Meyer et al., 2005a). van Tol et al's (2006) systematic quantitative review reports a 17.4% significant increase in VT, with a pooled effect size of 0.84 and 95% confidence intervals of 0.48 –1.20 $ml.kg^{-1}.min^{-1}$. Improvements in exercise capacity are associated with numerous improvements in central and peripheral function, as discussed below.

2.5.5 Improvements in cardiovascular function

2.5.5.1 Left ventricular function

Numerous studies confirm that there is no adverse effect on LV function (assessed by echocardiography) (Sullivan et al., 1988; Belardinelli et al., 1999; Conraads et al., 2004) which appears to remain largely unchanged by exercise training, although some studies have reported modest improvements. A meta-analysis of the effect of exercise training on LV remodelling reported 14 trials with ejection fraction (LVEF) data and 7 with end diastolic volume (EDV) and end systolic volume (ESV) data. Aerobic training, but not combined aerobic and strength training, significantly improved LVEF (weighted mean difference 2.59%) and reduced EDV (-11.49 ml) and ESV (-12.87 ml) (Haykowsky et al., 2007). Van Tol et al's meta analysis (2006) shows a small significant decrease in resting EDV and increase in HR and cardiac output during maximal exercise (van Tol et al., 2006). Small increases in stroke volume (Coats et al., 1990b; Hambrecht et al., 2000) and HR_{peak} (Keteyian et al., 1996; Keteyian et al., 1999) contribute to the increase in cardiac output. Parnell et al (2002) reported a 35% increase in systemic arterial compliance following exercise training, which would be expected to reduce afterload and myocardial oxygen demand and increase coronary perfusion. In Hambrecht et al's study (2000), improvements in stroke volume and LV end diastolic

diameter were significantly correlated with reduced peripheral resistance (Hambrecht et al., 2000).

LV remodelling appears to be a slower process than other improvements achieved in the shorter-term. Exercise performance was significantly improved and abnormal LV remodelling diminished following 6 months' moderate intensity training (Hambrecht et al., 2000; Giannuzzi et al., 2003b). Training programmes of shorter duration have not demonstrated such changes. This is confirmed in a more recent study (Beer et al., 2008) evaluating LV function using MRI, which is a more precise, reproducible and accurate technique than echocardiography for LV assessment (Rajappan et al., 2000). Although unchanged after 2 months of exercise training, significant improvements were measured in LVESV and LVEF at 8 months' follow up. Another study using MRI on CHF of ischaemic origin also reported improvements in LVEF, LVEDV and wall motion score index after 6 months' training. In the non-trained control group LV function deteriorated (Klecha et al., 2007).

2.5.6 Peripheral blood flow and endothelial function

Regular exercise training increases nitric oxide generation and responsiveness, thus improving endothelial function and reducing peripheral vascular resistance (Hornig et al., 1996; Walther et al., 2004; Parnell et al., 2005). Skeletal muscle blood flow is therefore increased (Sullivan et al., 1988; Hambrecht et al., 1998). It is not clear if the improved peripheral blood flow is specific to the exercised musculature (Demopoulos et al., 1997a; Kobayashi et al., 2003), or if the improvements are systemic (Linke et al., 2001; Roveda et al., 2003). Increases in systemic endothelium-dependent dilation are correlated with improvements in exercise capacity, suggesting a causal relationship (Hambrecht et al., 2000; Linke et al., 2001).

2.5.7 Anti-inflammatory effect

Exercise training modulates the inflammatory and skeletal muscle apoptotic process associated with CHF. The reductions in peripheral inflammatory markers correlate well with improvements in functional capacity (Adamopoulos et al., 2001; Adamopoulos et al., 2002). Interestingly, another study reported no change in plasma inflammatory markers, although muscle biopsy analysis did reveal a significant

reduction in local TNF-α, IL-1 and IL-6, and in inducible nitric oxide synthase (iNOS) (Gielen et al., 2003).

2.5.8 Skeletal muscle function

The delay in anaerobic metabolism and improvement in dynamic muscle strength following exercise training (McKelvie et al., 2002) are partly mediated by increased skeletal muscle blood flow (Sullivan et al., 1988) and improved endothelial and neurohormonal function. In addition there is evidence for training-induced improvements in histology, mitochondrial structure, and oxidative capacity. Exercise training is associated with increases in muscle fibre size and mitochondrial density, a histochemical shift from type II to type I fibres and improvements in oxidative capacity (Belardinelli et al., 1995b; Gordon et al., 1996; Hambrecht et al., 1997). Shorter periods (≤ 3 months) of lower intensity training did not result in increases in type I fibre expression or oxidative enzymes (Kiilavuori et al., 2000; Larsen et al., 2002). However, where the training was focussed on knee extensor exercises, improvements in oxidative vs glycolytic capacity were achieved after only 8 weeks' training (Gordon et al., 1996; Tyni-Lenné et al., 1997). A recent study reported that 6 weeks' knee extensor training improved skeletal muscle calcium handling in healthy controls, but not in CHF patients (Munkvik et al., 2010). Thus, reduced calcium release does not appear to be related to skeletal muscle fatigue in CHF. It appears that exercise training has beneficial effects on skeletal muscle both directly, on muscle function, histological and biochemical features) and indirectly, by attenuating muscle ergoreflex activation, as discussed in section 2.5.9 (Piepoli et al., 2001). Table 2.6 summarises the benefits of exercise training to skeletal muscle.

Table 2.6: Skeletal muscle benefit of exercise training

Morphology	↑ cross-sectional area
Function	↑ peak work rate ↑ strength ↑ endurance ↓ fatigability
Blood Function	↑ oxygen delivery ↓ vascular resistance ↑ arterio-venous oxygen difference
Metabolism	↑ oxidative metabolism ↑ adenosine triphosphate re-synthesis ↓ or ↔ anaerobic metabolism ↓ lacate accumulation & acidosis ↓ phosphocreatine depletion
Ultrastructural	↑ mitochondria content ↑ oxidative enzyme activity ↑ fibre size ↑ capillary density ↑ endothelial function ↑ nitric oxide release

2.5.9 Ventilatory function

Exercise training appears to reduce the contribution of the ergoreflex to ventilation due to the improvements in muscle function described above. It has been argued that an improvement in symptoms following exercise training, or indeed following other therapy, is dependent on the resolution of skeletal muscle abnormalities and the associated exaggerated ergoreflex response (Piepoli, 1996). An attenutation in ergoreflex response and an improved ventilatory response to exercise were demonstrated after 6 weeks' training of the forearm (Piepoli et al., 1996). Improvements in ventilatory efficiency have been reported following 8 weeks' cycle ergometer training (Coats et al., 1992a) and 3 weeks' cycle ergometer and treadmill exercise (Meyer et al., 1996c). Similar improvements have also been reported in CHF on optimal medical therapy participating in a 6 month training programme (Klecha et al., 2007). These studies suggest that an appropriate exercise programme mediates the

exaggerated ergoreflex activity that contributes to breathlessness in CHF, presumably due to improved peripheral muscle function.

2.5.10 Neuroendocrine and autonomic nervous system activity

Exercise training has direct and reflex sympatho-inhibitory effects on autonomic derangement and neurohumoral activation (Gademan et al., 2007). The mechanisms include improved baroreflex control of sympathetic activity due to reduction in circulating angiotensin II and/or improved cardiac output leading to augmented renal perfusion and thus reduced stimulation of the renin-angiotensin aldosterone system.

Decreases in plasma catecholamines and in muscle sympathetic nerve activity have been reported (Coats et al., 1992a; Hambrecht et al., 1995a; Passino et al., 2006b). Assessment of time domain HR variability has shown enhanced vagal activity (Coats et al., 1992a). ECG analysis of frequency rather than time domain showed increases in the parasympathetic component of HR variability during the day, probably via an increase in vagal tone (Kiilavuori et al., 1995). A similar analysis of patients on β-blocker therapy also demonstrated restored autonomic tone and reactivity to vagal and sympathetic stimuli following a 3 month low intensity rehabilitation programme. Further improvements were noted after 6 months' home-based training (Malfatto et al., 2002). Significant reductions in muscle sympathetic nerve activity recorded directly using microneurography to levels similar to those in healthy individuals (Roveda et al., 2003), and in resting, but not peak, levels of the plasma neurohormones angiotensin II, aldosterone, vasopressin and atrial natriuretic peptide (Braith et al., 1999) have also been reported following 4 months' training.

2.5.11 Cardiac energy metabolism

As discussed in section 2.5.8, exercise training improves skeletal muscle function and metabolism. It is less clear if these benefits occur in cardiac muscle. Direct assessment of mitochondrial function and energy transfer in CHF patients is lacking (Ventura-Clapier, 2009). The aforementioned improvements in cardiac function and

inflammatory markers following exercise training would, in theory, decrease oxidative stress and therefore improve energy transfer and utilisation (Ventura-Clapier et al., 2007). A small study of mild CHF with idiopathic dilated cardiomyopathy reported reduced biventricular oxidative metabolism and improved myocardial work efficiency, measured by positron emission tomography and echocardiography, alongside improvements in ejection fraction and end systolic diameter, after 5 months' training (Stolen et al., 2003). However, further evidence to support an improvement in myocardial energetics is lacking. Beer et al (2008) reported that PCr/ATP ratio, assessed by phosphorous-31 magnetic resonance spectroscopy, was unchanged following 8 months' training, suggesting that exercise training appears neither to improve or worsen cardiac metabolism (Beer et al., 2008).

2.5.12 Improvements in health-related quality of life

CHF reduces QoL therefore improving well-being in CHF and should be an important target for health care interventions (Hobbs et al., 2002). In an elderly CHF population, maintenance or improvement in QoL may be more valuable than prolonging survival (Swedberg et al., 2005). While some studies have reported no change in QoL following exercise training (Keteyian et al., 1999; Owen and Croucher, 2000; van den Berg-Emons et al., 2004), others have reported significant improvements (Belardinelli et al., 1999; Parnell et al., 2002; Passino et al., 2006b).

2.5.13 Cost-effectiveness

The estimated annual cost of heart failure to the NHS is £625 million, with 70% of that cost being due to hospitalisation (Commission for Healthcare Audit and Inspection, 2007). A cost-analysis based on the largest randomised trial at the time, involving 94 CHF patients in NYHA class II-III, aged 55-64 years, assigned to a 14-month training programme or a non-exercising control group (Belardinelli et al., 1999) concluded that exercise training is cost effective and prolongs survival by an additional 1.82 years at a cost of $1,773 per life-year saved (Georgiou et al., 2001). More recently, patients who participated in a short-term 8 week training programme had significantly fewer hospitalisation events and days spent in hospital due to cardiac problems at a 5 year follow-up than patients who did not participate in the training programme (Hagerman et al., 2005).

2.6 Current guidelines for exercise training

Current physical activity guidelines recommend that all healthy adults aged 10-65 years should aim to take part in at least 150 min of moderate-intensity aerobic activity or 75 min of vigorous intensity activity for health benefits (Haskell et al., 2007; O'Donovan et al., 2010). Depending on body weight, this amount of activity expends about 800-1200 kcal per week. These recommendations have been adapted for older individuals and/or those with chronic conditions or functional limitations that affect physical activity, but the guidelines for aerobic activity are maintained (Nelson et al., 2007). Exercise training for CHF is recommended by the American Heart Association (AHA) (Hunt et al., 2005), the European Society of Cardiology (ESC) (Swedberg et al., 2005) and the National Institute of Clinical Excellence (NICE, 2003) in their guidelines for the management of chronic heart failure. Standardised recommendations for exercise have been published, with the aim of applying aerobic and strength training with sufficient stimuli to skeletal muscles without overloading the cardiovascular system (Giannuzzi et al., 2001). These recommendations are based on the evidence accumulated from the various research studies on exercise training in CHF (as detailed in Tables A1 and A2 (Appendix 1). There is no agreement on a universal exercise prescription, partly due to the large variations in exercise trial interventions, in terms of frequency, duration, intensity and type of training, and thus an individualised approach is recommended (Pina et al., 2003). Exercise training guidelines specific to CHF are discussed in more details in section 2.6.3.

2.6.1 Safety of exercise training

Although regular physical activity reduces the risk of coronary heart disease events, vigorous physical activity can transiently increase the acute risk of acute myocardial infarction and sudden cardiac death (Thompson et al., 2007). In an apparently health population, based on the available evidence, the maximal risk estimates for an acute cardiovascular event during physical activity is 0.3-2.7 in men and 0.6-6.0 in women for 10,000 person hours. A summary of medically-supervised, contempary CR programmes showed 1 cardiac arrest per 116,906 patient hours, and 1 fatality per 752,365 patient hours (Thompson et al., 2007). For those at risk of, or with, CHD the benefits of regular physical activity appear to outweigh the risks. The risk is related to

the relative intensity of the exercise, with vigorous unaccustomed exercise (defined as ≥ 60% VO_2R) increasing the risk. The risk is reduced by observing guidelines on contraindications to exercise, and performing exercise testing in individuals with or at risk of known cardiovascular disease, before recommending vigorous exercise training (Gibbons et al., 1997; Fletcher et al., 2001).

The latest Cochrane Review concludes that there is no evidence that exercise training increases the risk of death in CHF (Davies et al., 2010). Smart and Marwick's (2004) sytematic review reported no exercise-related deaths in > 60,000 patient hours of training. The HF-ACTION trial reported that only 3% of patients in the exercise group were hospitalised for an event that occured during or within 3 hours after exercise, similar to the 2% of patients in the usual care group who were hospitalised during or within 3 hours after activity (Keteyian, 2010). These findings are likely to be influenced by the eligibility criteria in research studies; high risk patients, for example those with documented myocardial ischaemia, abnormal blood pressure responses or rhythm disorder, are usually excluded (Giannuzzi et al., 2001). Supervised hospital-based exercise programmes with appropriate risk stratification and pre-exercise screening, are recommended, at least in the initial stages of training (Giannuzzi et al., 2001; Association of Chartered Physiotherapists in Cardiac Rehabilitation, 2009). Optimal screening includes a maximal CPET, and data from the HF-ACTION trial reported that the major event rate was 0.45 per 1,000 tests and the minor event rate was 6.1 per 1,000 tests (Keteyian, 2010).

2.6.2 The exercise dose

The exercise dose is dependent on the interrelationship of frequency, intensity, duration (American College of Sports Medicine, 2006). There is evidence of a graded dose-response between the total volume of physical activity performed and cardiorespiratory fitness, but only weak evidence for a dose response for activity volume and health measures. The intensity of the the activity appears to be more important than the total volume for increasing cardiorespiratory fitness (Oja, 2001). There is compelling evidence that vigorous intensity activity is associated with a lower risk of cardiovascular disease, and of other chronic diseases (O'Donovan et al., 2010).

2.6.2.1 Exercise intensity

Exercise intensity has been defined and characterised in several ways. From a public health perspective, The British Association of Sport and Exercise Sciences (BASES) (O'Donovan et al., 2010) expresses intensity of physical activity in metabolic equivalents (METS) or rating of perceived exertion (RPE). In METS, where 1 MET is equivalent to the energy expended at rest, moderate intensity exercise is typically defined as 3-6 METS, and vigorous intensity exercise as > 6 METS. Using the 6-20 RPE scale (Borg, 1998), an RPE of 12-13 represents moderate intensity and 14-16 represents vigorous intensity. The ACSM guidelines recommend exercise intensity in the range of 50-85% VO_2R, which includes moderate intensity at the lower end and vigorous intensity at the higher end (Nelson et al., 2007).

In simple physiological terms, exercise is defined as being low or moderate intensity when there is no increase in oxygen uptake (VO_2) or blood lactate concentration (Lac) (beyond the initial adjustment to a new steady-state) with increasing time, or high intensity when it results in an elevation of oxygen uptake and Lac, and is non-sustainable (Brickley et al., 2007). More sophisticated physiological definitions include models based on Lac (Billat et al., 2003; Faude et al., 2009) and gas exchange measurements (Meyer et al., 2005b). Indicators of exercise intensity derived from gas exchange thresholds measured during CPET are attractive as they are non-invasive, and valid for athletes, healthy individuals and those with chronic diasease (Meyer et al., 2005b).

2.6.2.2 Exercise intensity domains

Meyer et al (2005b) propose a conceptual framework for the evaluation of endurance capacity and for the derivation of exercise intensity by the use of two gas exchange thresholds, each representing important landmarks within the spectrum of workloads. During incremental exercise, the level of exercise above which aerobic energy production is supplemented by anaerobic mechanisms leads to lactic acidosis. The subsequent bicarbonate buffering increases carbon dioxide (CO_2) partial pressure, which stimulates the ventilatory drive via the carotid bodies (Wasserman et al., 2005). The workload corresponding to these events is termed the aerobic gas exchange threshold (Meyer et al., 2005b), although it is primarily a metabolic phenomenon. It is

determined graphically by the V-slope method (Beaver et al., 1986). It has also been called the metabolic threshold (Cooper and Storer, 2001), the anaerobic threshold (Wasserman et al., 2005), the ventilatory threshold or first ventilatory threshold. In this thesis the threshold will be termed the ventilatory threshold (VT). After VT, circulating bicarbonate compensates for lactic acidosis to begin with. This is termed the isocapnic buffering stage. Once lactic acid production becomes so great that it cannot be compensated by circulating bicarbonate, ventilation is uncoupled from CO_2 production, and hyperventilation begins. Meyer et al (2005) call this point the anaerobic gas exchange threshold. It is detected graphically from the plot V_E against VCO_2 as the point where V_E increases disproportionately above VCO_2, confirmed by the point at which V_E/VCO_2 inflects upward and P_{ET} CO_2 decreases simultaneously. It has also been called the second ventilatory threshold and the respiratory compensation threshold (Jones et al., 2007), or respiratory compensation point (RCP) (Tanehata et al., 1999; Cooper and Storer, 2001), as it will now be termed in this thesis .

Figure 2.4 illustrates Meyer's model for the delineation of exercise training intensity zones by use of the gas exchange thresholds, and includes typical values for trained and untrained individuals and for patients with chronic disease.

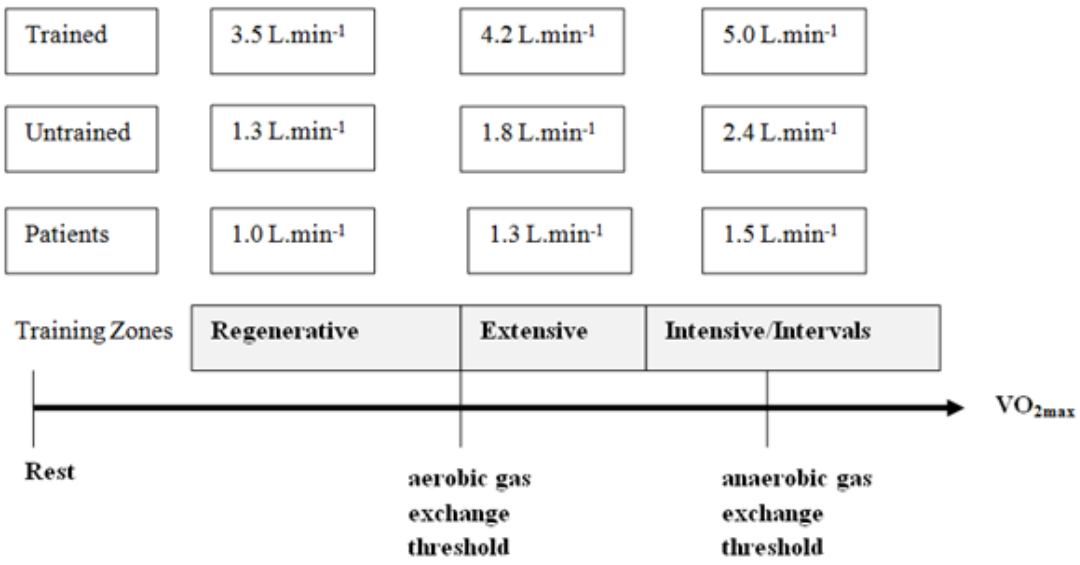


Figure 2.4: Model for the delineation of exercise intensity domains by use of gas exchange thresholds
(adapted from Meyer et al., 2005a)

These delineations of exercise intensity have more recently been termed "exercise intensity domains" (Jones and Poole, 2005; Jones et al., 2007). Figure 2.5 provides schematic representation of the VO_2 response to moderate, heavy and severe intensity constant load exercise.

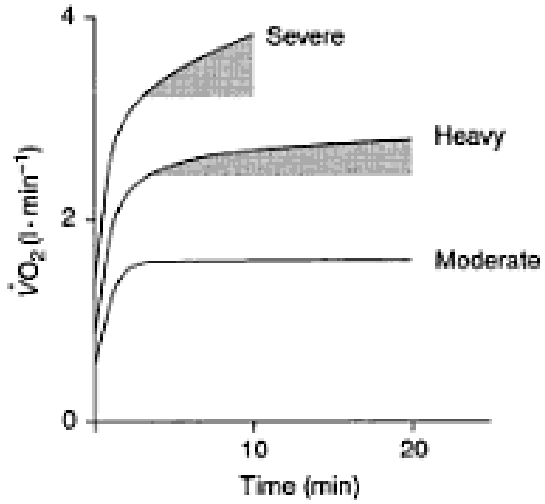


Figure 2.5: Schematic representation of the VO_2 response to moderate, heavy and severe intensity exercise
(adapted from Jones et al, 2007). The shaded areas represent the increase in VO_2 above the expected steady-state level.

The upper boundary for "moderate" intensity exercise is VT, or the lactate threshold (the intensity at which Lac begins to rise above baseline levels during incremental exercise). The upper boundary for "heavy" intensity exercise is the maximal lactate steady state (MLSS) (the highest intensity at which lactate production and elimination are in equilibrium), which corresponds broadly to RCP, although RCP may be approximately 10% higher (Dekerle et al., 2003). "Severe" intensity is exercise above MLSS/RCP, with the upper boundary being VO_{2max}. VO_{2max} is the demarcation between submaximal and supramaximal exercise, and intensities above VO_{2max} are defined as being "extreme" intensity (Jones and Poole, 2005; Jones et al., 2007). This thesis will follow the terminology of Jones et al for the exercise intensity domains, which will be called "moderate", "heavy", "severe" and "extreme". In the moderate intensity domain VO_2 reaches an early steady-state, and Lac remains close to resting levels. In the heavy intensity domain VO_2 and Lac reach a delayed but elevated steady-

state. In the severe intensity domain, both VO_2 and Lac will increase over time until VO_{2max} is reached and the exercise is terminated. In the extreme intensity domain, exercise tolerance is very limited and VO_2 remains lower than VO_{2max} when exhaustion is reached.

2.6.3 Exercise guidelines for chronic heart failure

Determining the appropriate exercise dose in CHF is important for reasons of safety and efficacy, but is not straightforward. Methodological issues, including variation in exercise testing protocols and different methods for measuring and defining intensity have confounded the exercise prescription guidelines to date. There is no consensus as to the optimal exercise intensity, nor indeed the best parameter for measuring exercise intensity. Exercise training studies, and recommendations arising from these, have used basic exercise prescription methods adapted from healthy populations, or the wider cardiac population. The exercise is generally described as "aerobic" and "moderate", and the recommended intensity is based on a percentage of maximal capacity, defined by VO_{2max}, VO_2R, HR_{max} or HRR. Current exercise guidelines from various organisations, including the, AHA, ESC, and American College of Sports Medicine (ACSM) recommend aerobic or endurance activities at intensities ranging from 25% to 80% VO_{2max} (Balady et al., 2000; Fletcher et al., 2001; Giannuzzi et al., 2001; American College of Sports Medicine, 2006). This variation in recommended intensity highlights that the principles of exercise training in terms of overload and progression should take into account the initial clinical status and functional capacity of the individual. However, there is a danger that these broad guidelines may lead practitioners setting exercise programmes that are either too low or too high for patients. The Association of Chartered Physiotherapists in Cardiac Reahabilitation (ACPICR) and British Association for Cardiac Rehabilitation (BACR) recommend target HR ranges of 60-75% predicted HR_{max} or 40-60% HRR in Phase III rehabilitation exercise classes, increasing to 60-80% and 40-70% respectively in Phase IV if appropriate, combined with an RPE of 12-15 (British Association for Cardiac Rehabilitation, 2006; Association of Chartered Physiotherapists in Cardiac Rehabilitation, 2009). For very deconditioned or compromised patients, the initial intensity might need to be lower than this. The exercise dose is usually progressed by increasing the duration and/or frequency of the exercise before the intensity.

The most detailed recommendations are provided by the ESC, who specify that exercise training should comprise an initial stage, an improvement stage, and a maintenance stage (Giannuzzi et al., 2001) During the initial stage, intensity should be kept at a low level (40-50% VO_{2peak}) until an exercise duration of 10-15 min is achieved. The primary aim of the improvement stage is to gradually increase the intensity (from 50% to 60% to $\geq$ 70% VO_{2peak}), with a secondary aim of prolonging the session to 15-20 min, and up 30 min if tolerated. After approximately 6 months, patients will be in the "maintenance" stage of their exercise programme. Training intensity should be readjusted on the basis of repeated exercise testing.

Details of the exercise interventions applied in training studies for CHF are provided in Appendix 1 (Tables 1A and 1B). The majority of these studies use aerobic training at a continuous or "steady-state" intensity, although the more recent studies have included different interventions. A meta-analysis of randomised controlled trials reported that exercise training was mainly aerobic (including walking, cycling, stepping), with a few studies including interval training and resistance training, and the intensity varied from 50-80% VO_{2peak} or 60-80% HR_{max} or HRR (van Tol et al., 2006). The average training period was 13 ± 8 weeks, with a session duration of 50 ± 22 min at a frequency of 3.7 ± 1.7 times a week.

It is difficult to assess how these exercise interventions agree with the recommended guidelines, partly due to the variation in what is recommended, and to the differences in age, severity of CHF and initial functional capacity in the study populations. Furthermore, many of the exercise interventions in these studies have actually contributed to the subsequent published recommendations for exercise, thus agreement between the two is to be expected. Some studies have applied shorter, more frequent exercise sessions (e.g. 4-6 10-20 min sessions per day) (Coats et al., 1990a; Hambrecht et al., 1995b; Linke et al., 2001), in line with the ESC guidelines for the "initial" and "improvement" stages. In other studies, the exercise volume was high, due to high frequency and duration of exercise sessions (e.g. 60 min walking twice daily, plus 45 min cycling @ 70-80% HR_{max} 4 times per week), although the training period was short (4-8 weeks) (Jette et al., 1991; Dubach et al., 1997; Myers et al., 2007). In the majority of studies, limited details are provided about exercise progression, repeated exercise testing to re-adjust exercise intensity, or the measurement of unsupervised exercise. However, some studies do demonstrate systematic training progression, for examples

an increase in frequency from 3 to 5, then to 7 days per week, and in duration from 30 to 60 min per session (Parnell et al., 2002). In the HF-ACTION trial, the aim was for exercise duration to be increased from 15-30 to 40 min, intensity to be increased from 60% to 70% HRR. Unsupervised exercise was monitored by activity logs and heart rate monitoring. However, the exercise actually performed by patients fell short of the goal of 90 min per week in the first 3 months, and 120 min per week thereafter, and only 30% of patients were exercising at or above the target exercise minutes at all time points (O'Connor et al., 2009). Such issues make it even harder to assess the real exercise dose experienced by patients in these studies.

It is clear from the paragraphs above that setting appropriate guidelines for exercise, and exercise intensity in particular, is challenging. There is considerable variability among methods of expressing exercise intensity in elderly individuals and cardiac patients, including CHF (Panton et al., 1996; Brawner et al., 2002; Mezzani et al., 2007). The thresholds that determine the exercise intensity domains occur at a different percentage of maximal capacity in individuals (Wasserman et al., 2005), hence intensities based solely on a percentage of maximal capacity are likely to elicit variable metabolic responses in individuals (Dwyer, 1994) including CHF (Coplan et al., 1986). Furthermore, chronotropic incompetence, defined as < 80% age-predicted maximum HR or HRR, is common in CHF, and current day medication is also likely to affect HR response, adding to the problems when using HR as a guide to exercise intensity (Witte et al., 2006; Whellan et al., 2007). The authors of a recent exercise training study explain that they had initially set training intensity at 70-80% HR_{max}, but had to abandon this method because of narrow HRR in most patients, atrial fibrillation and “other problems” (Prescott et al., 2009). For these reasons, it is likely that the exercise dose varies widely in training studies for CHF, and this has contributed to fact that there is no agreement on a universally recommended exercise prescription for CHF.

The American Heart Association recommend that CPET should be used to objectively evaluate functional capacity and prescribe exercise (Pina et al., 2003). In this way, training intensities can be aligned to robust physiological parameters using the gas exchange thesholds and exercise intensity domains. For example, an intensity within 10% of VT, has been proposed as safe, effective and able to be maintained over a prolonged exercise period for CHF (Meyer et al., 2005a).

Nevertheless, CPET is not feasible on many CR programmes, and although individual clinical history and symptoms are taken into account, exercise is still commonly prescribed from generic HR guidelines. ESC guidelines caution that RPE should be used only as an adjunct to determination of intensity by other methods as some patients are unable to reliably use the scale, and as ratings of fatigue and dyspnoea are often differently perceived, the recommendation is that the two symptoms should be monitored separately.

An additional issue is the effect of the mode of exercise on the subsequent calculation of exercise intensities. For example, some studies have used maximal treadmill exercise tests, then prescribed exercise at a percentage of VO_{2peak}, or a workload corresponding to a percentage of VO_{2peak} for a different mode of exercise such as cycle ergometry (Ennezat et al., 2001). However, it is not clear if workload on a treadmill, which is notoriously difficult to calculate, transfers to a cycle ergometer, and as VO_{2peak} is generally lower during cycling exercise, the relative percentage of peak is likely to be higher if the original value is from treadmill exercise. In order to maintain homogeneity of exercise intensity, the HF-ACTION trial used only moderate continuous training at 60-70% HRR. However, both walking and cycling were permitted. Hence there might have been some variation in relative exercise intensity as weight bearing and non-weight bearing exercise may elicit a different metabolic response and HR response in relation to percentage of maximum. It has been suggested that HR correlates with VO_2 during cyling, but not during circuit training exercise (Green et al., 2001).

In theory, patients with low baseline clinical and functional status respond well to low intensity exercise. The interrelationship of duration and intensity allows low intensity exercise to be partly compensated for by increasing the duration and/or frequency of the training sessions (Giannuzzi et al., 2001). In reality, the frequency of supervised sessions is low (Taylor et al., 2007), therefore it might be more appropriate to question whether this low frequency can be compensated for by higher intensity.

2.6.4 Intermittent exercise training

Although CR guidelines recommend moderate intensity exercise, which is often continuous in nature, they also acknowledge intermittent exercise as a potential training modality. Intermittent exercise (also known as interval training) consists of short bouts

of high intensity exercise interspersed with recovery periods, and is recommended for both healthy and clinical populations. Regardless of the population, the workload for short high intensity work phases, applied for between 20s and 2 min, is usually≥ 100% VO_{2peak} work rate achieved in a maximum incremental test (Poole and Gaesser, 1985; Meyer et al., 1990; Gorostiaga et al., 1991; Dimopoulos et al., 2006).

In healthy individuals, intermittent training produces a similar or greater increase in exercise capacity than continuous (or steady-state) exercise of an equal total workload (Poole and Gaesser, 1985; Gorostiaga et al., 1991; Tabata et al., 1996). In healthy sedentary participants, intermittent training improved muscle oxidative capacity to a greater extent than continuous training of a similar duration and total mechanical workload (Daussin et al., 2008). In a short term (< 4 weeks) programme, high intensity intermittent training was more effective than continuous training at improving maximal and sub-maximal exercise performance in cardiac patients, even though the total amount of work done was lower (Meyer et al., 1990). Meyer and colleagues subsequently demonstrated that short-term intermittent exercise training was effective for CHF patients with low functional capacity, who achieved improvements comparable to those reported in longer-duration training programmes of continuous exercise (Meyer et al., 1996b; Meyer et al., 1997b). In a 3 week randomised controlled trial, both intermittent and continuous training improved VO_{2peak} and VT (14% and 8-9% respectively) to a similar extent. Only the intermittent training group showed improvements in central haemodynamics, although the continuous group showed greater improvements in psychological well-being (Nechwatal et al., 2002).

Despite concerns that high intensity exercise may increase LV wall stress and induce deterioration in function in CHF patients (Demopoulos et al., 1997b) (Koike et al., 1989), LV function is reported to be equally stable during 16 min of either continuous or intermittent exercise (Meyer et al., 1998a). A few recent studies have confirmed that CHF can safely undertake high intensity intermittent training, and that some, although not all, beneficial training adaptations may be greater than those resulting from continuous moderate intensity training (Dimopoulos et al., 2006; Roditis et al., 2007; Wisloff et al., 2007).

2.6.4.1 Physiology of intermittent training

In healthy individuals, there is no substantial difference in haemodynamic responses, including HR, blood pressure (BP), cardiac output and ejection fraction, during intermittent and continuous exercise of matched average workload (Foster et al., 1999). Similarly, short work bouts alternated with rest or recovery intervals allow a relative balance to be achieved between the energy requirements of exercise and the level of aerobic energy transfer within the muscle. This was first demonstrated by Astrand & Christensen's group in the 1960s. For the same total workload, intermittent running results in lower HR, VO_2, V_E and Lac compared with continuous exercise (Astrand et al., 1960b). For the same reason, a greater amount of total work can be achieved during high intensity intermittent exercise compared to the same intensity of exercise performed continuously. Healthy males achieved 30 minutes' exercise, consisting of work-rest intervals of 10s:5s, 10s:10s or 15s:30s at work rates close to VO_{2max}, with a much lower Lac and distance run compared to continuous exercise, where exhaustion occurred after only 4 minutes (Christensen et al., 1960). In trained runners, high intensity intermittent running (30s at VO_{2max} velocity, alternated with 30s recovery @ 50% VO_{2max}) enables maximal work to be achieved without high Lac (Billat et al., 2000). During cycling exercise, the metabolic response to intermittent exercise was found to be similar to that found in continuous exercise with the same average power output when measured by blood-borne metabolites and muscle biopsies (Essen et al., 1977; Essen and Kaijser, 1978; Brickley et al., 2007). This response may be explained by a) the recovery of metabolites during the recovery phase, b) a dampening of metabolic responses due to the prior exercise (work and recovery phases) the reloading of myoglobin stores in the rest periods increasing the availability of oxygen and therefore a higher aerobic energy output, and higher ATP production per unit of glucose compared with lactate formation.

However, another study on sedentary adults reports that the fluctuating workload of high intensity intermittent training induces fluctuations in VO_2, whereas VO_2 remains steady in continuous training of the same duration and mechanical workload (Daussin et al., 2007). Further investigation by the same group demonstrates that the repeated fluctuations of VO_2 during intermittent training improve muscle oxidative capacity to a greater extent than continuous training, and this contributes to a greater improvement in

VO_{2max} (Daussin et al., 2008). It was proposed that the repeated variations in intensity imposed by intermittent training induced repeated disturbances of cellular homeostasis, inducing variations in VO_2, and contributing to adaptations in skeletal muscle mitochondrial function .

There have been few studies into the acute response of CHF to high intensity intermittent exercise. Meyer and colleagues' work suggests that CHF show similar responses to those described above; although Lac increases to a greater extent during short phases of high intensity cycling interspersed with recovery phases, the levels are low. Furthermore, rate-pressure product is similar to that during continuous exercise (Meyer et al., 1996b).

2.6.4.2 Rationale for high intensity intermittent exercise for CHF

In CHF, increased exercise capability following training is primarily due to peripheral rather than central adaptations (McConnell, 2005) and patients with a very low exercise capacity may not be able to achieve continuous endurance training workloads high enough to have an optimal training effect on the peripheral muscles without experiencing cardiac symptoms or local muscular fatigue. ESC and AHA guidelines suggest that intermittent exercise, based on Meyer et al's protocols, may be appropriate for CHF (Giannuzzi et al., 2001; Pina et al., 2003). It may provide an alternative and time-efficient means of exercise training with greater health benefits than the lower exercise doses used in are current practice. A similar hypothesis has been applied to other clinical populations, including individuals with pre-diabetes (Earnest, 2008) and chronic obstructive pulmonary disease (Puhan et al., 2006) and cancer (De Backer et al., 2007) .

2.6.4.3 Methods for intermittent exercise prescription

In intermittent exercise training research in healthy and cardiac populations the duration of the high intensity work phases is between 20s and 2 min at an intensity of≥ 100% VO_{2peak} work rate achieved in a maximal incremental test (Poole and Gaesser, 1985; Meyer et al., 1990; Gorostiaga et al., 1991). In CHF, some studies follow the traditional method of applying workloads of 100% VO_{2peak} work rate (Dimopoulos et al., 2006; Roditis et al., 2007). However, Meyer et al (1997) recommend that the

intermittent work phases are determined from a specific steep test that has increments of 25W every 10s and lasts only 30-120s (Meyer et al., 1997b; Meyer, 2001). The intermittent work phases of 30s duration are set at 50% peak work rate achieved in the steep test, interspersed with 60s recovery of unloaded cycling. The rationale behind this is that the steep test tests muscle strength and anaerobic capacity, both important in short bouts of high intensity exercise, whereas a standard maximal exercise test does not measure these, and may underestimate the training load. Despite limited scientific verification for this protocol, it is included in the European Society of Cardiology recommendations for exercise training (Giannuzzi et al., 2001), and has been used in studies in CHF (Sabelis et al., 2004; Kemps et al., 2008) and other clinical populations (Vogiatzis et al., 2002; Puhan et al., 2006; De Backer et al., 2007). It is not clear how the intermittent exercise intensity calculated from this test compares with the more traditional method of setting the intensity at the workload achieved at VO_{2max}, a robust physiological parameter of exercise intensity, calculated from a standard incremental exercise test.

2.6.4.4 A novel application of intermittent exercise prescription

The intermittent exercise dose, both in a single training session and over time, consists of the interrelating variables of intensity, volatility (the amplitude of the work phases above and below the mean), duration and frequency. Manipulating the intensity and volatility of intermittent exercise may alter the the amount of work achievable in a single session, and may affect the duration and frequency of activity required to achieve a training response, yet the research in this area is very limited. One study has examined the effect of manipulating the intensity and duration of the intermittent work phases in CHF (Meyer et al., 1996b). By decreasing the duration of the work phase to compensate for an increase in intensity, the exercise was tolerable, and did not induce an increase in VO_2 or Lac. In this study, the intensity of the work phases was determined by Meyer's steep test.

A novel and more robust physiological approach would be to alter the volatility of the work and rest intervals within the framework of the exercise intensity domains, as shown in figure 2.5. The example illustrated shows that the total work done is equal in all exercise protocols, but the intensity of the work and rest phases is manipulated. It includes a protocol where the volatility is zero, ie. constant-rate or continuous exercise,

set below VT in the moderate intensity domain. An investigation of this nature could assess whether moving the intensity of the work and rest phases across exercise intensity domain borders influences the physiological and perceptual responses to exercise.

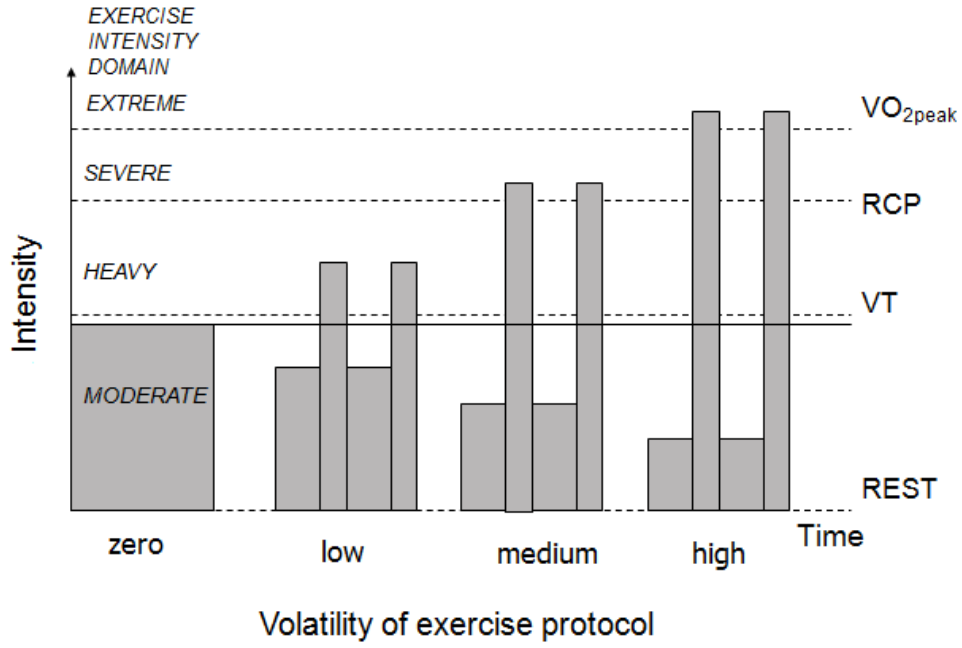


Figure 2.6: Diagram of 4 different exercise protocols.
Total work done is equal but amplitude above and below the mean is adjusted. When the volatility is zero, the work is maintained at constant rate The work:rest ratio of the low, medium and high volatility protocols is 1:2. The work phases are in different exercise intensity domains, depending on the volatility of the exercise.
VT: ventilatory threshold. RCP: respiratory compensation point

In order to determine the optimal exercise training dose for CHF, there is need for further investigation into robust methods for determining accurate exercise intensity prescription, particularly for intermittent exercise. In addition, further information about the acute and chronic responses to different intermittent exercise training protocols is required.

2.6.5 Circuit training

Numerous UK-based CR exercise classes comprise circuit-training where patients move around a series of different work stations to perform aerobic and/or muscular strength and endurance exercises for a pre-determined period (usually 1-2 min) (British

Association for Cardiac Rehabilitation, 2006; Association of Chartered Physiotherapists in Cardiac Rehabilitation, 2009). The recommended intensity for aerobic exercise is 60-80% HR_{max} or 40-70% HRR and/or an RPE of 12-15. One small study of 6 patients suggests that circuit-training is appropriate for CHF, and that it induces a similar oxygen and haemodynamic demand to continuous cycle ergometer exercise at 70-80% HR_{max} (Green et al., 2001). Circuit training is, arguably, a form of intermittent training in that there are periods of aerobic exercise interspersed with active recovery and/or muscular strength and endurance exercises. However, this differs from high intensity intermittent exercise because the intensity of the work phases is intended to be moderate.

2.7 Ecological validity: application to current practice

Despite the growing body of evidence in favour of exercise training for CHF, there is less evidence that the results of reported studies are transferable to clinical practice. Firstly, it has been reported that the exercise dose in randomised controlled trials of CR is more than four times greater than usual practice in the UK (Taylor et al., 2007). Secondly, the majority of studies are not representative of the total population of CHF patients, and tend to exclude older patients, females, individuals with implantable devices, and those with more severe heart failure and/or co-morbidities (Rees et al., 2004). The Medicare Beneficiaries study indicated that only 4% of CHF patients will be free from one or more co-morbidities (Braunstein et al., 2003). Therefore, as well as being important to study the effects of training in the "real life" CHF population, it is also important to consider the potential effect of the intervention on patients' co-morbidities.

More recent studies have demonstrated the safety and effectiveness of supervised exercise training on different sub-populations of CHF patients. These include: elderly patients, some with chronic atrial fibrillation (Owen and Croucher, 2000); those in NYHA class III (Freimark et al., 2007); those who have undergone cardiac resynchronisation therapy (Patwala et al., 2009); and those with implantable cardiac defibrillators (Fan et al., 2009). However, it is not clear how the aetiology or severity of heart failure or other characteristics of the patients affect the response to exercise

training. For example, some studies report greater improvements in patients with lower initial functional capacity and/or more severe LV dysfunction (Hambrecht et al., 1995a; Meyer et al., 1997a). By contrast, other studies report no, or lesser, improvements in these patients (Wilson et al., 1996; Belardinelli et al., 1999; Wielenga et al., 1999). Some studies demonstrate that patients with ischaemic aetiology are more responsive to exercise training (Willenheimer et al., 1998), whereas others suggest that patients with non-ischaemic aetiology are more likely to show a positive training response (Forissier et al., 2001).

Standard pharmacological treatment for CHF patients has developed since the initial exercise training studies in this population. β-blocker therapy is now standard for the majority of patients, but it is only the more recent studies that report the effect of exercise training in patients on this medication (Demopoulos et al., 1997a; Forissier et al., 2001; Fraga et al., 2007). VO_{2peak} improved to a similar extent after exercise training in CHF taking selective (14%), non-selective (17%) or no β-blockers (19%) (Forissier et al., 2001). β-blockers do not change maximal exercise performance, but they do appear to improve the ventilatory response to exercise (Witte et al., 2005), and to reduce symptoms of breathlessness (Wolk et al., 2005). Optimising medical therapy may increase functional capacity and measures of exercise tolerance by decreasing symptoms and thus allowing a spontaneous increase in activity (Fraga et al., 2007). Alternatively, as current medical therapy becomes increasingly effective at attenuating symptoms, the additional potential benefit from exercise training might be limited.

2.7.1 Cardiac rehabilitation

It is important to note the distinction between cardiac and exercise rehabilitation. CR is not a programme that consists solely of exercise training. It is a multi-faceted, long-term process, comprising comprehensive lifestyle intervention programmes that include psychological support and education. Advice on risk factors and lifestyle changes for secondary prevention, are offered in addition to structured exercise programmes (British Association for Cardiac Rehabilitation, 2006). CR is effective and economically justified for secondary prevention in numerous sub-populations of cardiac patients, including CHF (Giannuzzi et al., 2003a). Comprehensive CR is provided by a multi-disciplinary health care team, usually including a consultant

cardiologist, cardiac specialist nurses, an exercise professional, physiotherapist, psychologist and dietician. Ecologically valid research studies should include exercise training as part of a comprehensive CR programme.

2.7.2 UK based cardiac rehabilitation programmes

In the UK, CR is traditionally described in terms of phases of recovery (Table 2.7).

Table 2.7 UK Cardiac rehabilitation phases

		Number of UK centres providing each phase of rehabilitation (total n = 382)
Phase I	Inpatient stage	250
Phase II	Early discharge period	199
Phase III	Clinically supervised outpatient programme	361
Phase IV	Long term maintenance of physical activity and lifestyle change	114

There are approximately 382 UK cardiac rehabilitation centres (British Heart Foundation, 2009). The majority of referrals to CR are patients who have had an MI, percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). Uptake of CR is 30-34% for MI and PCI patients, and 68% for CABG patients. Despite the evidence that CR can benefit several other diagnostic groups (e.g. chronic stable angina, implantable devices and CHF), referral is still limited among these patients. The majority of individuals attending CR are white males aged 65-69 years.

There is evidence that UK hospital and community-based CR programmes improve functional status and QoL in CHF > 60 years (Austin et al., 2005b). One study demonstrated that CHF with a mean age of 82 years, including those with chronic atrial fibrillation, could safely participate in a once weekly CR class, and that 6-minute walk distance improved significantly (20%) after 12 weeks (Owen and Croucher, 2000). Exercise training may be particularly beneficial to these patients, who tend to have greater symptoms due to the overlapping effect of both ageing and CHF (Gielen et al.,

2005), yet they are often excluded from exercise-based rehabilitation because of their age and symptoms.

2.7.3 Current provision of cardiac rehabilitation for CHF patients

The ESC Position Paper sets out the core components of CR in CHF, and one of its objectives was to broaden the indication for CR in this population (Corra et al., 2005). Despite this, and the examples of CR schemes for CHF patients within the published literature, only 25% of CR programmes in England accept CHF (Brodie et al., 2006). The 2009 National Audit of CR reported that 25% of CR centres had a specific policy of not accepting CHF, and only 1% of referrals were in patients whose main referral reason was CHF (British Heart Foundation, 2009). This is partly due to lack of resources, since CHF patients are considered high risk and require a staff to patient ratio of 1:4. The low level of exercise tolerance of the majority of CHF patients also makes it difficult for them to be integrated into general CR classes. It is therefore not surprising that UK studies to date have typically included small subject numbers and had methodological limitations (Coats et al., 1992b; Taylor, 1999; Owen and Croucher, 2000; Austin et al., 2005b; Witham et al., 2007; Patwala et al., 2009). In Norway, exercise training was modified for CHF patients who were unable to participate in mainstream classes for individuals with coronary artery disease due to dyspnea, inability to keep up to pace, and inadequate counselling (Nilsson et al., 2008a). In Eastbourne, East Sussex, a separate class is run once a week for high risk patients and/or those with orthopaedic problems or co-morbidities that limit their ability to exercise (personal communication, Hilda Healy, Cardiac Rehabilitation Sister, 2008). Ideally, these patients should have access to twice-weekly sessions, in line with the provision for low-moderate risk cardiac patients.

2.8 Methodological considerations in the study of responses to exercise training in CHF

There are numerous methodological issues to consider in the study of acute and chronic exercise responses in CHF, and these have been discussed in several key papers (Fleg et al., 2000; Agostoni, 2006; Ingle, 2007). The following paragraphs will discuss those that are pertinent to this study. Appendix 2 includes discussion of methods commonly used by other authors, and a rationale for not including them in this study.

2.8.1 Cardiopulmonary exercise testing (CPET)

Maximal CPET using an incremental protocol to exhaustion is a valid and reproducible method of assessing functional capacity in CHF in clinical and research applications. It provides good prognostic information, assesses sub-maximal and maximal exercise capacity, and ventilatory efficiency (Fleg et al., 2000).

2.8.1.1 Exercise mode

In both healthy and clinical populations, one of the general recommendations for the assessment of VO_{2max} or VO_{2peak} is that the exercise should be rhythmic, and should engage a large muscle mass (Cooke, 2001). The influence of exercise mode on physiological responses is well-recognised. In athletes, the mode of exercise should be specific to the individual. In untrained individuals, treadmill exercise generally elicits VO_{2peak} values approximately 10% higher than cycle ergometer exercise, due to the larger exercising muscle mass, and this holds true for CHF (Page et al., 1994). A 16% higher VO_{2peak} in treadmill compared with cycle ergometer exercise, associated with an 7% higher cardiac output and an 8% higher a-vO_2 difference, has been reported in CHF, suggesting that central and peripheral factors contribute equally to the increased VO_{2peak} (Kim et al., 1999). Ventilatory response and V_E/VCO_2 slope are also higher in treadmill protocols due to their weight-bearing nature, which may increase the ergoreflex activation to a greater extent than weight-supported exercise, thus stimulating ventilation (Witte and Clark, 2005). Cycle-based exercise led to CHF and healthy controls stopping exercise more frequently because of fatigue rather than breathlessness, whereas breathlessness was the more frequent cause in treadmill exercise. Interestingly, for a given oxygen uptake, RPE was the same on the cycle ergometer as on the treadmill (Witte and Clark, 2005). Treadmill exercise might be more familiar than the cycle ergometer, and permits the use of handrails, although this will influence the energy cost. In older CHF with systolic dysfunction and co-morbidities (e.g. COPD, osteoarthritis, diabetes) cycle ergometer protocols with small and regular increases in work rate (e.g. 10 $W.min^{-1}$) are more appropriate (Ingle, 2008). Cycle ergometry is easier for patients with orthopaedic limitations, and allows other measurements, e.g. blood sampling and exercise echocardiography, to be performed. Subsequent exercise training on a cycle ergometer allows exercise at low workloads,

accurate reproduction of the prescribed workload, particularly in the application of intermittent training, and monitoring of HR, rhythm and BP. A cycle ergometer may be upright or semi-recumbent, and the exercise responses are likely to be influenced by differences in haemodynamics and the muscle mass engaged. Semi-recumbent cycling, which allows echocardiography to be performed more easily than upright cycling, appears to elicit lower HR, BP and VO_2 responses to submaximal and maximal exercise in healthy and mildly hypertensive adults (Walsh-Riddle and Blumenthal, 1989; Scott et al., 2006).

2.8.1.2 Effect of test protocol duration

The general consensus has long been held that the optimal duration for a maximal cardiopulmonary exercise test is 8-12 min, as shorter or longer tests tend to underestimate$VO_{2max.}$(Cooper and Storer, 2001). However, this premise has recently been challenged. Current evidence suggests that cycle ergometer tests should last between 7 and 26 min, and treadmill tests 5 and 26 min, in order to elicit valid VO_{2max} values, provided that short tests are preceded by an adequate warm-up (Midgley et al., 2008). In CHF, exercise protocols designed to elicit maximal exertion in either 5, 10 or 15 minutes appear to have a small effect on VO_{2peak} and the ratio of change in oxygen consumption to change in work rate ($\Delta VO_2/\Delta$ work), but do not affect VO_2 at VT, or V_E/VCO_2 slope. A short (5 min) test with steeper increments induced a significantly lower HR_{peak}, VO_{2peak}, and ventilation than tests of 10 or 15 min duration (Agostoni et al., 2005). Although VO_2 at VT was the same for all 3 protocols, the workload at which it was identified was influenced, varying from 58 to 74W, which has implications when using CPET to set training workloads below this threshold.

2.8.2 Reproducibility

Although maximal CPET is still considered the “gold standard” for assessing functional capacity, this method is still subject to variability, particularly in CHF. Measurements will be affected by individual patient motivation and variation in day-to-day health, as well as biological and technical variability, which is more likely at higher intensities (Meyer et al., 2004a). Serial assessment of exercise capacity presents greater challenges than the single determination used to characterise baseline function. There are no universal criteria for reproducibility, but guidelines for clinical populations

suggest that VO_{2peak} should vary < 10% and exercise duration < 60s (i.e. 10% of a 10 min test), on separate days for it to be considered reproducible (Fleg et al., 2000). There is comprehensive evidence that circadian rhythms influence measures of exercise performance, and serial exercise tests should therefore be conducted at the same time of day (Reilly, 2007). Tests should be performed > 2 hours after eating to avoid the effects of food on myocardial oxygen demand (Fleg et al., 2000). The issue of reproducibility of CPET parameters in CHF has been investigated by several authors. Some report good reproducibility in repeated exercise tests (Cohen-Solal et al., 1991; Meyer et al., 1997c; Marburger et al., 1998); others report an apparent learning effect, demonstrated by a lower exercise duration (-17%) and VO_{2peak} (-6%) between the first and second test compared with similar values between the second and third test (Elborn et al., 1990). The HF-ACTION trial showed substantial within-subject variability, but no apparent learning effect (Bensimhon et al., 2008). Further investigation is required to clarify the effects of familiarisation, within-subject variability, mode of exercise and the characteristics of individuals tested.

2.8.3 Outcome measures in CPET

2.8.3.1 VO_{2peak}

As discussed in section 2.5.4.1, VO_{2peak} is reduced in CHF, and the extent of the reduction is a prognostic indicator. In healthy adults, the accepted criteria for establishing VO_{2max} are: a plateau in the VO_2-intensity relationship (< 2 $ml.kg^{-1}.min^{-1}$ or 3% with an increase in exercise intensity), a respiratory exchange ratio (RER) value $\geq$ 1.15, a final HR within 5 $beats.min^{-1}$ of predicted age-related maximum, a post-exercise Lac $\geq$ 8 $mmol.L^{-1}$, subjective fatigue and volitional exhaustion, and an RPE of 19 or 20 on the Borg scale (Cooke, 2001).

CHF patients are often unable to exercise long enough for a plateau in VO_2 to be observed, therefore the term VO_{2peak} is used (Ingle, 2008). VO_{2peak} values in CHF patients may occur in the immediate post exercise period, due to slowed VO_2 kinetics in this population (Cohen-Solal et al., 1997), therefore it is good practice to measure VO_{2peak} as the highest average value over 20-30s in the final stage of the exercise test or in the immediate post-exercise period (up to 45s post exercise). The sampling interval of gas exchange data influences the reported VO_2 value (Johnson et al., 1998). In the

absence of standardisation in methodology across studies, the use of rolling averages, and the reporting of the specific sampling intervals chosen is the minimum recommendation (Myers, 2001). According to ESC guidelines, an RER > 1.0 suggests adequate patient effort (Tavazzi et al., 2001). However, VO_{2peak} is a better prognostic indicator in patients who achieve an RER $\geq$ 1.15 (Mezzani et al., 2003). Due to the effects of medication and chrontropic incompetence, the heart rate criteria are not appropriate for establishing VO_{2max} in CHF, nor are the standard Lac and RPE criteria likely to be applicable. Peak RPE in cardiac patients is lower than in healthy individuals (16 vs 18) (Whaley et al., 1997), and Lac of approximately 2 $mmol.L^{-1}$ has been reported after maximal exercise testing (Meyer et al., 1997b).

VO_{2peak} may be expressed in absolute ($ml.min^{-1}$ or $L.min^{-1}$) or relative to body mass ($ml.kg^{-1}.min^{-1}$) terms. In non-weight bearing exercise such as cycling in healthy individuals, values are often expressed in absolute terms. Relative values are more commonly reported in clinical trials and are useful for reflecting cardio-respiratory fitness in terms of health or disease, for example, in the Weber classification of the severity of CHF (Weber et al., 1982). As relative values are affected by weight fluctuations, it is useful to report change in absolute and relative values following an exercise training intervention. Some studies reporting larger improvements in VO_{2peak} have not reported familiarisation procedures, or have acknowledged that the improvements may be attributed in part to a learning effect (Arad et al., 2008). Studies that have specifically included a familiarisation maximal exercise test tend to report smaller improvements in $VO_{2peak.}$

2.8.3.2 Ventilatory threshold (VT)

VT reflects the disproportional increase in CO_2 above O_2 due to bicarbonate buffering in response to a rise in Lac (Beaver et al., 1986; Cooper and Storer, 2001; Wasserman et al., 2005). The exercise intensity at VT is a measure of endurance performance, or sub-maximal exercise capability, as it defines the highest work rate that can be sustained for a prolonged period of exercise. A rightward shift in VT is characteristic of a successful endurance training intervention, as it allows a higher absolute work rate and relative ($\%VO_{2max}$) exercise intensity to be sustained without the accumulation of Lac (Jones et al., 2007). For this reason, efficacy of training in CHF is arguably better assessed by VT rather than VO_{2peak}, and exercise at this intensity more closely reflects

daily activities (Larsen et al., 2001). VT is increasingly used in addition to VO_{2peak} as an outcome measure in exercise training studies in CHF (Willenheimer et al., 1998; Keteyian et al., 1999; Dimopoulos et al., 2006; Van Laethem et al., 2007). VT is considerably lower in CHF than in healthy individuals, and decreases according to the severity of the disease. However, the % VO_{2peak} at VT may be high (around 70% in CHF compared to 40-60% VO_{2peak} in a healthy population), due to an attenuated rise in VO_2 above VT, and/or the fact that VO_{2peak} is very low (Meyer et al., 2005a). VT is a valid indicator of functional capacity, if procedural recommendations are followed (Meyer et al., 1996a), and is responsive to training in CHF (Simonton et al., 1988; Meyer et al., 2005b). However, VT cannot be detected in approximately 16% of tests in CHF, due to insufficient or noisy gas exchange data, or oscillatory breathing (Myers et al., 2010). Automatic determination of VT via regression-based computer algorithms is available on modern metabolic systems, but these may not be accurate, and Myers et al (2010) recommended that experimenters ultimately determine VT via visual methods.

2.8.3.3 Ventilatory efficiency

The ventilatory response to exercise is increased in many CHF and may be characterized by the regression slope of minute ventilation to carbon dioxide output during exercise (V_E/VCO_2 slope). It is significantly correlated with aerobic capacity, cardiac function, and pulmonary perfusion, and there is evidence that it may be superior to VO_{2peak} in predicting outcome in CHF (Chua et al., 1997; Arena et al., 2007; Ingle, 2008). The normal range in healthy individuals is 20-29. In CHF a slope >34 defines a high ventilatory response to exercise, and indicates more severe heart failure and a poorer prognosis. The ventilatory response to cycle ergometer exercise is lower than in treadmill exercise, perhaps due to lower ergoreflex stimulation during weight-supported exercise (Witte and Clark, 2005).

There is some debate about whether the V_E/VCO_2 slope should be calculated from exercise data prior to RCP, i.e the linear part of the slope, or from all data points from the onset of exercise to peak exercise. Whilst the sampling interval (breath-by-breath, or average over 10s, 30s or 60s) has little impact on the value obtained or its prognostic utility (Arena et al., 2003), using data from rest to peak exercise has the greatest prognostic value (Tabet, 2003). The relation between V_E and VCO_2 becomes nonlinear

near the end of an incremental maximal CPET, this will influence the value of the slope. At this point (RCP), ventilation is driven both by CO_2 output and by a decrease in plasma pH, and increases disproportionately to VCO_2. Patients whose symptoms contribute to them stopping the exercise test prematurely are likely to have a linear slope, with a lower value than those who manage to exercise for longer. In Tabet's study, 64% of the patients showed two distinct slopes: an initial linear slope (31.8+/-7.5, 18-62) and a final steeper slope (48.6+/-15.7, 24-101). Patients in whom no second, steeper slope was observed had more severe CHF, presumably because they were unable to exercise beyond RCP. Nevertheless, the V_E/VCO_2 slope computed from all the data points had the highest prognostic value (Tabet, 2003). However, other authors calculate the V_E/VCO_2 slope by its linear part (Passino et al., 2006a). Standardising the measurement in this way is more valid, particularly when investigating the effect of an exercise training intervention on ventilatory efficiency.

A further consideration is the effect of β-blockers which inhibit the sympathetic activity that contributes to increased ventilation (Wolk et al., 2005), and thus reduces the V_E/VCO_2 slope (Witte et al., 2005). For this reason, values reported in studies of patients on current medical therapy may be lower than in older studies.

2.8.3.4 Oxygen uptake-work rate relationship ($\Delta VO_2/\Delta WR$)

Work "efficiency" is a measure of the metabolic cost of performing external work and for incremental exercise is often expressed as the change in slope of the relationship between VO_2 and work rate ($\Delta VO_2/\Delta WR$). The slope reflects the adequacy of oxygen flow and utilisation in the periphery and indicates whether oxygen supply can keep pace with demand. The predicted normal slope is 10.3 $ml.min^{-1}.W^{-1}$, with 95% of normal values lying between 8.3 and 12.3 $ml.min^{-1}.W^{-1}$. Conditions such as heart disease, including CHF, where oxygen delivery is impaired, can lower the slope (Cooper and Storer, 2001; Wasserman et al., 2005).

2.8.4 Heart rate response to exercise in CHF

A lowered resting HR is often used as an indicator of improved cardio-respiratory fitness, but may not be relevant in clinical populations where medical therapy, β-blockade in particular, exerts a greater effect at reducing HR. CHF show an attenuated

HR response to exercise, limiting their ability to increase cardiac output. Chronotropic incompetence, defined as the inability of a patient to achieve a peak HR > 80% of age-predicted maximum, is common in CHF, and is correlated with poor functional capacity (Vallebona et al., 2005; Witte et al., 2006). However, a reduced HR response to exercise does not determine exercise capacity. Although chronotropic incompetence is associated with higher mortality in patients not taking β-blockers, in patients on β-blockers it is not associated with higher mortality (Witte et al., 2006). The effect of chronotropic incompetence and/or β-blockers preclude the use of a HR within ± 10 beats.min^{-1} age-predicted HR_{max} as a criteria (Cooke, 2001) to determine the attainment of VO_{2max} in CHF.

HR recovery has been proposed as a simple marker of autonomic function that can be used to assess outcomes during CR (Myers et al., 2007). To some extent, it reflects the extent of vagal reactivation, i.e. the inhibition of sympathetic activity and predominance of vagal activity, and poor HR recovery is associated with poorer prognosis in cardiac patients (Arena et al., 2006). HR recovery in the first minute after exercise has been used to estimate parasympathetic activity in CHF (Dimopoulos et al., 2006). HR variability is a more sophisticated tool for assessing autonomic balance, and improvements in HR variability have been reported after exercise training in CHF (Malfatto et al., 2002).

2.8.5 Rating of perceived exertion (RPE)

Borg's Perceived Exertion Scale (Borg, 1998) is commonly used for quantifying an individual's subjective feelings of exertion during exercise as a means of determining or regulating the exercise intensity. RPE ratings increase linearly with exercise intensity, HR, VO_2 and Lac, and are highly correlated with these physiological markers of relative exercise intensity (Eston et al., 2009). The strongest stimuli influencing an individual's RPE are ventilatory work and sensations of muscle and joint strain (Buckley and Eston, 2007). Table 2.8 summarises the relationship between RPE and related physiological markers.

Table 2.8: Relationship between percentages of maximal oxygen uptake (% VO_{2max}), heart rate reserve (%HRR), maximal heart rate (%HR_{max}) and Borg's rating of perceived exertion (RPE)

(adapted from Buckley and Eston, 2007)

% VO_{2max}	< 20	20-39	40-59	60-84	≥ 85	100
%HRR	< 20	20-39	40-59	60-84	≥ 85	100
%HR_{max}	< 35	35-54	55-69	70-89	≥ 90	100
RPE	< 10	10-11	12-13	14-16	17-19	19-20

RPE is conventionally used for an "estimation-production" procedure to regulate exercise intensity. In this procedure, the RPE at a given heart rate, VO_2 or blood lactate value during a prior incremental exercise test is used to prescribe exercise at a chosen intensity. This is considered to be a physiologically valid method of regulating exercise intensity in individuals of varying age, gender, fitness and health (Eston et al., 2009). However, inter-individual variablity has been reported at 60% and 80% HRR during a maximal incremental exercise test in healthy individuals and cardiac patients (Whaley et al., 1997). In this study, 32% cardiac patients and 39% healthy controls had an RPE value either < or > 11-14 at 60% HRR, while 52% patients and 32% controls had an RPE value either < or > 14-17 at 80% HRR. It has previously been reported that RPE at VT is 11.0 ± 2.1, and does not differ between cardiac patients taking β-blockers, those not taking β-blockers or younger healthy individuals (McConnell et al., 1993). If there is a consistent relationship between RPE and VT, it is not surprising that there is individual variability between RPE and HR_{max} or HRR, because VT occurs at different percentages of these in individuals, as discussed previously.

RPE is useful in CR to prescribe and monitor exercise intensity. For example, exercise guidelines recommend that patients work at an intensity of 12-15 during the "aerobic" component of an exercise session (British Association for Cardiac Rehabilitation, 2006). The use of the 6-20 scale is recommended for whole body exercise, rather than the CR-10 which was developed to focus on localised muscle pain, fatigue or breathlessness (Borg, 1998). The accuracy of matching exercise intensity to RPE is dependent of familiarity and practice for both the production and estimation procedures, and may be influenced by medication, mental well-being and motivation to exercise (Buckley, 2006). The accuracy can be improved by ensuring that adequate

explanation and instruction is provided to the exerciser (Maresh and Noble, 1984) including the sensation of the "whole body" exercise responses, anchoring the perceptual strain, and identifying the verbal descriptor before relating to the numerical value (Noble and Robertson, 1996). Nevertheless, cardiac patients may "inflate" their RPE if they have low-self-efficacy, or are nervous of the exercise testing or training environment (Buckley and Eston, 2007).

It is not clear how RPE links to physiological responses during intemittent exercise training. However, Meyer and colleagues demonstrated that average ratings for leg fatigue and dyspnoea (assessed by the Borg 6-20 scale) were both 11 (light) during intermittent exercise, the same value as at VT during an incremental exercise test. Leg fatigue was rated at 13 (somewhat hard) during the work phases and 10 in recovery, whereas dysnoea was rated at 10 during both work and recovery (Meyer et al., 1997b). It is not clear why the authors used the 6-20 scale rather than the CR-10 scale which is arguably more appropriate for assessing leg fatigue and breathlessness.

2.8.6 B-type natriuretic peptide (BNP)

Plasma BNP, and its inactive N-terminal fragment NT-pro BNP, is released primarily from the left ventricle in response to increased filling pressure, and correlates with LV dysfunction. It is used in the diagnosis and prognosis of heart failure, is an important predictor of morbidity and mortality, and changes over time are associated with corresponding changes in morbidity and mortality. There has been considerable debate in recent years about the role of BNP monitoring in the diagnosis and management of CHF patients (Bhatia et al., 2003; Cowie et al., 2010). Plasma BNP appears to be a useful objective biomarker for monitoring CHF (Lee et al., 2002), and may be a less time-consuming and more cost-effective means of risk-stratification than CPET (de Groote et al., 2004). There is support for its role as a surrogate marker in interventional CHF trials (Anand et al., 2003).

BNP is associated with exercise capacity and correlates with VO_{2peak} and VT (Kruger et al., 2002). When combined with measurement of VO_{2peak}, BNP improves risk stratification in CHF (de Groote et al., 2004). Patients with plasma BNP < 109 pg/ml have an excellent prognosis, while those with BNP > 109 pg/ml benefit from a subsequent prognostic evaluation, including CPET and echocardiography. BNP > 109

pg/ml and % predicted $VO_{2peak} \leq 50\%$ are indicative of a poorer prognosis (de Groote et al., 2004). A more recent study confirms that the persistence of a high BNP level, combined with a poor ventilatory efficiency (V_E/VCO_2 slope > 35), identifies patients on optimal medical therapy, including β-blockers, with a poor prognosis (Pascual-Figal et al., 2008).

Although BNP levels show a significant correlation with the impairment of VO_2 at peak exercise and anaerobic threshold (Kruger et al., 2002), it is less clear whether BNP reflects improvements in exercise capacity following exercise training. Studies measuring the response of NT-proBNP levels following exercise training have reported no changes (Jonsdottir et al., 2006; Arad et al., 2008; Beckers et al., 2008) or a decrease (Conraads et al., 2004; Passino et al., 2006b; Berent et al., 2009) that correlates with increased exercise capacity, but not with LV dimensions or ejection fraction. The authors suggest that peripheral adaptations such as a decrease in afterload, as well as reduced diastolic wall stress, could have contributed to the observed decrease in NT-proBNP.

NT-proBNP is reportedly more stable than BNP under laboratory conditions, and is reproducible in a stable CHF population after a 4 month period (Conraads et al., 2004). the BNP is also considered to be a valid and reproducible tool for monitoring CHF (Lee et al., 2002; McNairy et al., 2002). Passino et al (2006) found similar reductions in both NT-BNP and BNP following exercise training, and a recent systematic review concluded that exercise training has a favourable effect on BNP (Smart and Steele, 2009). Nevertheless, there is some doubt over its reliability or usefulness in the serial monitoring and evaluation of CHF therapy (Packer, 2003; Wu and Smith, 2004). Until recently, the assay for BNP has been difficult and time-consuming to perform. A rapid point-of-care immunoassay for the quantitative analysis of B-type Natriuretic Peptide (BNP) has recently been developed: The Triage® BNP Test (Biosite Ltd, Belfast, or Biosite Diagnostice Inc, San Diego, California). This test is reported to be a sensitive (with a 98% negative predictive value at a blood concentration < 80 pg/ml and specific test used to diagnose CHF (Dao et al., 2001). However, there is little research into its use as a marker to evaluate therapies, including exercise rehabilitation. A small study examining its utility to evaluate the effect of exercise training in an outpatient setting reported a trend for BNP to decrease in the exercise group, mirroring improvements in functional capacity, whereas BNP increased in the control group (Butterfield et al.,

2008). This test was also used by Malfatto et al (2009), who reported reductions in BNP following exercise training that correlated with improvements in LV compliance..

2.8.7 Daily physical activity

When evaluating the effectiveness of a supervised exercise training intervention, it is important to monitor changes in physical activity levels outside the supervised programme which could contribute to changes in outcome measures. There are various methods, including objective measures such as HR, accelerometry and pedometry, and subjective recall questionnaires (Macfarlane et al., 2006). For the purpose of recording physical activity during daily life during an exercise training study in CHF, a physical activity log book is arguably the most appropriate tool. HR monitors are limited by the interference of environmental conditions and emotional stress while accelerometers do not measure non-ambulatory or upper body movements, and cannot determine exercise intensity. Physical activity questionnaires rely on subjective recall, and are generally designed for healthy young to middle age populations, rather than cardiac patients. Daily physical activity records also rely on subjective recall, but only for up to 24 hours. They are time-consuming to process, but are feasible for shorter studies with a limited number of participants.

2.8.8 Quality of life

The goal of health care for individuals with chronic disease is to improve function and well-being. An individual's perception of his or her QoL is a good indicator of this goal, and may be assessed by generic and disease-specific questionnaires. The effectiveness of a therapeutic intervention cannot be judged solely on improvements in functional capacity or disease progression. It is important to integrate laboratory and physical examination results with measurement of health status in order to assess the true "value" of the intervention to the patient (Jette and Downing, 1994). UK statistics suggest that 24-42% of CHF patients suffer from depression (British Heart Foundation), and interventions that improve QoL may be particularly beneficial to this population. There are a variety of instruments available to assess QoL, including those that assess generic health status, and those that focus on the problems associated with single disease-states or patients groups. Disease-specific measures are aimed to focus on the important aspects of health-related QoL in the patients being studied, and are

therefore often more likely to be senstive to clinical change (Guyatt et al., 1993). The majority of exercise training studies in CHF have used the disease-specific Minnesota Living with Heart Failure Questionnaire (MLHFQ) (Davies et al., 2010), and the Medical Outcomes Short Form 36 (SF-36), as illustrated in Table 1A (Appendix 1).

2.8.8.1 Disease-specific quality of life: Minnesota Living with Heart Failure Questionnaire (MLHFQ)

Disease-specific QoL is clinically relevant, and can be measured using the MLHFQ developed by Rector et al (1987) (Rector et al., 1987a; Rector et al., 1987b). This tool consists of 21 items recording patients' perceptions of how CHF affects their physical, psychological and socioeconomic lives, using a 6-point zero to five Likert scale, with a maximum possible score of 105 points. A higher score indicates a poorer perceived QoL. The reproducibility (r and Chronbach's alpha coefficient) is reported at 0.87-0.95, with estimates of the standard error of measurement between 5.8-8.6 points (Rector, 2005). The MLHFQ incorporates relevant aspects of the key dimensions of QoL, but was not designed to measure any particular dimension separately; hence it is recommended that the total score is the best measure of how heart failure and treatments affects the patient's QoL. However, a factor analysis of responses has demonstrated that a subgroup of 8 questions related to physical symptoms and a subgroup of 5 questions related to psychological symptoms are highly inter-related, and can be used to characterise the physical and emotional domains (Rector and Cohn, 1992).

Authors who have not found any improvement in MLHFQ following exercise training have suggested that, although this instrument has been used effectively in drugs trials, a more generalised tool such as the SF-36 might be more applicable in exercise training studies (Keteyian et al., 1999). The SF-36 is discussed in section 2.8.8.2 below. It has also been suggested that MLHFQ may not be appropriate for use on elderly CHF, as it was validated on a population aged 59 ± 11 years

The Kansas City Cardiomyopathy Questionnaire is a recently developed questionnaire for measuring health status in CHF, and there is evidence that it has greater sensitivity to clinical change than MLHFQ or SF-36 (Green et al., 2000). It measures physical limitations, and independently quantifies symptoms, social limitations, self-efficacy

and knowledge, and QoL. However, at the current time, it has only been used in one exercise training study in CHF (Whellan et al., 2007). This study, the HF-ACTION trial, demonstrated small but statistically significant improvements in self-reported health status assessed by the Kansas City Cardiomyopathy Questionnaire (Flynn et al., 2009).

2.8.8.2 Generic health status: Medical Outcomes Short Form 36 (SF-36)

The SF-36 is a validated generic health status measure (Davies et al., 2010) that assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions (Ware and Sherbourne, 1992). It has been used in several CR studies (Jette and Downing, 1994; Cohen et al., 1999), as well as in numerous exercise training studies in CHF (see Table 1A, Appendix 1). In CHF–specific studies, an exercise intervention is associated with improvements in physical and social functioning, physical role fulfilment and vitality (Quittan et al., 1999), and comprehensive CR, including exercise and education, improves mental health as well as physical functioning (Meyer and Laederach-Hofmann, 2003).

2.8.8.3 Clinical significance

The difficulty of ensuring that outcome measures in clinical trials accurately reflect changes in clinical status is widely acknowledged, and understanding the sensitivity of different assessment techniques to reflect clinically relevant changes is important (Spertus et al., 2005). Statistical analysis of group means, particularly on studies with small sample sizes, may not reflect clinical or practical meaningfulness, or changes in individual patient status. Equally, trials with sufficiently large sample sizes may detect changes that are statistically significant but not clinically meaningful. Recent exercise training studies that include a more heterogeneous CHF population tend to report smaller changes in physiological parameters than previous studies, and this may lead to a mistaken conclusion that exercise is of no benefit to many patients. However, it is important to integrate clinical results and prognostic markers with measurement of

health status in order to assess the true “value” of the intervention to the patient (Jette and Downing, 1994). This is complicated by the fact that there is no agreed criterion standard by which to define a change in patient disease status (Spertus et al., 2005).

2.9 Proposed aims of the thesis

The exercise intensity domains, delineated by VO_{2peak} and gas exchange thresholds (VT and RCP) may enable precise exercise training guidelines to be applied in CHF (Jones and Poole, 2005; Meyer et al., 2005a). Several authors have used a steep test (Meyer et al., 1997b) for setting intermittent exercise intensity work rates, yet this test has not been validated in CHF or in non-clinical populations. The two methods for prescribing intermittent exercise have not been compared.

The acute and chronic responses to intermittent exercise in CHF remain unclear. It may provide an alternative and time-efficient means of exercise training with greater health benefits than the lower exercise doses used in current practice, which might be more easily achievable or more enjoyable for some. The potential benefits of intermittent training are recognised by the ESC (Giannuzzi et al., 2001), but definitive guidelines on how it should be implemented are lacking. This thesis will examine the methodology for intermittent exercise prescription in order to find a reproducible and valid protocol, and to assess the effect of an intermittent exercise intervention compared with a training regimen in current practice.

Therefore, the aims of the current thesis are:-

1. (a) To examine the reproducibility of physiological parameters measured during a standard and a steep incremental cycle ergometer test, and (b) to compare the exercise training workloads derived from a standard and steep test in CHF patients and age-matched control participants.
2. To compare the acute respiratory, cardiovascular and metabolic responses to matched workloads of moderate continuous and intermittent exercise in CHF and control participants.
3. To examine the effect of volatility on acute cardiovascular, respiratory and metabolic responses to exercise by comparing an exercise bout where the amplitude of the work phases above the mean was increased (i.e. high volatility) with an exercise bout where the amplitude of the work phases was decreased (i.e. low volatility), whilst maintaining the same total work by adjusting the workload of the recovery phase.

4. To investigate whether there is a difference between the effect of high intensity intermittent exercise training and traditional circuit-based training on functional capacity, ventilatory efficiency, BNP and QoL in CHF patients in a short-term twice-weekly CR programme.

Hypotheses:-

1. a) Physiological parameters measured in duplicate standard and steep incremental cycle ergometer tests performed one week apart by CHF and control participants will show acceptable reproducibility in terms of statistical significance, re-test correlation and limits of agreement (LOA), and a difference < 10% between tests. b) Intermittent exercise training workloads derived from a steep test will differ to those derived from a standard test in CHF and control participants.

2. Intermittent exercise will elicit similar cardiovascular and respiratory responses, but higher metabolic and RPE responses, than continuous exercise, in CHF. In control participants there will be no difference in cardiovascular, respiratory, metabolic or RPE responses to intermittent or continuous exercise.

3. High volatility (i.e. a large amplitude between the work and recovery phases) intermittent exercise will elicit higher cardiovascular, respiratory, metabolic and RPE responses than low volatility (i.e. a small amplitude between the work and recovery phases) intermittent exercise or continuous exercise of matched total workload in CHF and control participants.

4. There will be no difference between the effect of traditional circuit-based training and high intensity intermittent training on functional capacity, ventilatory efficiency, BNP and quality of life in CHF on a 6 week CR programme.

CHAPTER 3: GENERAL METHODS

3.0 Introduction

The following section provides details of the methods common to more than one study of this thesis. Additional techniques and methods used in separate studies are described in the relevant chapters.

3.1 Study location

The study was carried out at Eastbourne District General Hospital, Eastbourne, BN21 2UD. Studies 1-3 were conducted on the Coronary Care Unit, in a dedicated testing area, curtained off to allow full privacy. Study 4 was conducted in the Cardiology Multifunction Room, and in the Physiotherapy gym. All testing sessions were conducted under the direct supervision of a cardiologist and an exercise physiologist.

Studies 1-3: Patients attended 6 separate testing sessions one week apart. Testing sessions were scheduled for the same time of day to minimise the effect of diurnal variability in exercise capacity (Fleg et al., 2000; Reilly, 2007). Patients were instructed not to perform exhaustive exercise during the 48 hours prior to testing, and not to consume alcohol or caffeine for 24 hours before testing. Patients continued to take routine medication before exercise testing. Exercise was performed at least 2 hours postprandially. All tests were performed on an electrically-braked upright Lode cycle ergometer (Lode Corival, Groningen, The Netherlands) (Figure 2.1). The seat and handlebar positions were measured and remained constant throughout all tests for each individual. None of the participants had any prior experience of either maximal or sub-maximal exercise testing on a cycle ergometer.

A B C

Figure 3.1: (A) Lode Corival cycle ergometer (B) Jaeger Oxycon Pro (C) Patient prior to cardipulmonary exercise test (Studies 1-3)

Study 4: All tests were performed on a semi-recumbent cycle ergometer (911 BP/LS, Schiller, Baar, Switzerland) (Figure 3.2).

A B

Figure 3.2: (A) Schiller semi-couch cycle ergometer and (B) patient prior to exercise test (Study 4)

3.2 Participants and ethics

CHF patients were recruited from the Heart Failure clinic at Eastbourne District General Hospital, under the inclusion and exclusion criteria detailed in Table 3.1. Patients meeting the criteria were initially identified by the Specialist Heart Function Nurse, and their medical details were then checked by a cardiologist to confirm that they met the criteria. All patients were receiving evidence-based care according to current guidelines (National Collaborating Centre for Chronic Conditions, 2003). Patients with pacemaker or ICD devices were excluded from Studies 1-3 to eliminate variability in heart rate response to exercise due to these devices. Furthermore, specific recommendations that patients with ICDs should be offered comprehensive CR (Corra et al., 2005) were not published until after the start of these studies. By Study 4, the published literature demonstrated that these patients were being included in exercise training studies (Whellan et al., 2007), and that exercise could safely be undertaken by those undergoing cardiac resynchronisation therapy (Conraads et al., 2007; Patwala et al., 2009) and those with ICDs (Vanhees et al., 2004). Provided they did not meet any exclusion criteria, these patients were therefore included in Study 4.

Table 3.1: Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Systolic heart failure Resting left ventricular ejection fraction < 40% (measured by echocardiography) Clinically stable for 4 weeks with no changes in medication New York Heart Association Class II – III	Acute coronary syndrome or surgery within previous 6 months Decompensated heart failure Severe valvular heart disease Hypertrophic obstructive cardiomyopathy Unstable angina Complex/sustained ventricular arrhythmia Severe systemic/pulmonary hypertension Aortic stenosis Presence of non-cardiac exercise limiting disorders or comorbidities (e.g. severe osteoarthritis or chronic obstructive pulmonary disease) Presence of any other absolute contraindications for exercise testing and training in CHF (Fletcher et al., 2001; Giannuzzi et al., 2001)

Age-matched asymptomatic control participants were recruited via poster advertisement, and 12-lead ECG analysis was performed to confirm that they were free from cardiac abnormalities.

3.2.1 Research ethics

The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki, and was approved by University of Brighton Ethics Committee and East Sussex Local Ethics Research Committee (Appendix 3). Participants' GPs were informed in writing of their enrollment in the study.

3.2.2 Informed consent

Participants were provided with written and verbal explanations of the aims, procedures, benefits and risks relating to the study, and of their right to withdraw from the study at any stage, before providing written informed consent (Appendix 4). They were given a minimum of 7 days from the date of receiving full information of the study to decide whether or not to participate. All data was stored on password-protected computers, and participant anonymity was maintained.

3.3 Procedures for maximal exercise testing

3.3.1 Maximal cardiopulmonary exercise test (standard test) and maximum short time exercise capacity test (steep test)

All patients performed two exercise tests: a standard incremental exercise test (Cohen-Solal et al., 1991) (standard test) and a maximum short time exercise capacity test (steep test), as described by (Meyer et al., 1997b) (Figure 3.3). These two tests were performed on the same day, in a fixed order, with patients resting for 1 hour between the first and second test.

Standard test: patients rested on the cycle ergometer for 3 minutes, then pedalled for 3 minutes without load as a warming-up period. The incremental exercise test then commenced, with CHF starting at a workload of 20 W, increasing by 10 W every minute. The starting workload (20 or 50 W) and ramp rate (10, 15 or 20 $W.min^{-1}$) for the control participants was adjusted according to age and fitness in order to maintain a test duration of ~ 10 minutes (Buchfuhrer et al., 1983; Wasserman et al., 2005). All participants pedalled at a self-selected constant cadence between 60 and 80 rpm and were verbally encouraged to exercise to exhaustion, as defined by intolerable leg fatigue or dyspnoea.

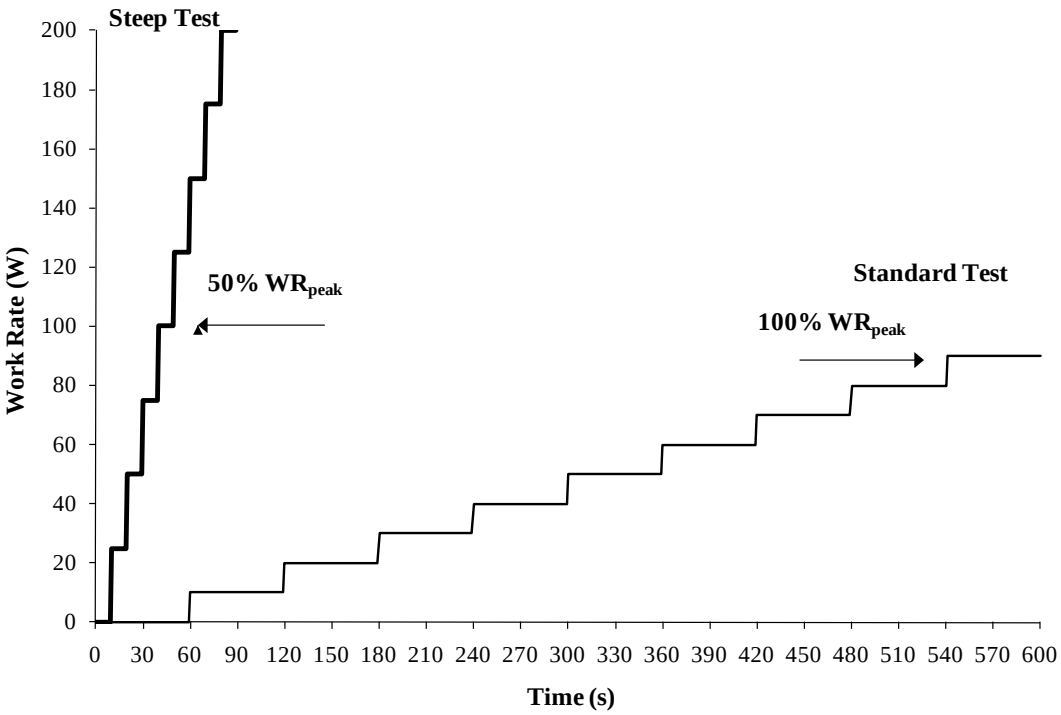


Figure 3.3: Protocol for steep and standard incremental exercise tests

3.3.2 Measurements

Height and body mass were recorded on the first visit, and body mass was recorded on each subsequent visit. Heart rate and rhythm were monitored continually via 3-lead ECG. BP was measured manually with a sphygmomanometer (Accosan, UK) at rest and every 2 minutes during exercise and the recovery period. RPE on the Borg 6-20 Scale (Borg, 1970) (Figure 3.4) was measured at the end of each stage, provided that this did not distract the patient from maintaining a regular pedal cadence or breathing pattern. Explanation and instruction on the use of the scale was provided according to the recommended guidelines (Noble and Robertson, 1996).

Ventilatory expired gases were obtained at rest, during exercise, and 5 minutes post exercise via a face mask using a breath-by-breath respiratory gas analysis system (Jaeger Oxycon Pro, Hoechberg, Germany). Calibration was performed before each test with known volumes of air and known concentrations of oxygen and carbon dioxide.

Steep ramp: after 1 hour of rest, a second maximal incremental exercise test was performed. After 2 minutes of unloaded pedalling, the workload was set at 25W for 10 seconds, and increased by 25W every 10 seconds until the pedal cadence could not be maintained above 60 revolutions per minute. Ventilatory expired gases were obtained at rest and during exercise, heart rate and rhythm were monitored continually by ECG , and BP was monitored with a sphygmomanometer (Accoson, UK) at rest and during the recovery period. Provided that no ECG abnormalities were present, patients were permitted to leave the hospital 15 min after completion of exercise, and/or when HR and BP had returned to resting values.

Both exercise tests were repeated one week later, using the same procedures as before, in order to determine reproducibility.

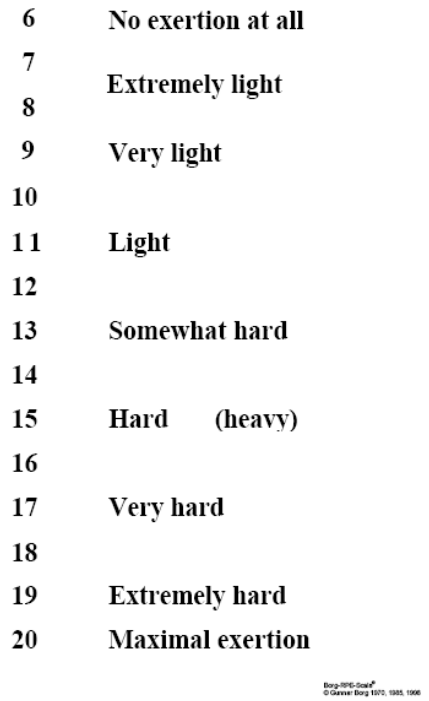


Figure 3.4: Borg 6-20 scale

3.4 Procedures for continuous and intermittent exercise tests

The exercise intensity domains, delineated by VT, RCP and VO_{2peak}, determined in the standard ramp test were used to determine the exercise workloads for four subsequent 20 min exercise bouts, to be performed in experiments 2 and 3. Exercise training sessions of this duration have been demonstrated to be achievable by and beneficial for

CHF patients (Coats et al., 1992a; Meyer et al., 1996b; O'Connor et al., 2009), and correspond with the guidelines for exercise duration in CHF starting an exercise training programme (Giannuzzi et al., 2001; Pina et al., 2003).

Firstly, a continuous protocol (CON) was set at a constant workload corresponding to 90% VT. In addition, there were three intermittent protocols with 30s work phases interspersed with 60s recovery phases at a low workload. The intermittent exercise protocols were defined as low (LOW), medium (MED) or high (HIGH) volatility, depending on the amplitude of the work and rest phases above and below the mean workload (i.e. the workload during CON). The workload for the work phases were set as follows:-

LOW: half way between VT and RCP ($\Delta 50\% = VT + ((RCP-VT)\ 0.5)$)

MED: 110% RCP

HIGH: 110% VO_{2peak}

CON and MED were performed in Study 2, and CON, LOW and HIGH were performed in Study 3.

Figure 3.5 illustrates the protocol for calculating these workloads. The duration for all 4 exercise bouts was 20 min, and 13 work phases were completed in each intermittent bout. The recovery phase workload was 15-30 W for CHF and 15-60 W for controls, adjusted so that the average workload was equal for all four exercise bouts. CHF patients with very low exercise capacities (peak work rate (WR_{peak}) < 70W) rested without pedalling during the HIGH recovery phases. The exercise bout commenced with a rest phase, and the intensity during the first 2 work phases of MED and HIGH was progressively increased to reach the final intensity by the third work phase. In LOW the intensity was constant throughout all 13 work phases. In all tests, after 10 minutes of exercise participants rested for 2 minutes before completing the final 10 minutes of exercise. The purpose of this 2 minute break was primarily to facilitate blood sampling. The four exercise protocols were performed in random order one week apart, starting one week after the incremental exercise test.

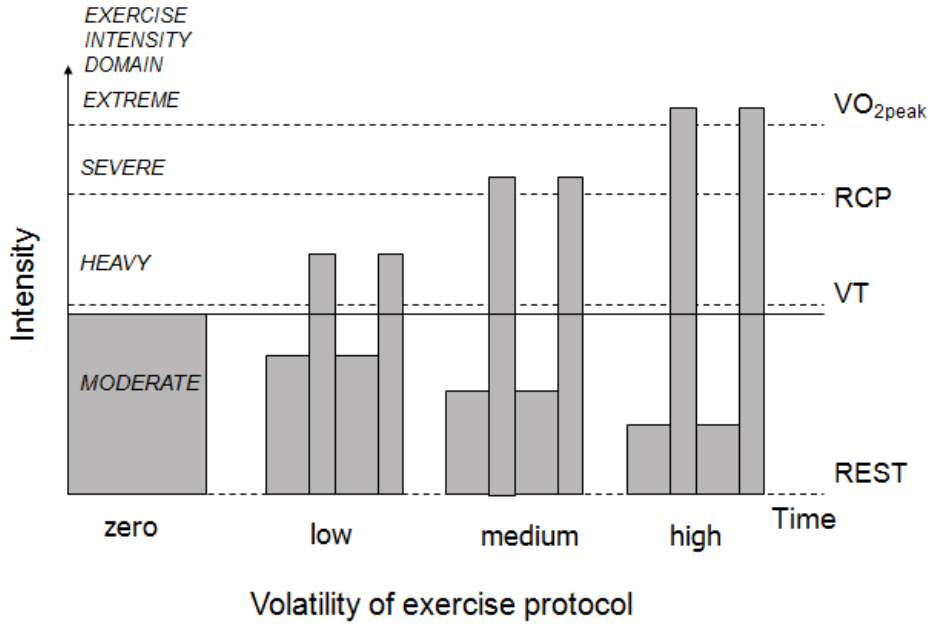


Figure 3.5: Continuous and intermittent exercise intensities based on exercise domain framework. The exercise domains are delineated by ventilatory threshold (VT), respiratory compensation point (RCP) and VO_{2peak}

3.4.1 Experimental procedures

HR was measured continuously by a 3-lead ECG. Average values were recorded for minute 4-5, 9-10, 14-15 and 19-20 during the continuous exercise bout. In the intermittent exercise bouts, HR was recorded at the end of the work phase at 4 min 30s, 9 min, 15 min and 19 min 30s, and at the end of the recovery phase at 5 min 30s, 10 min, 14 min 30s and 19 min. RPE on the Borg 6-20 Scale (as described in Section 3.3.2) was measured every 5 minutes during the continuous exercise bout, and every 5 minutes in both the work and recovery phases (at the same time points specified above for HR) during the intermittent exercise bouts. BP was recorded with a sphygmomanometer at rest, during minutes 10 and 20 of exercise, and at 2 minute intervals post exercise until it returned to resting level. Venous blood samples (5 ml) were taken from an intravenous cannula in the ante-cubital vein at rest, after 10 minutes of exercise, and 2 minutes post exercise.

3.5 Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 15). The mean ± standard deviation of the mean (SD) was calculated for descriptive statistics of participant characteristics in order to illustrate the distribution of individual scores around the mean. The mean ± standard error of the mean (SEM) were calculated for variables on which statistical significance testing was performed, in order to indicate the accuracy of the sample mean. This method is conventional in the discipline of exercise science, and allows for easy comparison with the results of previous studies. Statistical analyses specific to individual studies are described in each experimental chapter. For all statistical analyses an α level of $P \leq 0.05$ was accepted as significant.

EXPERIMENTAL CHAPTERS

CHAPTER 4: REPRODUCIBILITY OF VARIABLES DERIVED FROM MAXIMAL INCREMENTAL CYCLING TESTS IN CHF AND HEALTHY CONTROLS

4.0 Introduction

CPET is an objective means for assessing functional capacity and for prescribing exercise training in CHF patients. Repeated tests of exercise performance are used to evaluate changes in functional capacity attributable to exercise interventions as well as medical treatment and progression of the disease process. It is important that the results do not fluctuate between trials to an unacceptable degree, particularly in CHF patients who have a low functional capacity, and for whom small changes in cardiopulmonary parameters may be important (Fleg et al., 2000; Fletcher et al., 2001; Bard, 2005). The effect of familiarisation is widely acknowledged, and it is therefore recommended that individuals complete a "practice" test in advance of the real test. Improvements in performance between the first and second test of 1.2% (likely range 0.5-1.9%) have been reported in healthy populations (Hopkins et al., 2001). This effect is greater in a clinical population, particularly in a maximal test, as few patients habitually undertake exercise at this intensity, and they may be less familiar with the ergometer used. A study in which CHF performed three maximal cardiopulmonary exercise tests on a treadmill demonstrated that at least two tests should be performed, as the first test underestimated exercise capacity by 20% (Elborn et al., 1990). Nevertheless, in clinical practice a familiarisation trial is often omitted due to time and financial constraints. There are no universal criteria for reproducibility, but the American Heart Association recommend that VO_{2peak} should vary by less than 10% on separate days for it to be considered reproducible, while exercise duration should vary by less than 60s (i.e. 10% of a 10 minute test) (Fleg et al., 2000). Good reproducibility (differences of 2-7% between 2 tests) of VT and VO_{2peak} in cycle ergometry has been reported in elderly patients with both mild-moderate and severe CHF (Simonton et al., 1988; Cohen-Solal et al., 1991; Meyer et al., 1997c; Marburger et al., 1998). However, in all of these studies patients had already performed the exercise tests before, either during a separate study, or as a practice test on a separate day. Up-to-date studies report a greater variability in repeated exercise tests. The HF-ACTION trial reported a 9% difference, with approximately half of patients increasing and half decreasing their VO_{2peak} in a second test (Bensimhon et al., 2008). Results from the PEERLES-HF trial demonstrate that patients who do not achieve a peak RER $\geq$ 1.05 are more likely to increase their VO_{2peak} in a repeat test (Keteyian et al., 2010). The authors suggest that the variability between tests should be assumed to be approximately 6%.

Exercise test results are also used to prescribe subsequent exercise training. Determining the appropriate intensity in this population is important for safety reasons as well as for achieving optimal adaptations, but is not straightforward. Exercise training workload is often determined from the identification of VO_{2peak}, although several authors now recommend using VT to guide exercise intensity. VT reflects the buffering of bicarbonate in response to a rise in Lac, and represents the highest work rate that can be sustained for a prolonged period of exercise. It is suggested that an intensity within 10% of VT is safe, effective and able to be maintained over a prolonged exercise period (Gordon and Scott, 1995; Strzelczyk et al., 2001; Meyer et al., 2005a).

In the 1990s Meyer demonstrated that high intensity intermittent exercise was an alternative method of training for CHF (Meyer et al., 1996b; Meyer et al., 1997b), and recent studies have reinforced this finding (Dimopoulos et al., 2006; Roditis et al., 2007). These studies have used different methods for defining intermittent intensities, resulting in variations in the exercise dose. There is no universally accepted set work rate for interval training, but CPET provides an objective measure from which to set training intensities aligned to robust physiological parameters (Meyer et al., 2005b). In this model, interval training intensities at or close to VO_{2max} work rate are applied, as demonstrated in studies comparing acute physiological responses to interval and continuous exercise (Astrand et al., 1960a; Poole and Gaesser, 1985; Gorostiaga et al., 1991; Billat, 2001). Some studies follow a traditional method of applying workloads of 100% VO_{2peak} work rate (Dimopoulos et al., 2006) (Roditis et al., 2007). However, Meyer et al. (1997) introduced a novel method, setting the intermittent training intensity at 50% WR_{peak} achieved on a "maximum short time exercise capacity" test (steep test). This protocol is included in ESC recommendations for exercise training in CHF, despite limited scientific verification, and has been used in exercise training studies for CHF (Sabelis et al., 2004; Kemps et al., 2008) and other clinical populations (Vogiatzis et al., 2002; Puhan et al., 2006; De Backer et al., 2007). Meyer proposed that this test, which has increments of 25W every 10s, and lasts only 30-120s, is appropriate as it tests "muscle strength" and "anaerobic capacity", both of which are relevant for short high intensity exercise bouts, whereas a standard incremental exercise test does not measure these, and may underestimate the training load. In fact neither "muscle strength" nor "anaerobic capacity" is either defined or measured during this

test and there is no information on its reproducibility. It is not clear if the rationale for the steep ramp test is justifiable, or how workloads compare with those derived from a standard test. Furthermore, since the test has not been used in non-clinical populations, there is no information about whether the test would prescribe different relative exercise intensities in healthy individuals compared with CHF patients.

It is proposed that the exercise intensity domains, delineated by the gas exchange thresholds (VT and RCP) and VO_{2peak} (see section 2.6.4), may enable more precise exercise training guidelines to be applied. Although maximal CPET is becoming more routinely used both for diagnosis and exercise prescription, this method of exercise prescription has not yet been established in CHF. The reproducibility of these thresholds is important for accurate exercise prescription, as well as for assessing changes in functional capacity following an intervention. Analytical goals are more useful than the significance of hypothesis tests to determine the acceptable level of measurement error in repeated tests (Atkinson and Nevill, 1998). In the context of this thesis, that means deciding on a value that would indicate unacceptable test-retest reproducibility in order to accurately prescribe exercise intensity, and to measure changes following an exercise training intervention.

VO_{2peak} values for NYHA class II and III CHF patients are generally between 12 and 19 $ml.kg^{-1}.min^{-1}$ (Cohen-Solal et al., 1990). The Weber classification includes VT values in addition to VO_{2peak} values (Class B: VO_{2peak} 10.1-15.9, VT 8-11 $ml.kg^{-1}.min^{-1}$; class C: VO_{2peak} 16-20, VT 11-14 $ml.kg^{-1}.min^{-1}$) (Weber et al., 1982). The Cochrane Review evaluated 29 randomised controlled trials, with 1126 patients in NYHA class II and III. Exercise training significantly increased VO_{2peak} by 2.16 $ml.kg^{-1}.min^{-1}$ (95% CI 2.82 to 1.49 $ml.kg^{-1}.min^{-1}$) and WR_{peak} by 15 W (95% CI 18 – 13 W). A systematic quantitative review reports a 13% (+2.6 $ml.kg^{-1}.min^{-1}$) increase in VO_{2peak} and a 17% (+1.9 $ml.kg^{-1}.min^{-1}$) increase in VO_2 at VT following exercise training (van Tol et al., 2006). Given these values, this thesis accepts the American Heart Association guidelines that a repeat measurement for VO_2 at peak exercise, and at VT and RCP, > 10% would indicate unacceptable test-retest reproducibility a) in terms of evaluating the effectiveness of a training intervention and b) for calculating accurate exercise training intensities.

A few studies have previously reported reproducibility of cardiopulmonary variables in CHF, but these have used different exercise protocols, different methods for determining the variables, and some have included familiarisation trials. In addition, the statistical methods used to assess reproducibility have been limited. Furthermore, no studies have reported the reproducibility of RCP, oxygen uptake-work rate relationship ($\Delta VO_2/\Delta WR$) or V_E/VCO_2 slope. This study specifically examines the protocols to be used in subsequent studies in this thesis, and its purpose is (a) to examine the reproducibility of physiological parameters measured during a standard and a steep incremental cycle ergometer test, and (b) to compare the exercise training workloads derived from a standard and steep test in CHF patients and healthy controls. The statistical tests have been chosen to allow:-

1) comparisons of the mean to detect systematic bias

2) description of "relative reliability" using the intraclass correlation coefficients (degree to which individuals maintain their position in a sample with repeated measurements)

3) detection of heteroscedasticity, if present, using Bland and Altman's 95% LOA (existing relationship between the error and the size of the measured value) and description of "absolute reliability" (degree to which repeated measurements vary for individuals) (Bland and Altman, 1986; Atkinson and Nevill, 1998; Hopkins, 2000a; Hopkins, 2000b).

In addition a practical analytical goal of > 10% difference between tests has been chosen to indicate unacceptable reproducibility.

Hypotheses

a) Physiological parameters measured in duplicate standard and steep incremental cycle ergometer tests performed one week apart by CHF and control participants will show acceptable reproducibility in terms of statistical significance, re-test correlation and LOA, and a difference < 10% between tests.

b) Intermittent exercise training workloads derived from a steep test will differ to those derived from a standard test in CHF and control participants.

4.1 Methods

4.1.1 Participants

Ethical procedures and patient inclusion and exclusion criteria were adhered to as detailed in the General Methods. Ten chronic heart failure (CHF) patients (8 men and 2 women) in NYHA class II (n=8) or III (n=2) (mean age 75 ± 8 years) and 7 healthy controls (4 men and 3 women; mean age 67 ± 7 years) were studied. The aetiology of the CHF patients was ischaemic cardiomyopathy (n=5), idiopathic dilated cardiomyopathy (n=5). All patients had been in a stable condition for the preceding 4 weeks, with unchanged medication doses: beta-blocker (9), diuretic (8), ace inhibitor (4) angiotensin receptor antagonist (4), anti-arrhythmic (3), calcium-channel blocker (2). Control participants were not on any medication.

4.1.2 Experimental design

General methods were followed as described in Chapter 3.

4.1.3 Data analysis

Following the removal of outlying breaths (value ± 500 ml different from the previous and following breaths), breath-by–breath respiratory gas exchange variables (VO_2, VCO_2, V_E) were interpolated to give second-by-second values. VO_{2peak} in the standard test protocol was expressed as the highest value from a 30s moving average during the final stage of, or within 30s of completion of the exercise test. VO_{2peak} in the steep test protocol was expressed as the highest value from a 10s moving average. The highest value from a 10s moving average was also recorded in the standard test, in order to compare the two peak values. From the standard test data, VT was identified by the V-slope method (Beaver et al., 1986). RCP was determined as the point when ventilation increased disproportionately to carbon dioxide output. Both VT and RCP were confirmed by plots of the ventilatory equivalents and end tidal pressure for oxygen and carbon dioxide (Cooper and Storer, 2001; Wasserman et al., 2005). Figure 4.1 illustrates the determination of VT & RCP from the data of one CHF.

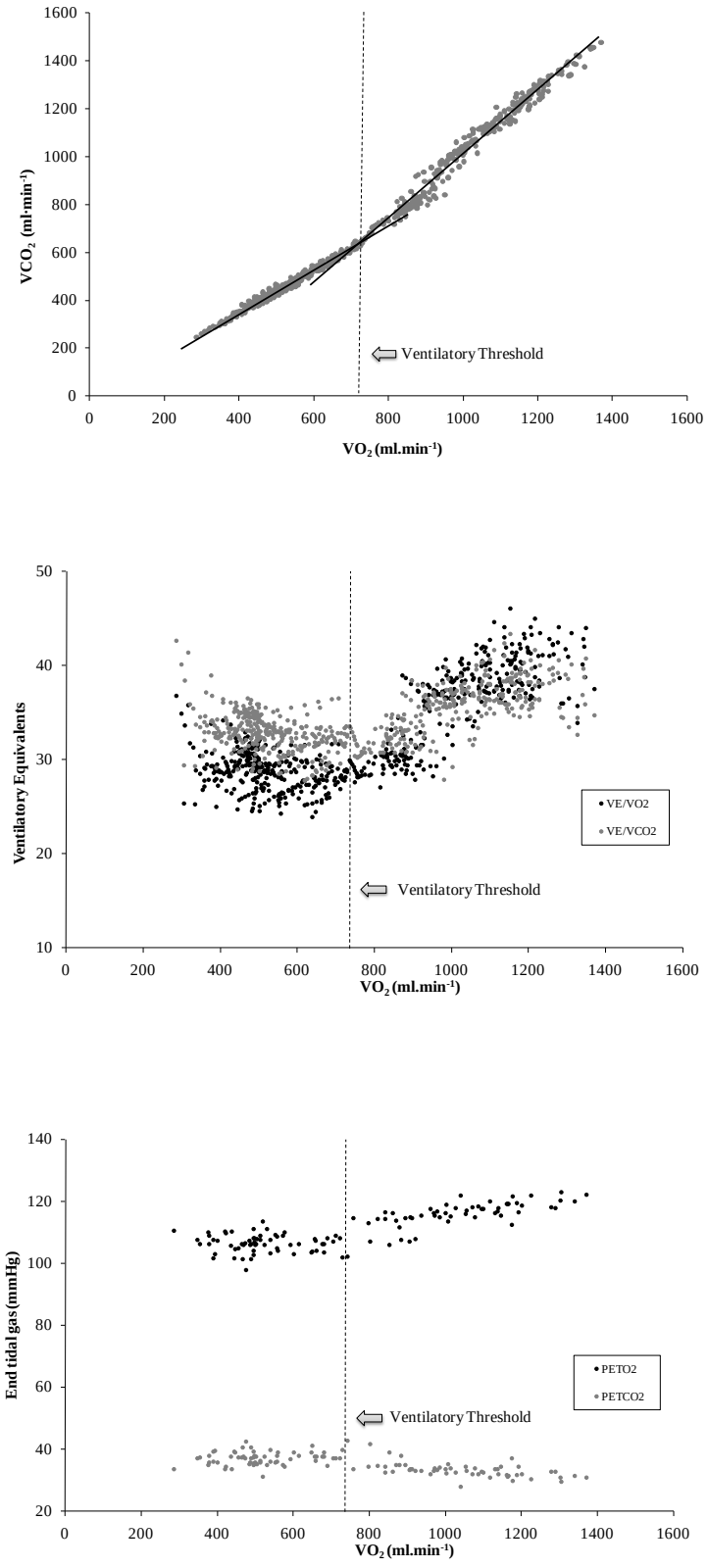


Figure 4.1: Determination of ventilatory threshold in one CHF patient from plots of VCO_2 and VO_2, ventilatory equivalents (V_E/ VO_2 and V_E/ VCO_2) and end tidal gas ($PETO_2$ and $PETCO_2$)

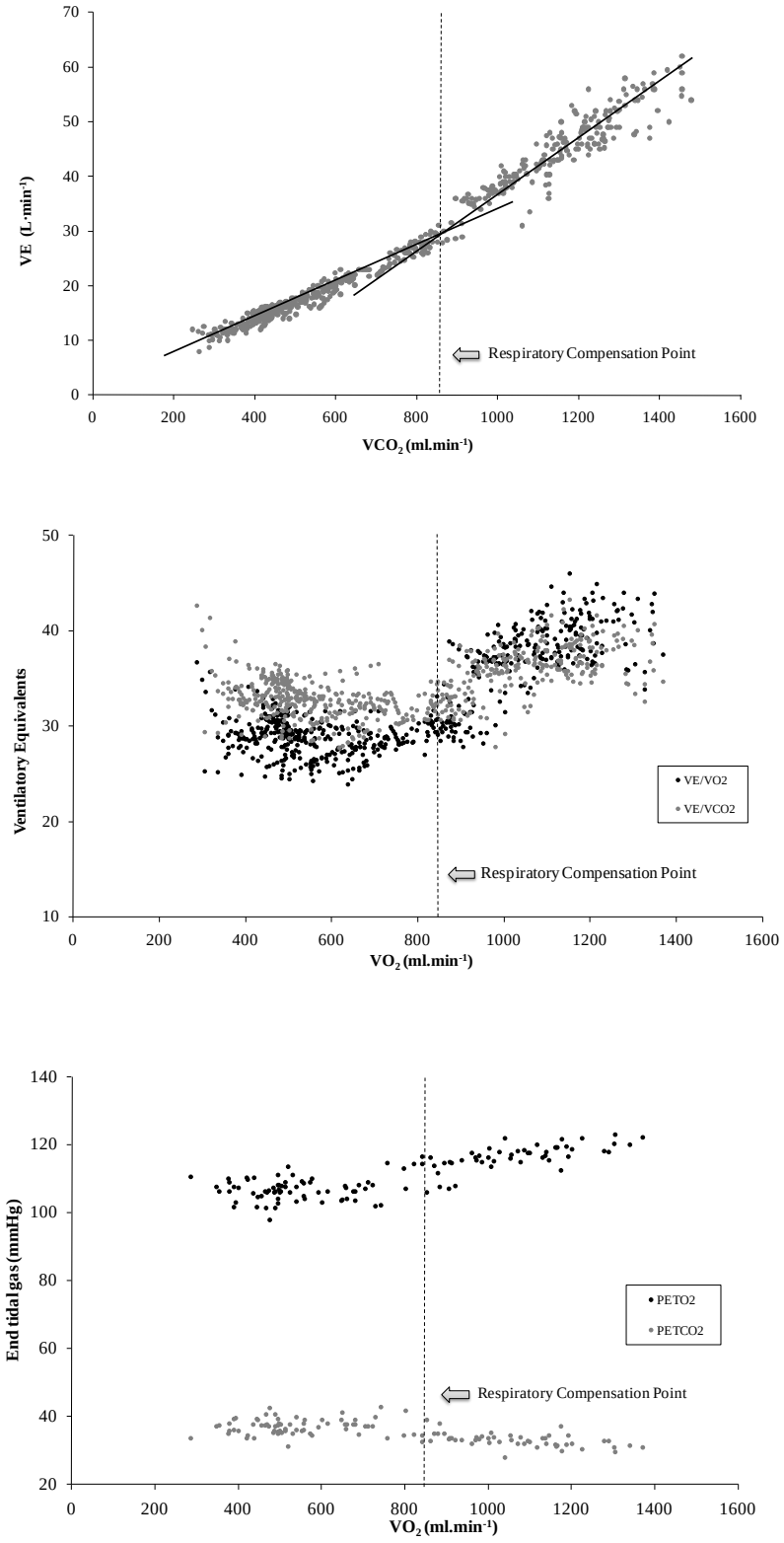


Figure 4.2: Determination of respiratory compensation point in one CHF patient from plots of V_E and VCO_2, ventilatory equivalents (V_E/ VO_2 and V_E/ VCO_2), and end tidal gas ($PETO_2$ and $PETCO_2$)

VT and RCP were identified by two independent observers. If there was no consensus, a third independent observer decided on the values to be used. This occurred in 4 of the 34 tests. The oxygen uptake-work rate relationship ($\Delta VO_2/\Delta WR$) and V_E/VCO_2 slope were calculated by linear regression from the data from 2 minutes from the start of exercise until RCP, i.e. the linear part of the slope. HR_{peak} was the highest heart rate recorded in the final stage of the standard test. WR_{peak} was the highest workload measured during a completed stage in each of the tests.

4.1.3.1 Calculation of continuous and intermittent exercise workloads

The workloads for CON and for LOW, MED and HIGH were calculated as described in section 2.4. Work rate at VT, RCP and $\dot{V}O_{2\,peak}$ were calculated via 2 different methods: (a) via linear regression from the $\Delta VO_2/\Delta WR$ equation and (b) from the work rate corresponding to the test stage at which VT, RCP and $\dot{V}O_{2\,peak}$ were identified. The value of 2/3 of the ramp rate was deducted in both (a) and (b) to allow for the lag in ventilatory response to each workload (Whipp et al., 1981; Davis et al., 1982). The method that showed the greatest reproducibility was to be used subsequently. Workloads for intermittent exercise training according to the protocol described by (Meyer et al., 1997b) were calculated as 50% of the steep test WR_{peak} (STEEP), with rest phases of 15W, and these were compared with those derived from the standard test data (LOW, MED, HIGH).

4.1.4 Statistical analysis

Data from CHF and controls were analysed together (n=17) to examine the reproducibility of the steep and the standard tests. Data from CHF only (n=10) was then used to examine the reproducibility in this patient population. There was insufficient data from the control participants to perform a separate analysis on this group (n=7). The distribution of individual mean values and absolute differences between the 2 tests were examined for normality using the Kolmogorov-Smirnov test and Q-Q plots. Student's t-test for paired data were carried to determine the difference (change in the mean) in VO_{2peak}, VT, RCP, $\Delta VO_2/\Delta WR$, V_E/VCO_2 slope, HR_{peak} and WR_{peak} between test 1 and test 2. Intraclass correlation coefficients (ICC) were calculated and used to assess the significance of relationships between test 1 and 2, and

the corresponding 95% confidence intervals of the mean for each ICC were calculated (Hopkins, 2000b). LOA (Bland and Altman, 1986) were used to assess the agreement between variables from the first and second test of both the standard and the steep test. In addition, LOA were used to assess the agreement in VO_{2peak} in the 2nd standard and steep tests. No heteroscedasticity was detected, and the 95% LOA are reported as mean ± 2SD. All other data are reported as mean and SEM unless stated otherwise.

4.2 Results

Participant characteristics are shown in Table 4.1.

Table 4.1: Characteristics (mean ± SD) of CHF patients and healthy controls

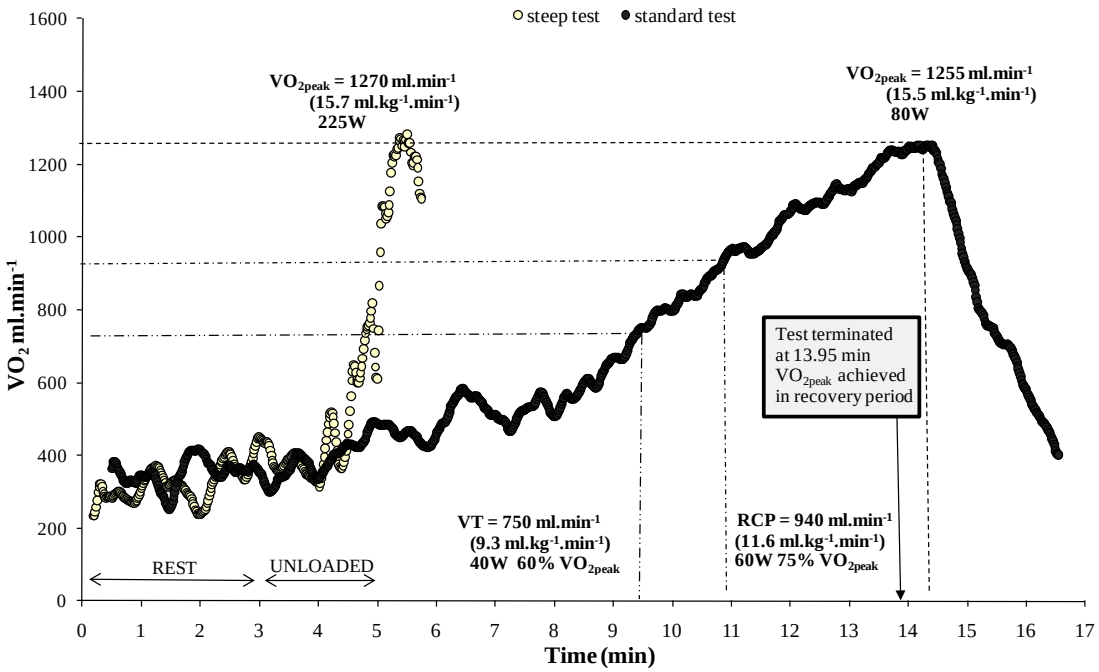
Characteristic	CHF (n=10)	Controls (n=7)
Age (years)	75 ± 8	67 ± 7
Male/ Female	8/2	4/3
Height (cm)	172 ± 11	173 ± 10
Body Mass (kg)	86 ± 18	79 ± 13
NYHA Class II/III	8/2	-
Ejection Fraction (%)	36 ± 9	69 ± 7
Aetiology (ischaemic/dilated cardiomyopathy)	7/3	-
Co-morbidities		
COPD	1	-
Diabetes	1	-
Hypertension	1	-
Medication		
ACE inhibitor	4	-
Angiotensin II receptor blocker	4	-
Anti-arrhythmic	3	-
β blocker	9	-
Calcium channel blocker	2	-
Diuretic	8	-

The data were normally distributed. VO_{2peak} and VT were identified in both standard tests in 9 CHF, V_E/VCO_2 slope, $\Delta VO2/\Delta WR$ and HR_{peak} in 8 CHF, and RCP in 7 CHF. Complete data from both standard tests was collected for 5 controls. In the steep test, VO_{2peak} was identified in 9 CHF and 7 controls. WR_{peak} was identified in all

participants in all tests. The distribution of individual mean values and absolute differences between the 2 tests were normally distributed for all variables.

When asked to give their subjective RPE by pointing to the Borg 6-20 scale during the exercise test, the majority of patients were unable to do this without slowing their pedalling rate or stopping completely, and/or talking, thus compromising the exercise test results. It was therefore decided not to take this measurement.

An example of the VO_2 response to the standard and steep tests in one CHF and one control participant is illustrated in Figure 4.3. Figure 4.4 shows the V_E/VCO_{2slope} in the same CHF patient and control participant.



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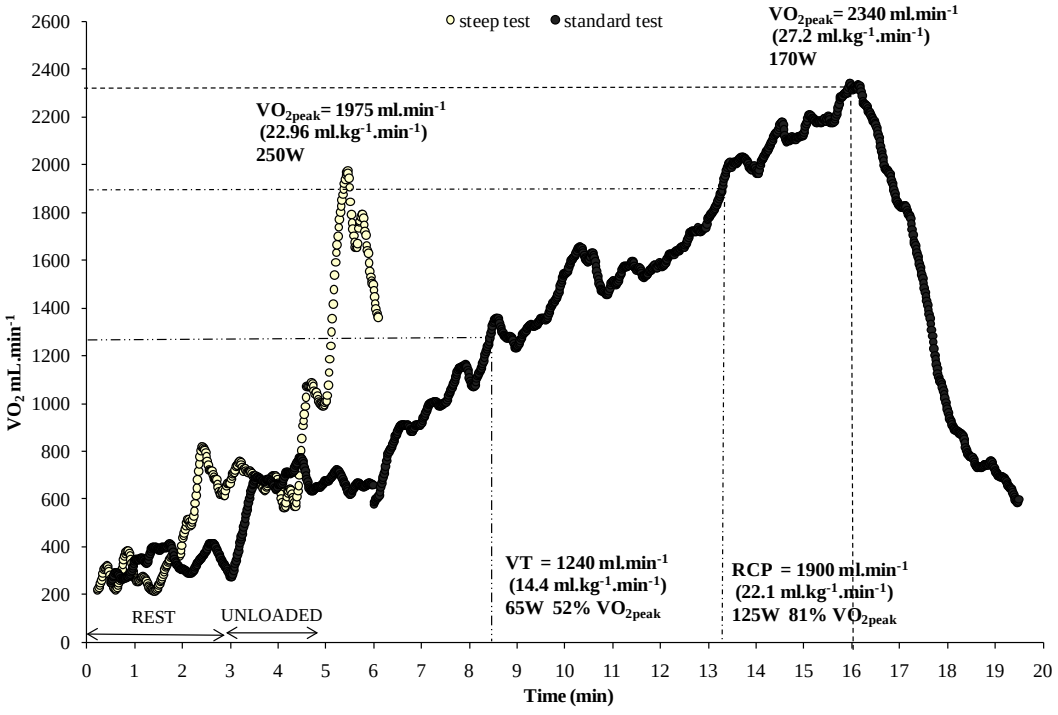


B

Figure 4.3: Oxygen uptake response to standard & steep Test in (A) CHF (male, 66 years, body mass 81 kg) **and (B) Control** (male, 62 years, body mass 86 kg). VO_{2peak}, RCP and VT are shown.

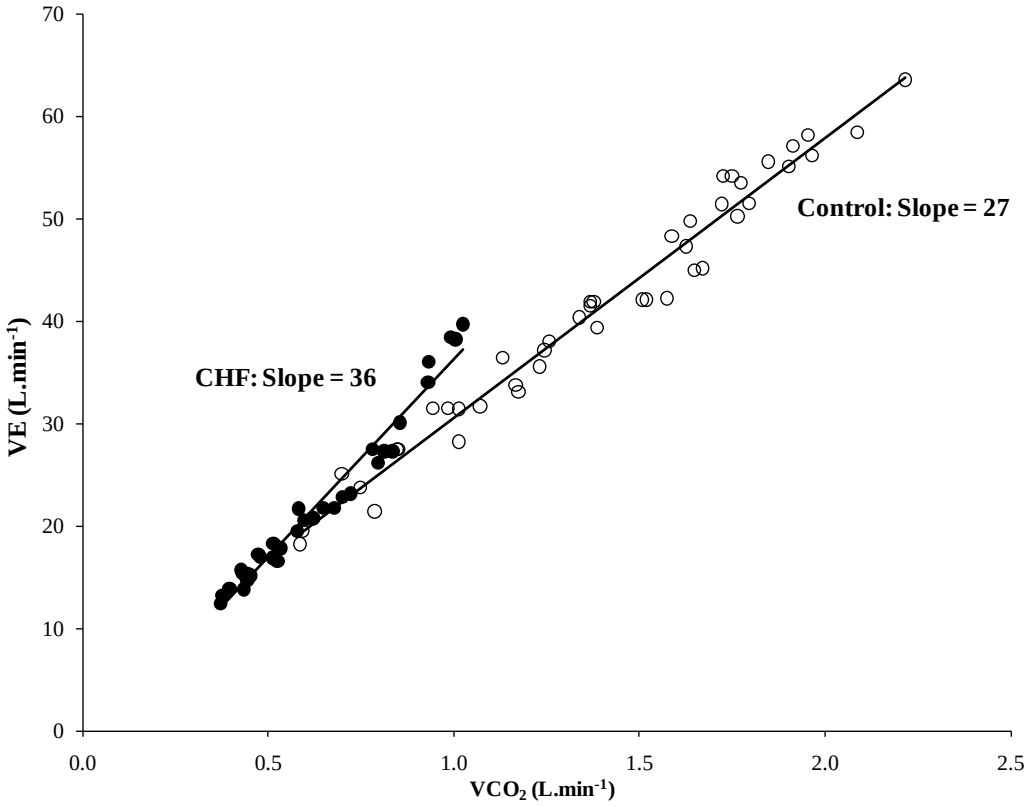


Figure 4.4: V_E/VCO_2 slope in a CHF (male, 66 years, body mass 81 kg) and Control (male, 62 years, body mass 86 kg).

4.2.1 Reproducibility of standard test

Paired t-tests revealed no significant differences in VO_2 at VT or RCP, or in $\Delta VO_2/\Delta WR$ or V_E/VCO_2 slope between test 1 and test 2 ($P > 0.05$), but VO_{2peak} ($P = 0.008$), WR_{peak} ($P = 0.047$) and HR_{peak} ($P = 0.048$) were all significantly higher in test 2. Mean RER values at peak exercise for CHF and controls were 1.13 ± 0.05 and 1.22 ± 0.10 for test 1 and 1.10 ± 0.07 and 1.26 ± 0.18 respectively. All participants reached a peak RER > 1.0, with 2/10 CHF and 5/7 controls reaching values > 1.15 in both tests, indicating that near-maximal, if not maximal, effort was achieved. Table 4.2 displays the data for the two standard tests for all participants (n=16). Using the simple goal that test 2 should differ by no more than 10% to test 1, table 4.1 shows that all variables met this criteria. However, in test 2 VO_{2peak} increased in 79% participants (increase > 10% in half of these), whereas it remained the same, or decreased slightly, in 21% participants.

Table 4.2: Mean ± SEM data for CHF and Controls for standard test 1 and test 2. Mean values ± 10% different to test 1 are also shown.

	$VO_{2\ peak}$ ($ml.kg^{-1}.min^{-1}$)	VT ($ml.kg^{-1}.min^{-1}$)	RCP ($ml.kg^{-1}.min^{-1}$)	$\Delta VO_2/\Delta WR$ ($ml.min^{-1}.W^{-1}$)	V_E/VCO_2slope	WR_{peak} (W)	HR_{peak} ($beats.min^{-1}$)
Test 1	16.6 ± 1.7	10.8 ± 0.9	15.6 ± 1.5	9.2 ± 0.6	29.9 ± 1.3	106 ± 12	117 ± 8
Test 2	17.9 ± 1.7*	10.8 ± 0.8	15.6 ± 1.6	9.4 ± 0.5	30.3 ± 1.4	112 ± 13*	120 ± 8*
Test 1 ± 10%	15.3 – 18.7	9.59 – 11.72	14.4 – 17.54	8.3 – 10.2	26.9 – 32.8	93 - 114	105 - 128
* Test 1 and Test 2 significantly different ($P < 0.05$)							

Table 4.3: Reproducibility data and confidence intervals (CI) for CHF and Controls for standard tests 1 and 2.

	VO_{2peak} ($ml.kg^{-1}.min^{-1}$)	VT ($ml.kg^{-1}.min^{-1}$)	RCP ($ml.kg^{-1}.min^{-1}$)	$\Delta VO_2/\Delta WR$ ($ml.min^{-1}.W^{-1}$)	V_E/VCO_2 slope	WR_{peak} (W)	HR_{peak} $beats.\ min^{-1}$
ICC values	0.97	0.96	0.98	0.58	0.80	0.99	0.99
(CI)	(0.93-0.99)	(0.89-0.98)	(0.95-0.99)	(0.12-0.84)	(0.53-0.93)	(0.97-0.99)	(0.96-0.99)
LOA bias	1.57	0.00	0.27	0.18	0.44	6	3
random error	1.88	1.02	1.33	1.64	2.99	8	5
(CI)	(-2.12-5.26)	(-2.00-1.99)	(-2.34-2.88)	(-3.04-3.39)	(-5.4-6.3)	(9-21)	(-7-13)

The relationships between cardiopulmonary variables in standard tests 1 and 2 are illustrated in Figures 4.5 – 4.7.

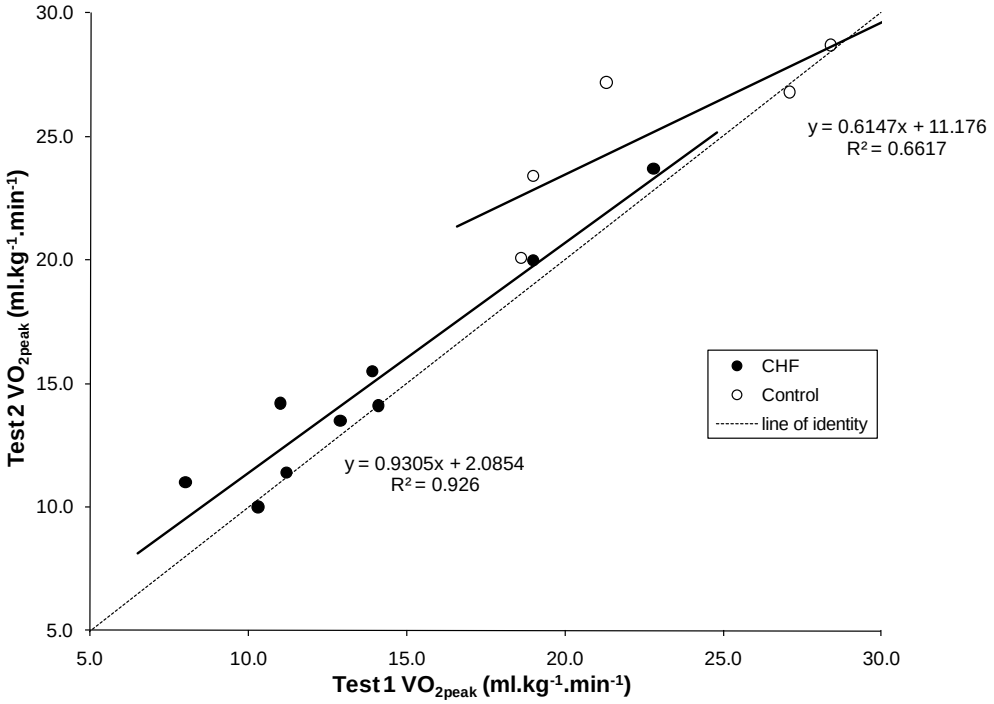


Figure 4.5: Reproducibility of VO_{2peak} in standard tests 1 and 2

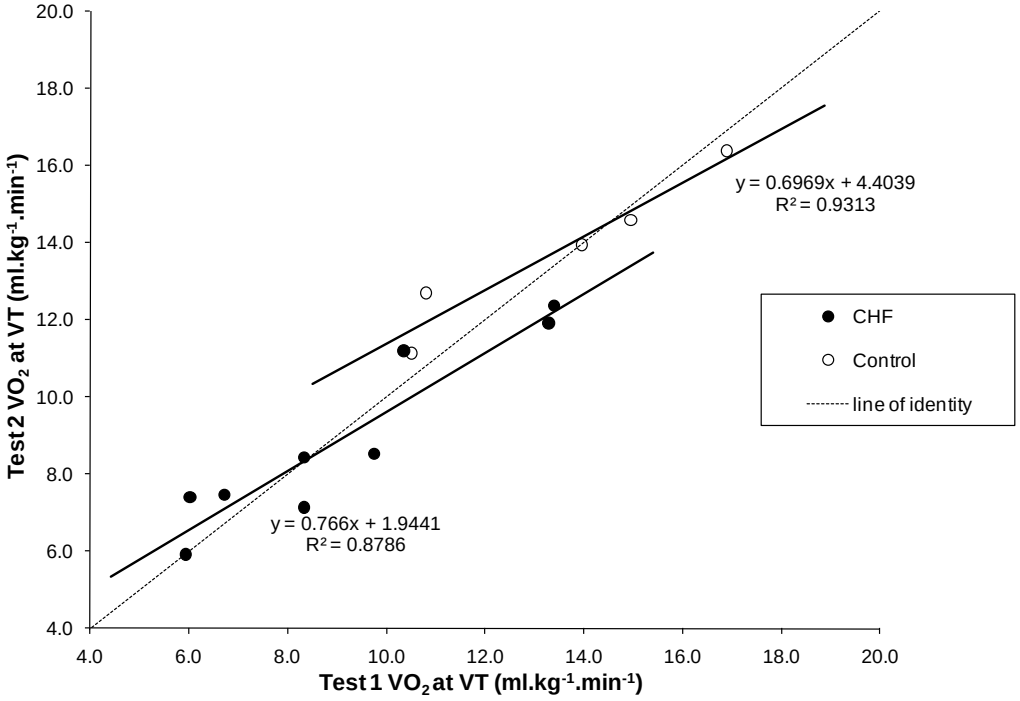


Figure 4.6: Reproducibility of VO_2 at VT in standard tests 1 and 2

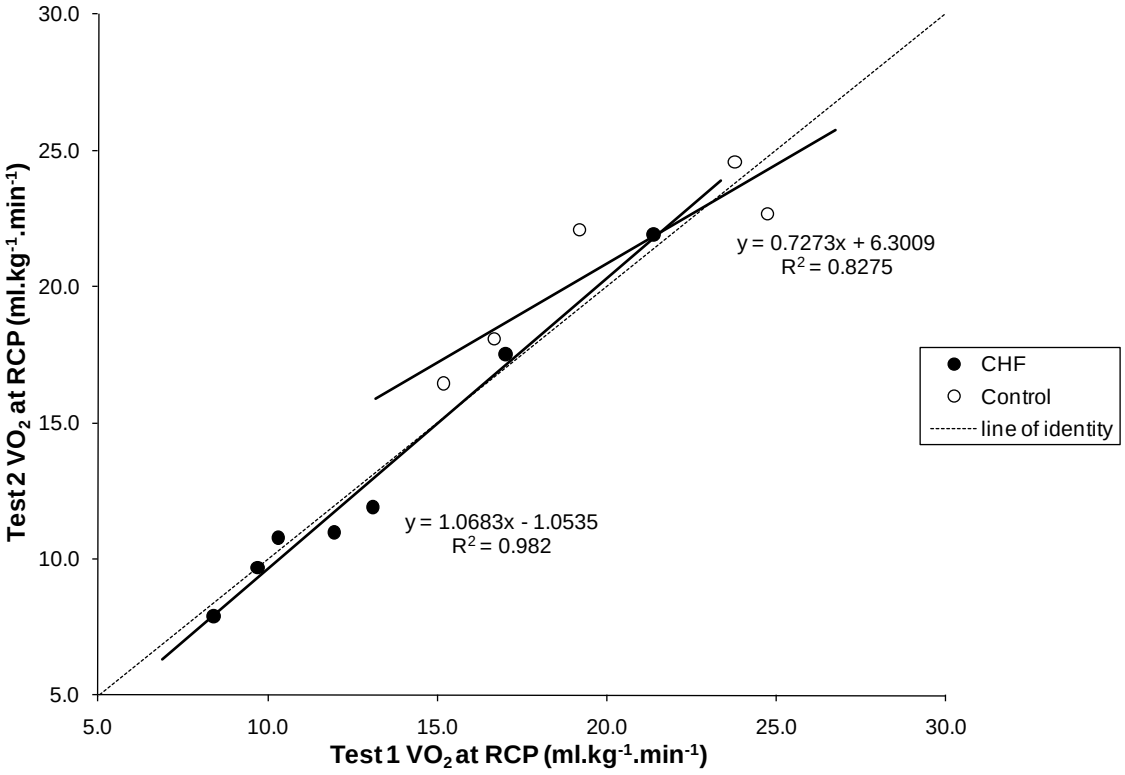
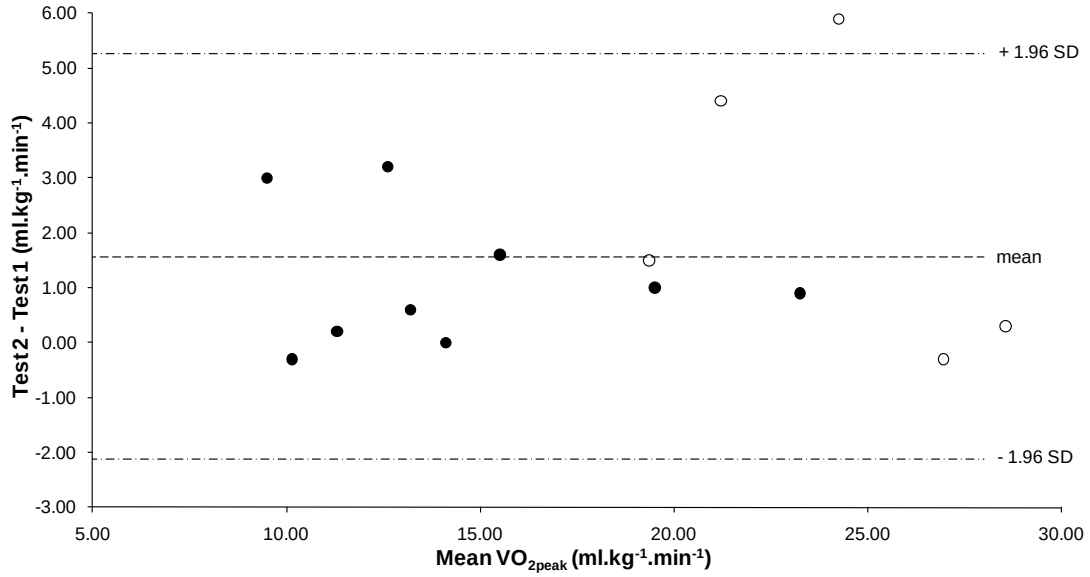
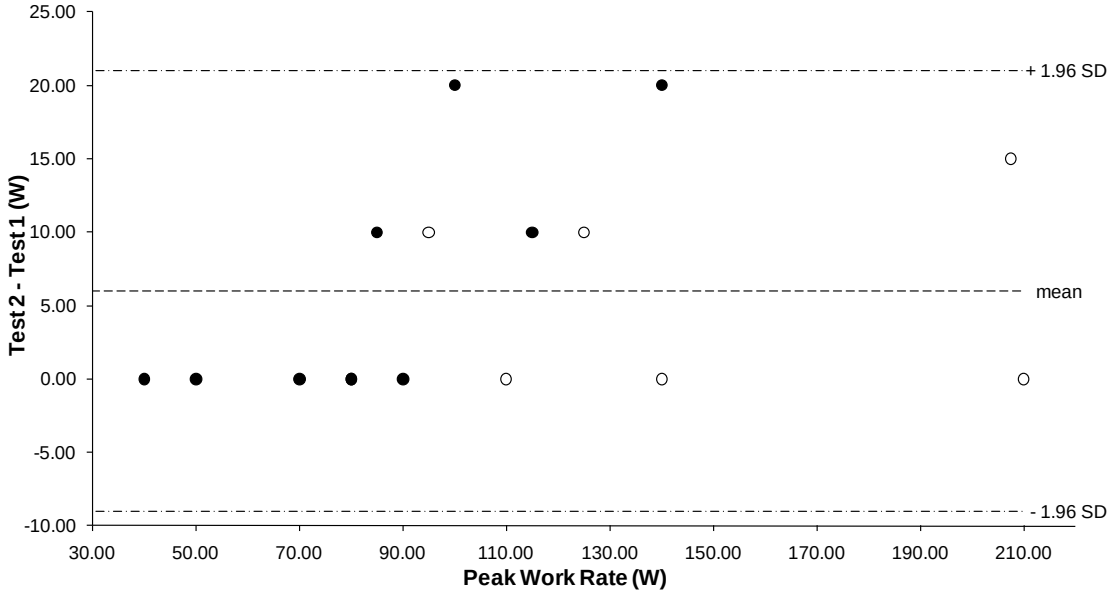


Figure 4.7: Reproducibility of VO_2 at RCP in standard tests 1 and 2

There was no relation between the error (difference) and the size of the measured value (mean), (i.e. the data was homoscedastic), and thus the reliability was assessed using the 95% absolute LOA (Figure 4.8). The results of the tests for reproducibility are shown in Table 4.3, and indicate high reproducibility for VO_2 at VT and RCP, and for WR_{peak} and HR_{peak}, with ICC values $\geq$ 0.96, and low systematic bias (change in the mean) and random error (standard deviation of the mean difference). Nine participants reached the same WR_{peak} in test 2, while 7 participants increased WR_{peak} by 10-20W. Although the ICC for VO_{2peak} was high (0.97), there was a 9% increase in the mean (CI 3 – 15%) in test 2 and the systematic bias and random error were higher than for VO_2 at VT and RCP, indicating lower reproducibility. ICC was low (0.58) for $\Delta VO_2/\Delta WR$, theefore it was decided that method b should be used to calculate work rate at the different thresholds. The systematic bias and random error for work rate at VT and RCP were - 1 ± 6W and 2 ± 12W, giving 95% absolute LOA of between -13 and 11W for VT and between -21 and 25W for RCP.

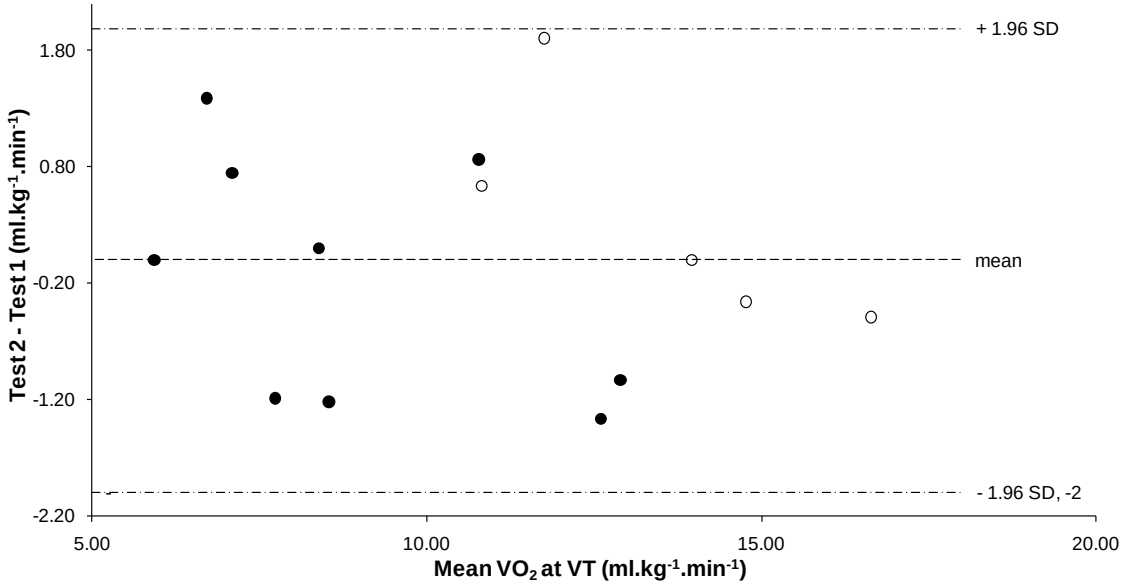


A

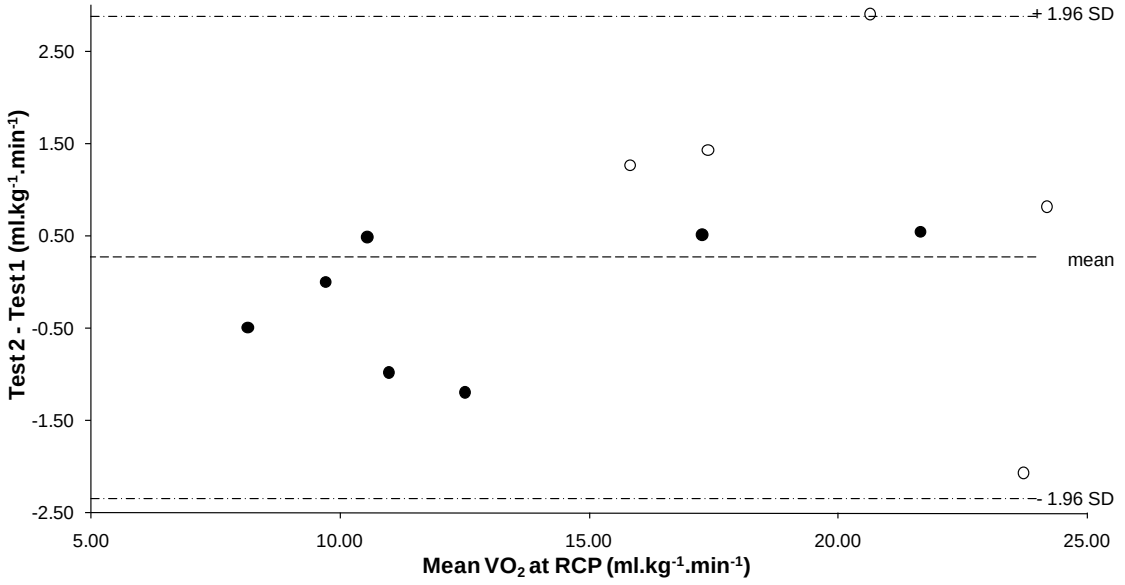


B

Figure 4.8: Bland and Altman plots of the absolute differences (test 2–test 1) in VO_{2peak} (A) and WR_{peak} (B) versus mean differences in the standard tests (CHF closed circles, Control open circles).



C



D

Figure 4.9: Bland and Altman plots of the absolute differences (test 2–test 1) in VO_2 at VT (C) and VO_2 at RCP (D) versus mean differences in the standard tests (CHF closed circles, Control open circles).

4.2.1.1 Reproducibility of standard test for CHF patients

Paired t-tests revealed no significant differences in VO_2 at VT or RCP, $\Delta VO_2/\Delta WR$, V_E/VCO_2 slope, WR_{peak} or HR_{peak} between test 1 and test 2 ($P > 0.05$), but VO_{2peak} was significantly higher in test 2 ($P = 0.026$). Table 4.4 displays the data for the two standard tests for CHF patients. Using the simple goal that test 2 should differ by no more than 10% to test 1, table 4.4 shows that all variables met this criteria in CHF.

The differences between test 1 and 2 were normally distributed for all variables, and thus the reproducibility was assessed using the 95% absolute LOA (Figure 4.9). The results are displayed in Table 4.5. As with the combined CHF and control data, VO_2 at VT and RCP, WR_{peak} and HR_{peak} showed high reproducibility, but VO_{2peak} was less reproducible, and increased between the 1st and 2nd tests. Similarly, $\Delta VO_2/\Delta WR$ and V_E/VCO_2 slope also showed poor reproducibility. Work rate at VT and RCP varied between tests to a similar extent as in the whole group data. The systematic bias and random error for work rate at VT and RCP were 3 ± 5W and 4 ± 11W, giving 95% absolute LOA of between -13 and 7W for VT and between -18 and 27W for RCP.

Table 4.4: Mean (± SEM) data for CHF for standard test 1 and test 2. Mean values ± 10% different to test 1 are also shown.

	$VO_{2\ peak}$ ($ml.kg^{-1}.min^{-1}$)	VT ($ml.kg^{-1}.min^{-1}$)	RCP ($ml.kg^{-1}.min^{-1}$)	$\Delta VO_2/\Delta WR$ ($ml.min^{-1}.W^{-1}$)	V_E/VCO_2slope	WR_{peak} (W)	HR_{peak} ($beats.min^{-1}$)
Test 1	13.6 ± 1.5	9.2 ± 0.9	13.2 ± 1.7	9.2 ± 0.8	31.2 ± 1.1	82 ± 8	100 ± 6
Test 2	14.8 ± 1.5 *	9.0 ± 0.8	13.1 ± 1.9	9.1 ± 0.7	32.7 ±1.3	88 ± 10	104 ± 5
Test 1 ± 10%	12.2 – 15.0	8.3 – 10.1	11.9 – 14.5	8.3 – 10.1	28.0 – 34.3	74 – 90	90 – 110
* Test 1 and Test 2 significantly different ($P \leq 0.05$)							

Table 4.5: Reproducibility data and confidence intervals (CI) for CHF for standard test 1 and test 2.

	VO_{2peak} ($ml.kg^{-1}.min^{-1}$)	VT ($ml.kg^{-1}.min^{-1}$)	RCP ($ml.kg^{-1}.min^{-1}$)	$\Delta VO_2/\Delta WR$ ($ml.min^{-1}.W^{-1}$)	V_E/VCO_2 slope	WR_{peak} (W)	HR_{peak} $beats.\ min^{-1}$
ICC values	0.96	0.93	0.99	0.59	0.67	0.96	0.96
(CI)	(0.87-0.99)	(0.75-0.98)	(0.94-0.99)	(0.05-0.88)	(0.08-0.91)	(0.87-0.99)	(0.84-0.99)
LOA bias	1.13	0.19	0.16	-0.15	1.56	6	4
random error	1.25	1.05	0.74	1.82	2.79	9	5
(CI)	(-1.32-3.59)	(-2.24-1.86)	(-1.60-1.28)	(-3.72-3.42)	(-3.92-7.03)	(11-23)	(-6-13)

4.2.2 Reproducibility of steep test

Table 4.6 displays the steep test data for CHF and controls together, and CHF alone. No significant differences were found ($P > 0.05$). Mean peak RER was 0.98 ± 0.02 in CHF and 1.08 ± 0.08 in controls.

Table 4.6: Mean ± SEM data for CHF and controls for steep test 1 and test 2. Mean values ± 10% different to test 1 are also shown.

	CHF and controls		**CHF**	
	$VO_{2\ peak}$ ($ml.kg^{-1}.min^{-1}$)	**WR_{peak} (W)**	**$VO_{2\ peak}$ ($ml.kg^{-1}.min^{-1}$)**	**WR_{peak} (W)**
Test 1	18.6 ± 1.7	207 ± 15	14.2 ± 1.6	188 ± 17
Test 2	18.7 ± 1.5	210 ± 16	15.2 ± 1.0	193 ± 18
Test 1 ± 10%	16.7 – 20.5	186 - 228	12.8 – 15.6	169 - 207

The relationships between peak values in steep tests 1 and 2 are illustrated in Figures 4.9 - 4.10. The differences between test 1 and 2 were normally distributed for all variables and therefore the reproducibility was assessed using the 95% absolute LOA (Figure 4.11). Reproducibility data for CHF and controls together, and CHF alone, are displayed in Table 4.7. VO_{2peak} was less reproducible than in the standard test, in the whole group and in CHF patients in particular. Although the systematic bias was smaller, the random error, and thus the 95 % absolute LOA, was greater (All: -4.07 – 5.37 $ml.kg^{-1}.min^{-1}$; CHF: -4.77 – 6.88 $ml.kg^{-1}.min^{-1}$). The 95% absolute LOA of WR_{peak} in the steep test were similar in CHF and controls together, and CHF alone. These values are higher than in the standard test, reflecting the greater increments in work rate in the steep test.

Table 4.7: Reproducibility data and confidence intervals (CI) for CHF and controls for steep test 1 and test 2.

	CHF and Controls		**CHF**	
	VO_{2peak} ($ml.kg^{-1}.min^{-1}$)	WR_{peak} (W)	VO_{2peak} ($ml.kg^{-1}.min^{-1}$)	WR_{peak} (W)
ICC values	0.92	0.93	0.74	0.93
(CI)	(0.82-0.97)	(0.84-0.97)	(0.27-0.92)	(0.84-0.98)
LOA bias	0.65	-3	0.96	5
random error	2.41	23	2.92	20
(CI)	(-4.07-5.37)	(-43 – 48)	(-4.77-6.88)	(-34-44)

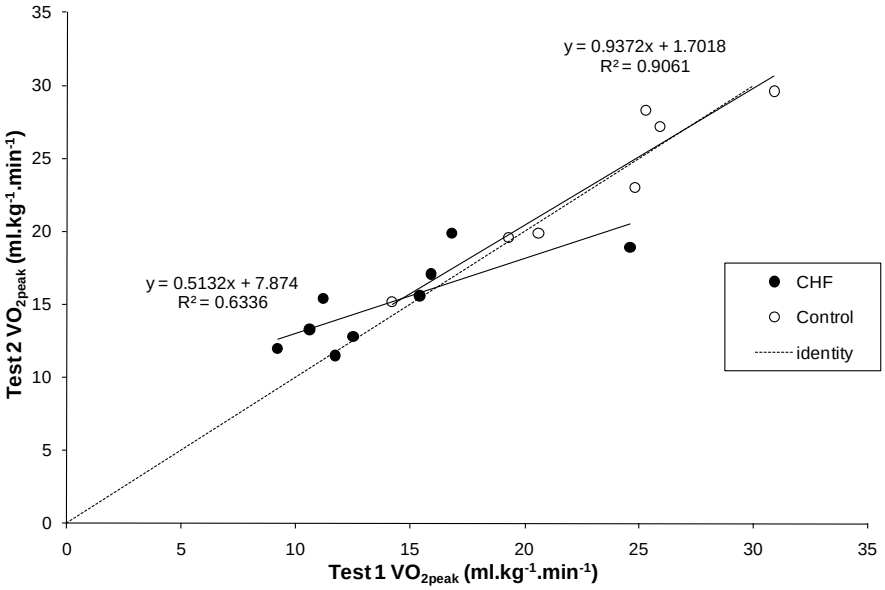


Figure 4.9: Reproducibility of VO_{2peak} in steep tests 1 and 2

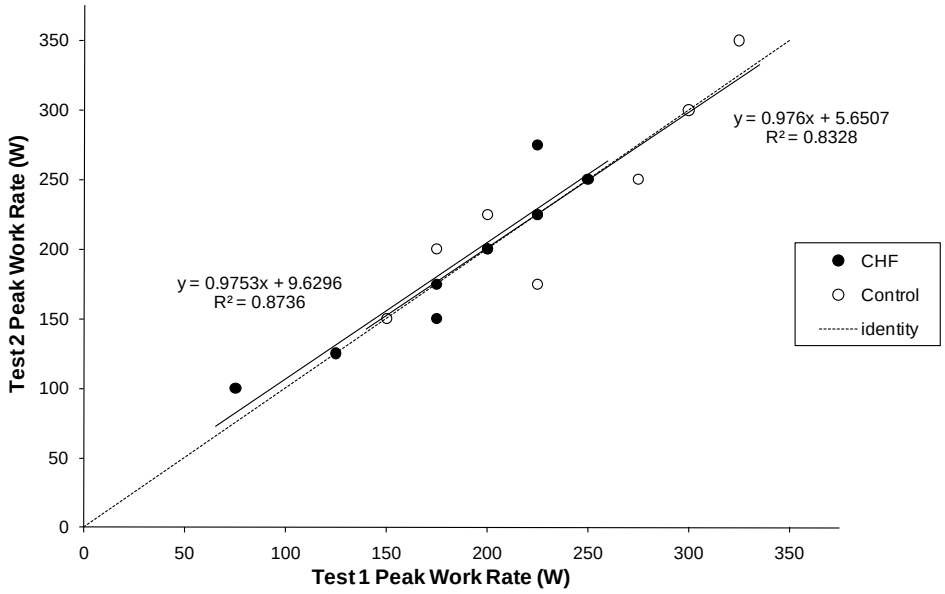
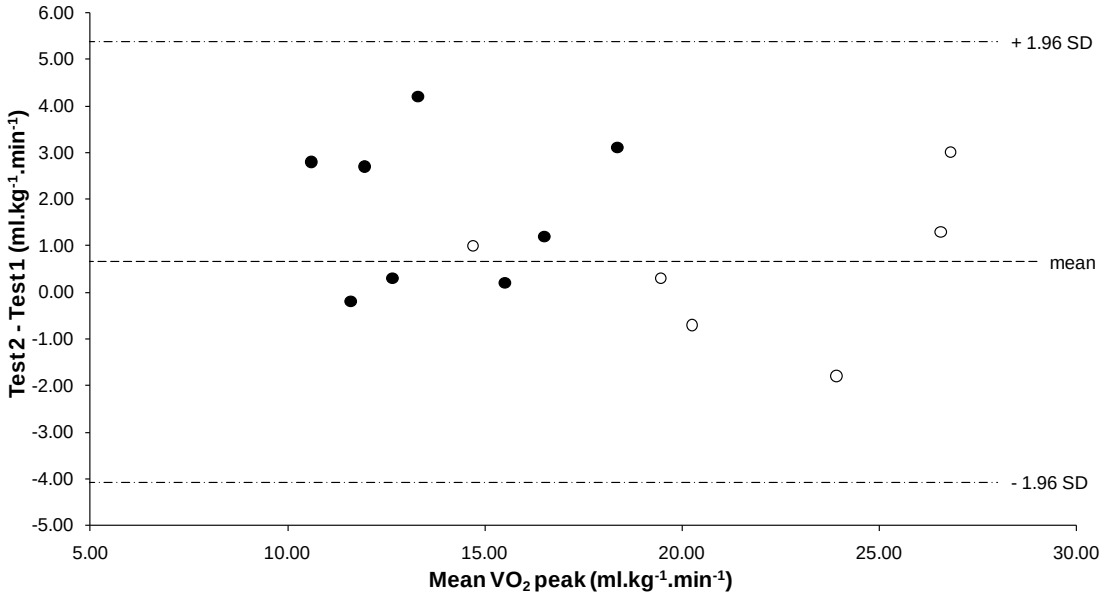


Figure 4.10: Reproducibility of peak work rate in steep tests 1 and 2



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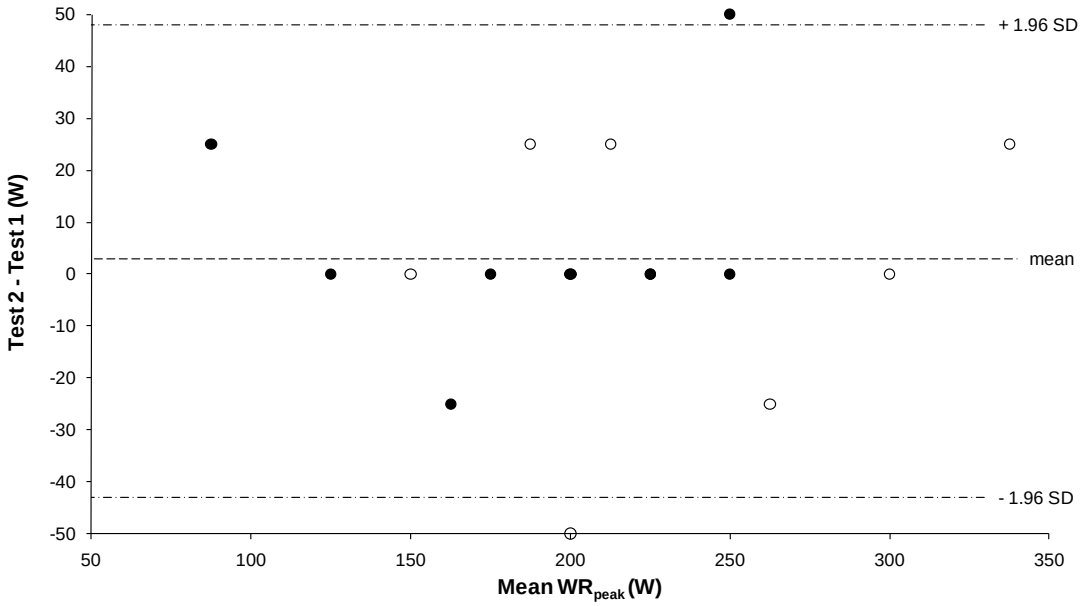


B

Figure 4.11: Bland and Altman plots of the absolute differences (test 2 – test 1) in VO_{2peak} (A) and WR_{peak} (B) versus mean differences in the steep test
(CHF closed circles, Control open circles).

4.2.3 Comparison of intermittent exercise intensity derived from standard and steep tests

Mean intermittent exercise workload derived from the steep test ($WR_{peak}/2$) was 105 ± 32 W (STEEP). This was significantly higher than the workload for MED derived from the standard test (90 ± 38 W, $P = 0.009$), but not significantly different from the intensity for HIGH (111 ± 45 W, $P = 0.891$). However, when the workloads for the CHF and control groups were calculated separately, there were differences between the 2 groups. The data are displayed in Table 4.8, and show that there was no significant difference between STEEP and MED in Controls, or STEEP and HIGH in CHF. In 70% CHF patients STEEP work rate was higher than HIGH work rate, whereas in all controls STEEP work rate was lower than HIGH work rate by 10-40 W.

Table 4.8: Intermittent exercise workloads derived from the standard test (LOW, MED, HIGH) and the steep test (STEEP) (mean ± SEM).

Intermittent Protocol	CHF Work Rate (W)	Control Work Rate (W)
LOW	54 ± 8 *	81 ± 10 *
MED	72 ± 10 *	116 ± 13
HIGH	88 ± 10	141 ± 16 *
STEEP	96 ± 9	118 ± 13
*significantly different to STEEP		

In controls the steep test WR_{peak} was 156 ± 6% of the standard test WR_{peak}. In CHF the steep test WR_{peak} was 227 ± 12% of the standard test WR_{peak} (Figure 4.12) The difference between the steep and standard tests was significantly greater in CHF than in controls ($P < 0.01$).

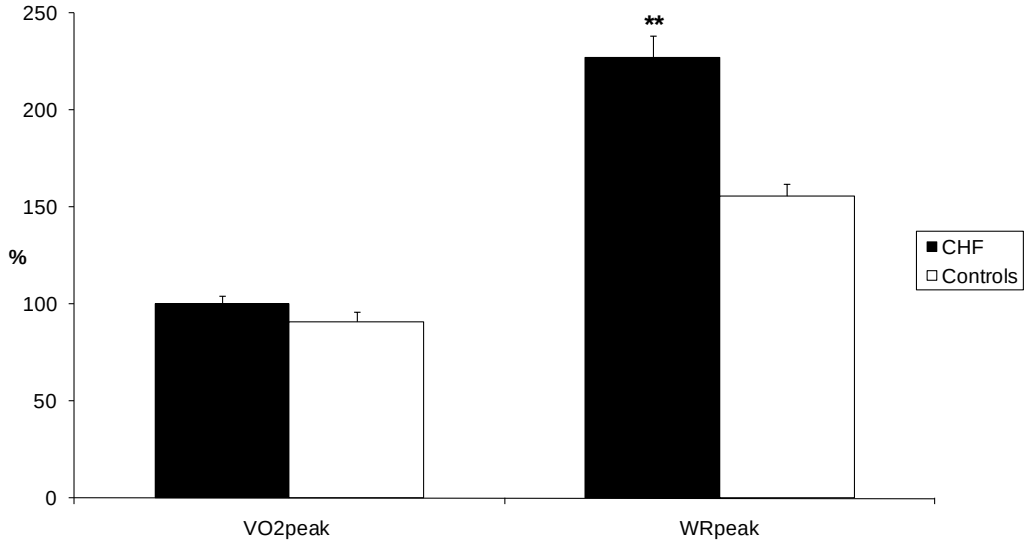


Figure 4.12: Percentage of standard rampVO_{2peak} and WR_{peak} reached in the steep test in CHF and controls.
** $P < 0.01$: CHF significantly different to control

4.2.4 Comparison of VO_{2peak} in standard and steep tests

VO_{2peak} in the steep test reached 100 ± 4 % of the standard test value in CHF, and 91 ± 5 % in controls, and there was no significant difference between tests (P > 0.05) (Figure 4.12). Correlation between VO_{2peak} in the standard and steep tests was high for CHF (r = 0.90), and slightly lower for controls (r = 0.84) (Figure 4.13). However, the bias and random error for VO_{2peak} in all participants was 1.17 ± 2.64 $ml.kg^{-1}.min^{-1}$, giving 95% absolute LOA of -4.00 to 6.34 $ml.kg^{-1}.min^{-1}$. The bias and random error for CHF was 0.45 ± 2.30 $ml.kg^{-1}.min^{-1}$, thus the steep test may overestimate the standard test by 4.96 $ml.kg.min^{-1}$ and underestimate by 4.06 $ml.kg.min^{-1}$ (Figure 4.14). However, in 7 of the 10 CHF, the difference in VO_{2peak} was ≤ 1.4 $ml.kg^{-1}.min^{-1}$.

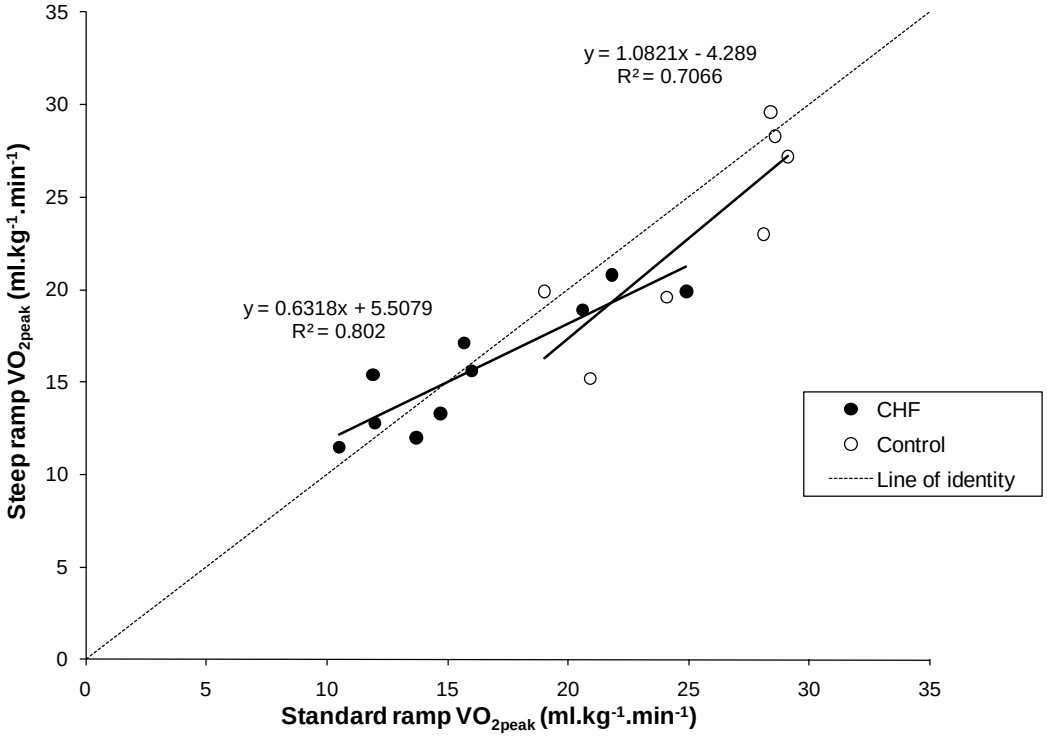


Figure 4.13: Correlation between VO_{2peak} in the standard and steep tests, with line of identity

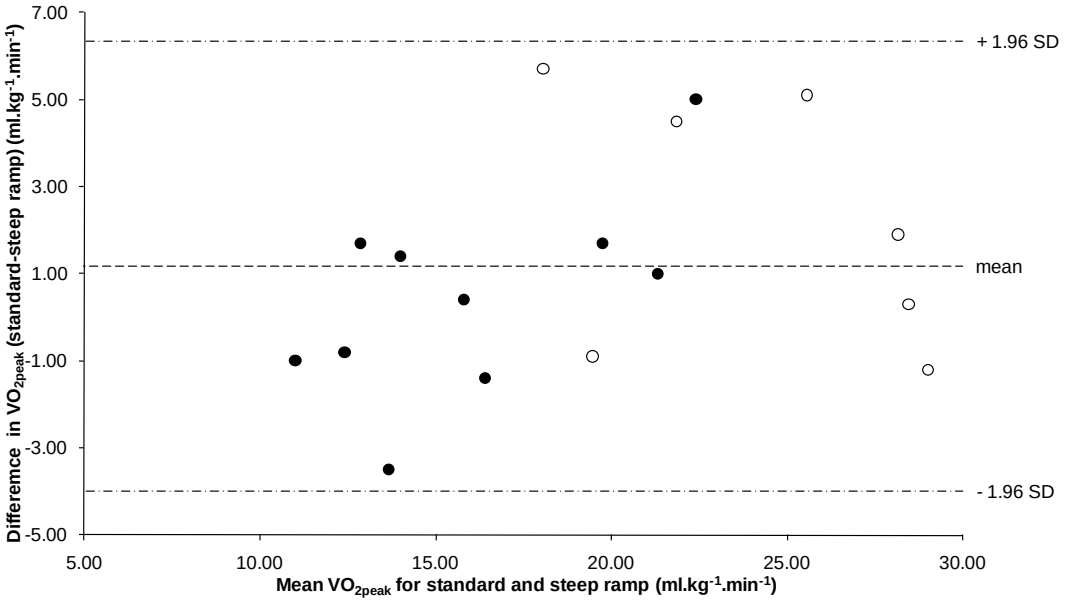


Figure 4.14: Bland and Altman plots of the absolute differences in VO_{2peak} versus the mean differences in the standard and steep tests
(CHF closed circles, Control open circles).

4.3 Discussion

The primary aim of this study was to examine the reproducibility of cardiopulmonary variables and derived exercise workloads from (a) a standard test and (b) a steep test in CHF patients and age-matched controls.

4.3.1 Reproducibility of standard test

There were no significant differences in VO_2 at VT or RCP, or in $\Delta VO_2/\Delta WR$ or V_E/VCO_2 slope between test 1 and test 2, whereas VO_{2peak}, WR_{peak} and HR_{peak} were all significantly higher in test 2. These results suggest that there is a learning effect on peak values, whereas sub-maximal measures are not affected. However, although the t-test detects statistically significant bias between the tests, it is not useful on its own as large amounts of random error mean that systematic bias is less likely to be detected (Atkinson and Nevill, 1998). The ICC is sensitive to the presence of systematic bias, and values, including CI, for VO_{2peak}, VO_2 at VT and RCP, WR_{peak} and HR_{peak} were all > .9, indicating reproducibility in the repeat measurements. Nevertheless, ICC is still affected by heterogeneity (range of values in the sample), and thus a high ICC might still mean an unacceptable measurement error. Bland and Altman's LOA assume a population of individual test-retest differences, and are therefore a better measure of absolute reliability. The 95% LOA indicate that, in a population of CHF and age-matched controls, a repeat measurement of VO_{2peak} could be lower by 2.12 $ml.kg^{-1}.min^{-1}$ or higher by 5.26 $ml.kg^{-1}.min^{-1}$. The LOA for CHF patients alone were smaller; for an initial VO_{2peak} value of 14.0 $ml.kg^{-1}.min^{-1}$, a repeat measurement might lie between 12.7 and 17.6 $ml.kg^{-1}.min^{-1}$. WR_{peak} is likely to be higher by 9-21W in the whole group, or 11-23W in CHF alone. This has implications for the usefulness of using VO_{2peak} and WR_{peak} to accurately assess improvements in exercise capacity following a therapeutic intervention.

VO_2 at VT and RCP were less variable than VO_{2peak} between the 2 tests, with a systematic bias of 0% and +2% respectively, and a random error of 9% for both variables. In CHF for an initial VT value of 9.0 $ml.kg^{-1}.min^{-1}$, a repeat measurement will lie between 6.8 and 10.9 $ml.kg^{-1}.min^{-1}$ in 95% of cases, and for an initial RCP value of 13.0 $ml.kg^{-1}.min^{-1}$, a repeat measurement will lie between 11.4 and 14.3 $ml.kg^{-1}.min^{-1}$. These values might show greater reproducibility than peak values, but

still represent substantial alterations in exercise intensity between repeat tests in this population. However, LOA present the "worst scenario" individual difference (Atkinson and Nevill, 2007) and may be too large as a reference range for making a decision about a change in a subject's measurements (Hopkins, 2000b). The results from test 2 were < 10% different to test 1, thus fulfilling the American Heart Association recommendation that values should vary by less than 10% on separate days to be considered reproducible (Fleg et al., 2000).

Comparison with previous studies is limited by different methodologies and statistical analyses. Table 4.9 shows the results of this study in comparison to those of previous authors, who concluded that reproducibility of VO_2 at VT and at peak exercise was high. Apart from the values from Cohen-Solal et al (1991), the results of the current study are similar to previous studies, although the standard deviation from the mean value is higher. No studies have reported the reproducibility of RCP or $\Delta VO_2/\Delta WR$.

Table 4.9: Reported values for VO_2 at ventilatory threshold and at peak exercise during repeated cycle ergometer tests in CHF patients (mean ± SD).

Authors	**VO_2 at VT ($ml.kg^{-1}.min^{-1}$)**		**VO_{2peak} ($ml.kg^{-1}.min^{-1}$)**	
	Test 1	**Test 2**	**Test 1**	**Test 2**
Cohen-Solal et al (1991) n=25/29	14.3 ± 4.6	15.3 ± 5.1	20.9 ± 6.3	20.9 ± 6.9
Simonton et al (1988) n=15	8 ± 2	9 ± 2	13 ± 3	14 ± 2
Marburger et al (1998) n=9	10.7 ± 1.7	11.3 ± 2.1	16.2 ± 3.4	16.7 ± 3.5
Meyer et al (1997b) n=11	10.8 ± 1.5	10.4 ± 1.5	14.1 ± 3.1	13.8 ± 3.0
Current study n=9	***9.1 ± 2.8***	***8.9 ± 2.3***	***13.7 ± 4.4***	***14.8 ± 4.5***

Cohen-Solal et al (1991) reported that variations in VT and VO_{2peak} values between two consecutive exercise tests < 8 days apart were low enough to allow repeated evaluation of functional capacity in CHF (Cohen-Solal et al., 1991). The 29 patients in their study were younger (30-76 years), had greater functional capacity (mean VO_{2peak} 21 $ml.kg^{-1}.min^{-1}$) than the patients in this study, and were already familiar with cycle ergometer exercise testing. Using the same 10 $W.min^{-1}$ incremental protocol, they reported no systematic bias in VO_{2peak}, and a random error of 2.6 $ml.kg^{-1}.min^{-1}$. Based on this data,

and assuming that the values are homoscedastic, the 95% absolute LOA for VO_{2peak} would be -5 and 5 $ml.kg^{-1}.min^{-1}$, i.e an upper confidence limit > 1 $ml.kg^{-1}.min^{-1}$ greater and a lower confidence limit > 3 $ml.kg^{-1}.min^{-1}$ greater than in this study. VT was determined using the point at which V_E increases disproportionately to VO_2 and the first crossing of the VO_2 and VCO_2 curves, when RER = 1. These methods are less reproducible than the V-slope method because ventilation is influenced by numerous factors, and VT is difficult to detect from RER (Meyer et al., 2005b). Systematic bias and random error were 1 ± 2.4 and 0.8 ± 2.3 $ml.kg^{-1}.min^{-1}$ respectively, giving absolute LOA of -3.7 and 5.7, and -3.7 and 5.3 $ml.kg^{-1}.min^{-1}$. Once again, the results indicate that VT, as determined by their methods, showed lower reproducibility than in CHF patients in this study.

In the same way, the raw data have been taken from a small study (n=9) which examined the reproducibility of CPET in CHF patients > 65 years who had previously undertaken a familiarisation test. (Marburger et al., 1998). The resulting bias and random error for VO_{2peak} and VT have been calculated as 0.52 ± 1.39 and 0.62 ± 1.32 $ml.kg^{-1}.min^{-1}$ respectively, giving 95% absolute LOA of -2.21 and 3.24, and -1.97 and 3.20 $ml.kg^{-1}.min^{-1}$, similar to the values in this study.

Meyer et al (1997) reported high short-term reproducibility of sub-maximal and maximal cycle ergometry exercise data in 11 patients with severe CHF, using the error of the standard deviation (SD) $[\sqrt{(\sum d^2/2n)}]$. The error of SD was 0.2 $ml.kg^{-1}.min^{-1}$ for VO_2 at VT, and 0.6 $ml.kg^{-1}.min^{-1}$ for VO_{2peak} (Meyer et al., 1997c). Using the same calculation, the data from this study show a higher error of SD for VO_{2peak} (4.16 $ml.kg^{-1}.min^{-1}$ for the whole group, and 2.4 $ml.kg^{-1}.min^{-1}$ for the CHF group alone), but similar values for VO_2 at VT (0.01 $ml.kg^{-1}.min^{-1}$ for the whole group, and 0.4 $ml.kg^{-1}.min^{-1}$ for the CHF group alone). HR_{peak} and WR_{peak} in the current study were also higher (8 $beats.min^{-1}$ and 13 W) than the values in Meyer et al's study (2 beats. min^{-1} and work rate 3 W). This could be explained by the more homogenous patient sample in Meyer et al's study, or by the fact that patients were familiar with the exercise testing procedure and equipment from two previous exercise tests, whereas patients in the current study showed a learning effect by achieving higher maximal values in the 2nd test. Sub-maximal values were similar, possibly because moderate intensity exercise values are less affected by familiarisation.

Simonton et al (1988) studied the reproducibility of VT and VO_{2peak} in 18 men with CHF (mean age 60 ± 5 years). VT was determined using two of the same methods as in this study, i.e. ventilatory equivalents and end tidal partial pressures, in addition to a non-linear increase in V_E and in RER. The ventilatory equivalent method was reported to be the most reproducible, and identified VT in 15 of the 18 patients. The authors reported that day to day reproducibility of VT (r = 0.91, SEE 1.74 $ml.kg^{-1}.min^{-1}$) was higher than that of VO_{2peak} (r = 0.95, SEE 3.31 $ml.kg^{-1}.min^{-1}$), but acknowledged that a day-to-day variation of 3.48 $ml.kg^{-1}.min^{-1}$ in VO_2 at VT represents a significant alteration, and this degree of variability may prevent assessment of small changes in individuals (Simonton et al., 1988). Equally, the variations of 6.62 $ml.kg^{-1}.min^{-1}$ reported in VO_{2peak} would preclude its usefulness in assessing changes in functional capacity following an intervention.

An additional issue is the intra-observer variability in the measurement of VT, which has been reported as 5-10% (Myers et al., 2010). This means that a given VT might vary by this magnitude if the same exercise test data are evaluated by the same reviewer on a different day. The variability increases to 20-27% when different reviewers are involved in VT measurement.

The values for $\Delta VO_2/\Delta WR$, a measure of exercise economy, were in the normal range (8.3 – 12.3 ml. $min^{-1}.W^{-1}$), but showed poor retest reproducibility. This might be explained by fluctuations in exercise economy due to poor technique or fatigue, by the biological variability in respiratory variables or irregular breathing due to discomfort from the face mask, or the oscillatory ventilation reported in some CHF patients (Corra et al., 2002). Although none of the patients met the criteria for exercise oscillatory breathing (cyclic fluctuations in V_E persisting for $\geq 60\%$ of exercise duration with an amplitude $\geq$ 15% cyclic fluctuations at rest) defined by Corra et al (2002), smaller fluctuations could still affect the ventilatory measurements. Consequently, when linear regression of VO_2 versus work rate (method a) is used to calculate WR_{peak} at VT, RCP and VO_{2peak}, errors may be magnified. Although reproducibility is higher in method b (the work rate corresponding to the stage at which VT, RCP and $\dot{V}O_{2\,peak}$ were identified, minus 2/3 of the ramp rate), it may not be appropriate to use 2/3 ramp rate to compensate for the lag in VO_2 uptake in a CHF population, in whom VO_2 kinetics are reportedly slowed (Meyer et al., 1998b). Other studies have reported that VO_2 kinetics

during incremental exercise are normal, but slower during recovery (Picozzi et al., 1999), and are influenced by training (Roditis et al., 2007), indicating the difficulty of controlling for the time lag in this population.

V_E/VCO_2 slope, a measure of ventilatory efficiency, and a prognostic marker in CHF, reportedly has a high reproducibility (CV 6.2%, r = 0.93) (Chua et al., 1997). However, the measure showed poor retest reproducibility in this study, although the values were within the normal range for the CHF population. The difference in V_E/VCO_2 slope between repeat tests was > 2 in all but one control participant and in 5 out of 8 CHF. As with the $\Delta VO_2/\Delta WR$ measurement, this could be due to irregularity in breathing patterns. As the V_E/VCO_2 slope is recognised as a valuable prognostic marker in CHF (Ingle, 2007), the issue of its reproducibility merits further investigation.

Recently published data from the HF-ACTION trial suggests that there is substantial within-subject variability in repeated tests in VO_{2peak}, VO_2 at VT and V_E/VCO_2 slope (Bensimhon et al., 2008). Approximately half of the patients increased and half decreased their VO_{2peak} and VT on the second test, suggesting that the variation was more likely to be due to daily haemodynamic and volume status fluctuations, rather than a learning effect. By contrast, in the current study VO_{2peak} increased in 79% participants in the second test, whereas it did not change, or decreased slightly in 21%, indicating that there does appear to be a learning effect on maximal values. The HF-ACTION trial conducted tests at 83 different clinical sites, therefore variations in testing conditions are likely to have influenced the results. In addition, only 12% of the 398 participants performed cycle ergometer rather than treadmill tests, hence the findings may not apply to cycle ergometry. Additional methodological differences to the current study, including determination of the V_E/VCO_2 slope from the whole of the exercise test data, rather than from the linear part of the slope, add to the difficulty of relating the results of the two studies to one another.

Consideration should also be given to the effect of β-blockers which are currently standard medical therapy in CHF (National Collaborating Centre for Chronic Conditions, 2003). The timing of the β-blocker dose will influence it's effect on HR, and although patients were instructed to take their medication at the same time on both testing days, variations in timing could have affected the results (Whellan et al., 2007).

Although β-blockade in CHF reduces HR, reflected by the reduced HR_{peak} in patients compared with age-predicted HR_{max} and HR_{peak} in controls, it does not appear to reduce VO_{2peak} (Witte et al., 2005). Chronotropic incompetence also occurs in patients not taking β-blockers (Witte et al., 2006), although this was not seen in the one patient in this study who did not tolerate β-blockers. Anti-arrhythmic medication may also reduce HR, but there is little information about the extent of this effect (British Association for Cardiac Rehabilitation, 2006).

4.3.2 Reproducibility of steep test

There was a smaller bias in VO_{2peak} in the steep test but a larger random error than in the standard test, both in the whole group and in CHF patients alone. The 95% LOA showed that a repeat measurement might vary from -4.77 to 6.88 $ml.kg^{-1}.min^{-1}$ in CHF. This lack of reproducibility is not surprising, given the large and rapid increases in workload in this protocol, whose aim is to measure the work rate achievable rather than VO_2. It is the reproducibility of WR_{peak}, from which intermittent exercise workloads are calculated, which is more important. The 95% LOA were high (-43 to 48 W for the whole group, or -34 to 44 W for CHF), but this is partly due to the large increments in workload between stages. Figure 6 shows that 7 out of 10 CHF but only 2 of the 7 controls reached the same WR_{peak} in test 2 as in test 1. The remainder had a difference in WR_{peak} of one or two test stages, i.e. 25 or 50 W, which translates to an increase in intermittent training workload of 12.5 or 25 W, potentially a substantial increase for CHF patients with a low initial WR_{peak}. This would add an extra 4875 - 9750 J to the total workload of a 20 min intermittent training session with 13 x 30s work bouts. However, studies using the steep test to set exercise workloads generally repeat the test weekly in order to readjust the intermittent work rates, and to allow training progression, which would resolve this issue (Meyer et al., 1997b; Vogiatzis et al., 2002; Puhan et al., 2004). Nevertheless, it does perhaps illustrate the difficulty of determining precise training workloads in this population. The advantages of the steep test are that it requires less equipment, time and effort, both from the exercise professional and the patient, and it can be performed weekly to adjust the training load in line with patient progress.

4.3.3 Comparison of intermittent exercise intensity derived from standard and steep tests

A secondary aim of the current study was to compare the exercise training workloads derived from a standard and steep test in CHF patients and healthy control participants.

The work rates for the continuous and intermittent exercise bouts were set according to exercise intensity domain framework (Section 2.6.4.4). VT and RCP occurred at 62 ± 9% and 84 ± 6 % of VO_{2peak} in CHF, and 54 ± 6% and 82 ± 6 % in controls. In a small study of healthy younger individuals, VT and RCP occurred at 62% and 90% VO_{2max} respectively (Lonsdorfer-Wolf et al., 2003). Normative values for the percentage of VO_{2peak} at which the VT will occur for men and women aged 70 years are 58% and 65% respectively, but it is well known that there is considerable variability in both healthy and diseased populations (Wasserman et al., 2005). As discussed previously, mean VT in CHF has been reported to occur at 64-75% of VO_{2peak} (Simonton et al., 1988; Cohen-Solal et al., 1990; Meyer et al., 1997c; Marburger et al., 1998). In this study, in CHF there was a mean (± SD) difference of 27 ± 20 W between the moderate and heavy, and 24 ± 9 W between the heavy and severe domains, whereas in controls the mean differences were 42 ± 20 and 40 ± 22 W respectively. The work rates delineating the exercise intensity domains for CHF and controls are shown in Figure 4.15 (RCP could not be clearly identified in 3 CHF and 1 control). This highlights the difficulty of accurately prescribing exercise work rates in individual intensity domains in CHF, where the range in work rate in each domain is very narrow, and the test-retest variability is relatively high (95% absolute LOA for work rates at VT: -13W to 7W; RCP: -18W to 27W; VO_{2peak} 11W to 23 W).

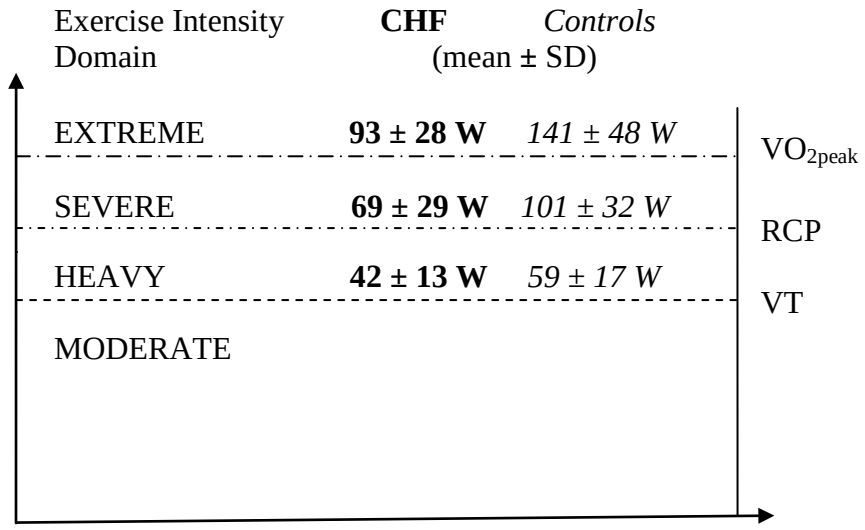


Figure 4.15: Exercise intensity domains for CHF (n=7) and Controls (n=6)

The intermittent work rates, determined from the results of the 2nd standard test, were compared to those derived according to the protocol of Meyer et al. (1997), i.e. 50% of WR_{peak} achieved in the 2nd steep test. For CHF and controls combined, work rate was similar in STEEP (105 ± 8W) and HIGH (111 ± 11W), but there were interesting differences between the 2 groups. In controls, STEEP (118 ± 13W) was closest to MED (116 ± 13W), whereas in CHF, STEEP (96 ± 9W) was closest to HIGH (90 ± 11W). This was because the WR_{peak} reached by the majority (7/10) of CHF in the steep test was more than double that in the standard test, whereas in controls it was only 35 - 80% higher. This suggests that CHF are less limited by their symptoms in short duration high intensity exercise. In a standard maximal exercise test a reduced exercise capacity in CHF is associated with an increased ratio of type II to type I fibres and decreased oxidative capacity (Drexler et al., 1992), but these factors are less likely to influence performance in the shorter steep test. The results in controls were similar to those reported in younger cancer patients, where steep test WR_{peak} was 61% higher than standard test WR_{peak} (De Backer et al., 2007).

It is surprising that similar mean VO_{2peak} values were achieved in the standard and steep tests. Meyer (1997) reported that VO_{2peak} in the steep test reached only 87% of the value attained in the standard test. In the current study, there was no statistically significant difference between VO_{2peak} in the two tests in either the whole group or in

CHF patients, although controls reached only 91% of standard test VO_{2peak}, compared to 100% in CHF. This suggests that it may be possible to measure VO_{2peak} using a steep test rather than a standard test. However, the 95% LOA were unacceptably large (All: -4 to 6.34 $ml.kg^{-1}.min^{-1}$; CHF -4.96 to 4.06 $ml.kg^{-1}.min^{-1}$), showing that the steep test cannot reliably be used to assess VO_{2peak} in either population. Interestingly, controls and less severe CHF tended to reach higher values in the standard ramp, whereas de-conditioned, or more severe CHF attained similar or higher peak values in the steep test (difference $\leq \pm$ 1.4 $ml.kg^{-1}.min^{-1}$ in 70% patients). With increasing severity of heart failure, cardiac output response and oxygen delivery to the exercising muscles are increasingly reduced, and peripheral abnormalities reduce aerobic capacity further (Wilson et al., 1996; Tavazzi et al., 2001). Thus it is perhaps not surprising that these patients show greater limitations during the longer test which imposes a more prolonged stress on the aerobic energy system than the shorter test.

The steep test has previously been evaluated as a substitute for maximal CPET to prescribe intermittent training and to monitor the effects of this training in cancer patients (De Backer et al., 2007). The authors reported a high correlation between standard and steep test WR_{peak}, and similar improvements in both tests following a training intervention. Although LOA between tests was not reported, the prediction error from regression analysis to predict standard test WR_{peak} and VO_{2peak} from the steep test was 53 W and 616 $ml.min^{-1}$ (~ 8 $ml.kg.^{-1}min^{-1}$) respectively. These findings agree with the current study in suggesting that although the steep test might be a useful practical tool to guide interval training intensity, it is no substitute for the standard test for assessment of VO_{2peak}.

The standardised test order, in which the steep test was performed 1 hour after the standard test, may have influenced the results. In younger healthy individuals prior heavy exercise appears to have a "priming effect" on VO_2 kinetics during subsequent heavy exercise, although this effect is no longer apparent after 1 hour of recovery (Burnley et al., 2006). Hence a 1 hour recovery period has previously been used in our laboratories for healthy individuals because Lac and gas exchange parameters to return to resting levels in this time. In CHF, repeated testing with a fixed test order and a recovery period of 90 minutes has been used with no apparent influence on maximal exercise performance (Kim et al., 1999). Furthermore, elderly individuals who performed 2 exercise tests per day for 3 consecutive days, also in a standardised order,

achieved their best 6 min walk test score on their final test, despite having performed a maximal cardiopulmonary exercise test earlier that same day (Kervio et al., 2003).

4.4 Conclusion

This chapter investigated the reproducibility of physiological parameters measured in duplicate standard and steep incremental cycle ergometer tests in terms of statistical significance, re-test correlation and LOA, and a 10% difference between tests. Peak measures showed poor reproducibility in terms of statistical significance and LOA, and the positive bias of 1.57 $ml.kg^{-1}.min^{-1}$ in VO_{2peak} between the first and second test suggests that there is a learning effect. Although the re-test correlation was high, and the difference between tests was < 10%, the finding that ~80% participants increased their VO_{2peak} in the second test reinforces the likelihood of a learning effect. Sub-maximal measures showed good reproducibility in terms of statistical significance, re-test correlation and a < 10% difference between the first and second test, but poor reproducibility in terms of LOA. However, the bias was smaller, and participants were as likely to show a decrease as an increase in values, suggesting that variations were not due to a learning effect.

The results of this study reinforce the recommendation that a practice test should be performed in advance of a maximal CPET in CHF and in older individuals. Sub-maximal measures, which are less dependent on subject motivation, are more reproducible than peak measures, but are still prone to within-subject variation between tests. Consequently, it is difficult to accurately define exercise intensity domains via this method. Derived variables such as $\Delta VO_2/\Delta WR$ and V_E/VCO_2 slope are less reproducible, and changes in these measurements following exercise or medical interventions should be interpreted with caution. However, some of this variability may be eliminated when patients are more familiar with the equipment and testing procedure. It remains difficult to judge to what extent the within-subject variability will limit the usefulness of cardiopulmonary exercise test results in assessing the effectiveness of an intervention. A limitation of this study is the inability to control patients' symptom status between tests. Equally, defining a change in patient disease or symptom status is difficult, and there is no agreed criterion standard (Spertus et al.,

2005). Day-to-day variation in fatigue, breathlessness or general well-being is inevitable, and this may have influenced the results.

This chapter also compared methods for setting intermittent exercise intensity. The hypothesis that workloads derived from the two methods would differ is supported in controls, but not in CHF. In controls, workloads set at 50% steep test WR_{peak} were significantly lower than those set by the traditional method (100% standard test WR_{peak}), whereas in CHF there was no difference in workload between the two methods.

CHAPTER 5: ACUTE RESPONSES TO CONTINUOUS AND INTERMITTENT EXERCISE IN CHF AND HEALTHY CONTROLS

5.0 Introduction

Exercise training is beneficial for CHF, but the optimal type of training is less clear. Numerous studies have demonstrated the benefits of continuous moderate exercise training for patients in New York Heart Association (NYHA) Class II and III (Giannuzzi et al., 2001; Piepoli et al., 2004; Rees et al., 2004), and some studies have reported that intermittent exercise is also an effective mode of training in this population (Meyer et al., 1997b; Dimopoulos et al., 2006; Roditis et al., 2007). However, many CHF experience fatigue and dyspnoea on exertion, and find it difficult to sustain exercise beyond a short duration. In healthy individuals, exercising intermittently rather than continuously significantly prolongs the amount of work achieved before exhaustion (Astrand et al, 2003; Christensen et al, 1960). In non-clinical populations, intermittent exercise achieves a similar (Eddy et al, 1977; Poole and Gaesser, 1985; Cunningham et al, 1979), or greater (Gorostiaga et al., 1991; Tabata et al., 1996; Daussin et al., 2008) training adaptation than continuous exercise of an equal total workload. Intermittent exercise may therefore be an appropriate exercise mode for populations who find it difficult to perform continuous exercise, and may allow for a higher training stimulus. In healthy individuals, exercise capacity is ultimately limited by oxygen delivery (Bassett and Howley, 2000), whereas peripheral limitations appear to be the main determinant of exercise capacity in CHF (Clark et al, 1996; Foster al at, 2004). The increased exercise capacity following training is primarily due to peripheral rather than central adaptations in this population. CHF with a very low exercise capacity may not be able to achieve continuous endurance training workloads high enough to have an optimal training effect on the peripheral muscles, and compensating for low exercise intensities by increasing the duration of exercise is likely to be limited by premature fatigue (Meyer et al, 1997). By alternating short intervals of exercise with recovery periods, CHF can theoretically work at a higher intensity and/or achieve a greater total workload than from continuous exercise, while minimizing cardiac stress but optimising the peripheral training effect.

Intermittent exercise may also allow patients to achieve greater benefits than continuous exercise for a smaller amount of exercise training. In coronary bypass surgery rehabilitation, intermittent exercise training resulted in a greater increase in aerobic capacity, and decrease in HR, rate pressure product (RPP) and lactate at sub-

maximal work rates than continuous exercise despite the fact that the total amount of work performed was significantly lower (Meyer et al., 1990). CHF patients with a very low baseline capacity achieved significant improvements in aerobic and ventilatory capacity, and reduction in dyspnoea and leg fatigue, after short-term intermittent exercise training. Improvements after only 3 weeks were similar to the improvements reported in longer-duration training programmes of continuous rather than intermittent exercise bouts (Meyer et al 1996b; Meyer et al, 1997).

Studies on healthy individuals report that LV function during high intensity intermittent exercise is not different to that during continuous moderate intensity training of the same total work load (Foster et al., 1999), and that pulmonary haemodynamics adapt well to intermittent work bouts of near maximal intensity (Lonsdorfer-Wolf et al., 2003). There is some concern that high intensity exercise may induce deterioration in LV function (Koike et al., 1989), and over stress the LV wall in CHF (Demopoulos et al., 1997b). However, Meyer et al (1998) reported that LV function was equally stable during a 16 min bout of both continuous and intermittent exercise in CHF, although HR, systolic BP, Lac and rating of leg fatigue and dyspnoea were all significantly higher at the end of the intermittent exercise (Meyer et al., 1998a). The authors concluded that intermittent exercise is more strenuous than continuous exercise despite the same average power output, but that it does not create any higher short-term cardiac stress. The same authors also reported that intermittent training at 50% of the work rate achieved on a specific steep test was markedly higher, but elicited a mean HR 13 beats.min^{-1} lower than that recorded at VT during an incremental exercise test (Meyer et al., 1997b). The implication of these studies is that intermittent exercise training allows a more intense exercise stimulus to be applied than the traditionally prescribed steady-state or continuous exercise, without compromising LV function.

In low or moderate intensity exercise, VO_2 reaches an early steady-state, and Lac remains close to resting levels (Jones et al., 2007). In heavy intensity exercise VO_2 and Lac reach a delayed but elevated steady-state. In severe intensity exercise, both VO_2 and Lac will increase over time until VO_{2max} is reached and the exercise is terminated (Jones et al., 2007). The term high intensity exercise has also been used to define exercise above or around VO_{2max} that is non-sustainable (Brickley et al., 2007). It might be expected that high intensity intermittent exercise would induce a higher VO_2 and Lac response when compared to continuous moderate intensity exercise. However, in

healthy individuals if the total workload is matched, large variations in exercise intensity have no significant effect on exercise metabolism (Essen et al., 1977; Brickley et al., 2007), while VO_2 may be lower if the exercise is intermittent (Astrand et al., 2003).

Current guidelines recognise the potential benefits of intermittent training in CHF (Giannuzzi et al., 2001), but it is questionable whether this type of training is being implemented in practice. UK guidelines for CR exercise instructors do not explain how this type of training mode can be applied to CHF (British Association for Cardiac Rehabilitation, 2006). A survey of CR programmes in Sussex revealed that intermittent exercise is not incorporated into training for CHF. Examining acute responses to both intermittent and continuous exercise in CHF patients benefiting from up-to-date medication is an important prelude to designing and implementing an optimised exercise training programme. To date, only one study has compared the acute responses to intermittent and continuous exercise of matched total work in this population, and this was at a continuous exercise intensity above VT (Meyer et al., 1998a). This, and studies examining the longitudinal effects of intermittent compared with continuous exercise, have set the intermittent work intensities first, e.g. at 100% maximum workload or 50% if a steep test is used, then matched the continuous workload to this. This study used a different approach; the continuous exercise was set in the moderate domain, at 90% VT, which, in theory, allows a steady-state to be achieved, is sustainable and appropriate for CHF (McConnell et al., 1993; Meyer et al., 2005a); the intermittent work bouts were set in the severe domain in order to challenge the physiological responses to exercise. The aim of this study was to compare the acute respiratory, cardiovascular and metabolic responses to matched workloads of moderate continuous and intermittent exercise in CHF and age-matched control participants.

Hypotheses

In CHF patients intermittent exercise will elicit similar cardiovascular and respiratory responses, but higher metabolic and RPE responses, than continuous exercise.

In control participants there will be no difference in cardiovascular, respiratory, metabolic or RPE responses to intermittent or continuous exercise.

5.1 Methods

5.1.1 Participants

Ethical procedures and patient inclusion and exclusion criteria were adhered to as detailed in the General Methods (Chapter 3). Ten CHF and 7 control participants, as described in Study 1 (Chapter 4), participated.

5.1.2 Experimental design

General methods were followed as described in Chapter 3. CON and MED were performed in this study, as described in Section 3.4.

5.1.3 Data analysis

Respiratory gas exchange variables (VO_2, VCO_2, V_E) were calculated, displayed for every breath and then interpolated to provide one value per second. Following the removal of outlying breaths (value ± 500 ml different from the previous and following breaths), breath-by–breath respiratory gas exchange variables (VO_2, VCO_2, V_E) were interpolated to give second-by-second values. Resting values were taken from a 30s rolling average during min 4-5 of rest, and unloaded values were taken from a 30s rolling average during the final minute of unloaded cycling. Exercise VO_2 was calculated as the average of the measured VO_2 value minus the value for unloaded cycling, during min 1-5, 5-10, 10-15 and 15-20. The oxygen cost of exercise, or exercise "economy", was calculated as total VO_2 above unloaded cycling divided by the total work done (ml/W). The recovery VO_2 was determined as the VO_2 during the first 3 minutes of recovery above the resting VO_2. HR was recorded at rest, at the end of the final minute of unloaded cycling, and at the end of minutes 5, 10, 15 and 20 during CON, and during the same time period during MED, at the end of both work and recovery phases 4, 7, 10 and 13. Values for the work and recovery periods in MED were averaged for the purpose of comparison with CON (work phase + (2 x recovery phase)/2). BP was recorded with a sphygmomanometer at rest, and during minutes 10 and 20 of exercise. Rate pressure product (RPP) was calculated at rest, and during minutes 10 and 20 of exercise (BP x HR/100). RPE on the Borg 6-20 Scale was measured after every 5 minutes of continuous exercise, and during the same time

period during intermittent exercise, at the end of both recovery and work phases 4, 6, 10 and 13, with values being averaged in the same way as HR. Five µl venous blood samples were taken according to the methods described in Chapter 3, and analysed for lactate (Lac) (YSI Yellow Springs Instruments, Ohio).

5.1.4 Statistical analysis

A two-way mixed design analysis of variance (ANOVA) was used to detect within subject (difference between CON and MED) and between subject variation (difference between Controls and CHF). Where appropriate, a three-way mixed design ANOVA, with repeated measures across time, was used to detect within subject and between subject variations in dependent variables at different time points. Where significant differences were indicated, follow-up t-tests with a Bonferroni adjustment for multiple comparisons were performed to see where they differences lay. Mauchly's test was used to check the sphericity of the data, and the Greenhouse-Geisser adjustment was made for non-spherical data. Levene's test was used to test homogeneity of variance, and the equal variance not assumed statistic was used where the assumption of homogeneity was violated. Where the data were not parametric, Wilcoxon's test for matched pairs or Friedman's test for 3 or more samples was used to detect differences between CON and MED, and at different time points during exercise, for CHF and controls. The Mann-Whitney test was used to compare differences between exercise bouts and groups for non-parametric data.

5.2 Results

Participant characteristics are shown in Table 5.1.

Table 5.1: Characteristics (mean ± SD) of CHF patients and healthy controls

Characteristic	CHF (n=10)	Controls (n=7)
Age (years)	75 ± 8	67 ± 7
Male/ Female	8/2	4/3
Height (cm)	172 ± 11	173 ± 10
Body Mass (kg)	86 ± 18	79 ± 13
NYHA Class II/III	8/2	-
Ejection Fraction (%)	36 ± 9	69 ± 7
Aetiology (ischaemic/dilated cardiomyopathy)	5/5	-
Co-morbidities		
COPD	1	-
Diabetes	1	-
Hypertension	1	-
Medication		
ACE inhibitor	4	-
Angiotensin II receptor blocker	4	-
Anti-arrhythmic	3	-
β blocker	9	-
Calcium channel blocker	2	-
Diuretic	8	-

The Q-Q plots of normality and Kolmogorov-Smirnov tests showed that the assumption of normality had been met in all variables except RPE, where non parametric tests were therefore used. The assumption of sphericity was violated for the change in La and HR over time, hence the Greenhouse Geisser adjustment was applied. Levene's test showed variances were homogenous for all levels of the repeated measures variables. Maximum exercise capacity measured during CPET and work rates for CON and MED are shown in Table 5.2. Exercise was well-tolerated by all CHF and controls. All controls and 8 out of 10 CHF completed both 20 minute exercise bouts. Due to fatigue, one CHF stopped CON after 17 min and MED after 16 min, and another CHF stopped MED after 16 min. In these cases, the gas exchange data from 11-16 min instead of 15-20 min were used for both exercise bouts.

Table 5.2: Maximum exercise capacity and training work rate (mean ± SD)

	CHF	Control
Maximum exercise capacity		
VO_{2peak} ($ml.min^{-1}$)	1,310 ± 432	1,973 ± 505
VO_{2peak} ($ml.kg^{-1}.min^{-1}$)	15.4 ± 4.2	24.7 ± 3.7
Peak work rate (W)	81 ± 30	142 ± 42
Exercise training work rate		
CON (W)	34 ± 12	55 ± 15
MED (W): work phase	72 ± 6	116 ± 32
MED (W): recovery phase	18 ± 6	28 ± 7

Table 5.3 presents data collected during CON and MED, for CHF and controls. Further details of statistical results are included in Appendix 5. V_E, RER, HR, BP, Lac & RPE are presented as average values during each exercise bout. V_E was higher in MED than CON (P = .034) in both groups. There were no significant differences in any other variable between CON and MED in either group ($P > 0.05$). VO_2 in CHF was lower than controls during exercise, and HR and BP were lower at rest and during exercise, while RPE was higher for CHF than for controls in CON (P = .045) and MED (P = .001).

Table 5.3: Responses to continuous (CON) and intermittent (MED) exercise in CHF patients and control participants

Values for Ventilation, RER, Heart Rate, Blood Pressure, Blood Lactate Concentration and Rating of Perceived Exertion are mean values for the 20 min exercise bout.

	CHF		**CONTROL**		
	CON	**MED**	**CON**	**MED**	
Resting VO_2 ($ml.min^{-1}$)	265 ± 14	261 ± 15	298 ± 22	313 ± 27	
Unloaded VO_2 ($ml.min^{-1}$)	422 ± 30	431 ± 38	562 ± 62	650 ± 56	†
Total net exercise VO_2 (ml) (work-rest)	11,098 ± 1,441	11,228 ± 1,309	15,969 ± 1,541	16 ,237 ± 1,607	†
Average 15-20 min net VO_2 ($ml.min^{-1}$)	462 ± 67	445 ± 44	605 ± 67	618 ± 64	†
% VO_{2peak}	64 ± 3	65 ± 1	57 ± 3	57 ± 3	
Exercise economy (VO_2/W)	11.7 ± 1.1	12.2 ± 0.9	9.9 ± 0.8	9.2 ± 0.3	†
Recovery VO_2 (3 min) (ml)	962 ± 159	896 ± 125	887 ± 122	1,085 ± 169	
Ventilation ($L.min^{-1}$)	27 ± 0.7	28 ± 0.7 *	32 ± 1.0	34 ± 1.1 *	
RER	0.92 ± 0.01	0.93 ± 0.01	0.91 ± 0.01	0.94 ± 0.01	
Heart Rate (beats. min^{-1})	78 ± 3	76 ± 3	112 ± 9	113 ± 8	†
% Peak Heart Rate	76 ± 3	74 ± 3	70 ± 3	71 ± 4	
% Heart Rate Reserve	46 ± 4	43 ± 5	47 ± 5	48 ± 5	
Blood Pressure (systolic) (mmHg)	127 ± 5	127 ± 4	151 ± 6	153 ± 5	†
Rate Pressure Product	101 ± 8	99 ± 7	182 ± 10	187 ± 8	†
Blood Lactate Concentration ($mmol.L^{-1}$)	1.9 ± 0.2	2.2 ± 0.3	2.1 ± 0.4	2.6 ± 0.6	
Rating of Perceived Exertion	11.8 ± 0.2	12.2 ± 0.2	10.9 ± 0.3	9.8 ± 0.3	†

Difference between exercise bouts: * P < 0.05 CON vs MED
Difference between groups † *P* < 0.05 CHF versus Controls in CON & MED

Analysis of VO_2 at 5, 10, 15 and 20 min did not reveal any significant difference between CON and MED (P = 0.425). Analysis of average VO_2 between 5-10 min and 15-20 min showed a significant main effect of time (P < 0.001) and a significant interaction between time, exercise protocol and group (P = 0.015). Follow-up tests (Bonferroni adjustment: α level $P \leq 0.0125$) showed that VO_2 did not increase significantly in CHF from the first to the second half of the 20 min exercise bout in either CON (P = 0.053) or MED (P = 0.558), whereas in controls VO_2 increased in MED (P = 0.001) but not in CON (P = 0.493). This response is illustrated in Figure 5.1 with data from one CHF and one control participant.

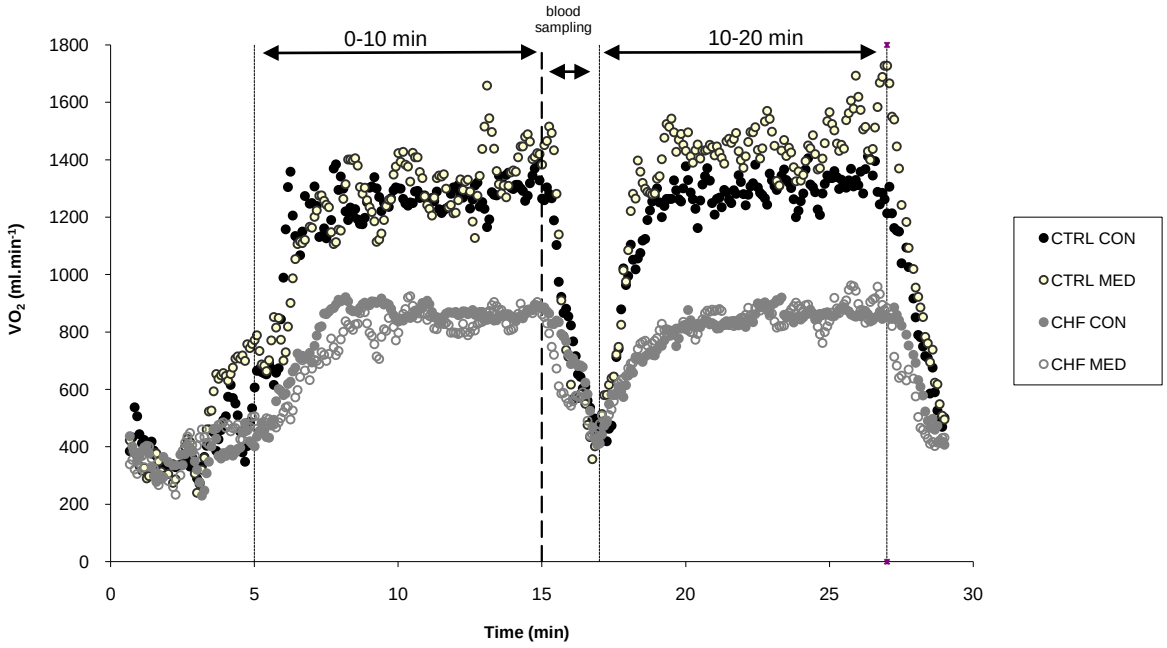


Figure 5.1: Example of oxygen uptake response to CON and MED in one CHF and one control participant (CTRL)

Average HR values were not different between MED and CON in controls or CHF (P = 0.765). There was an upward drift in HR in both groups over time, with but there were no significant differences in HR at 5, 10, 15 and 20 min between exercise modes once the rest and recovery phase values were averaged (P > 0.05) Figure 5.2 illustrates the significantly lower HR (P =0.001) in CHF compared with controls, and the blunted HR response between work and rest phases in CHF. When average HR during CON and MED was calculated as a percentage of HR_{peak} and HRR, values for CHF were slightly, but not significantly, higher than for controls (Table 5.2).

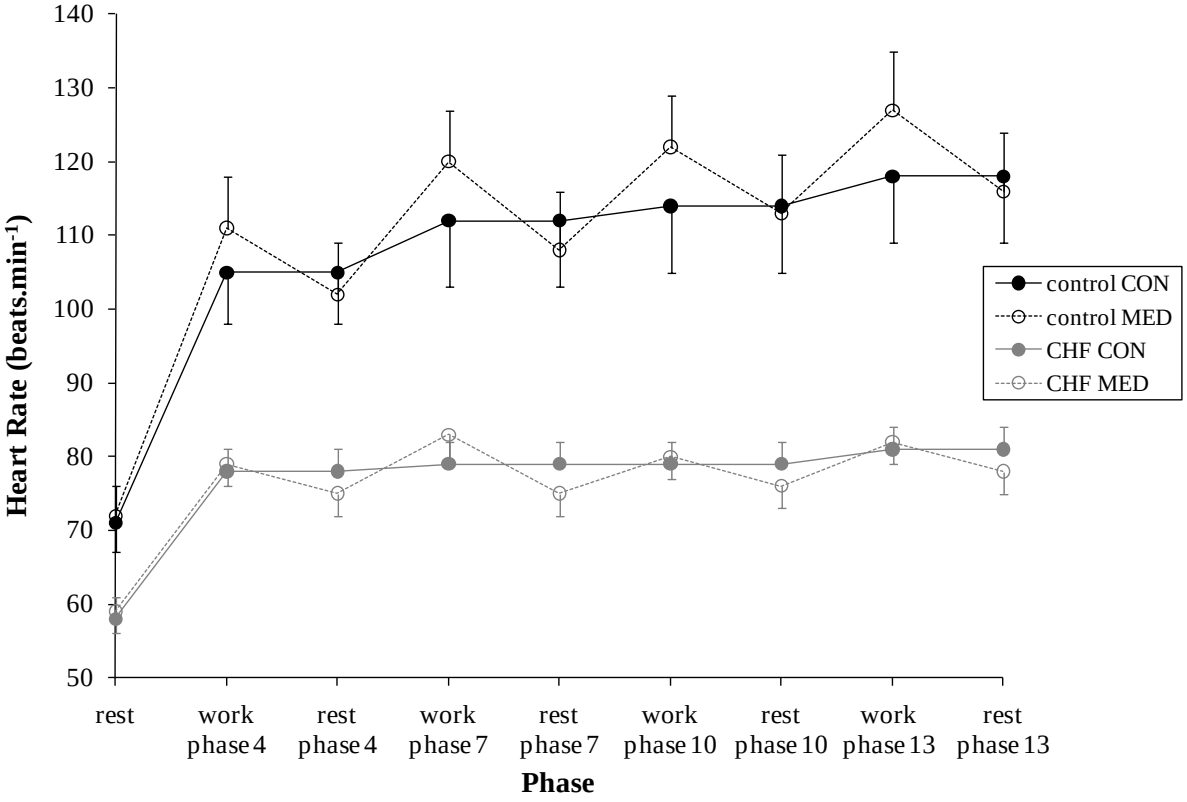
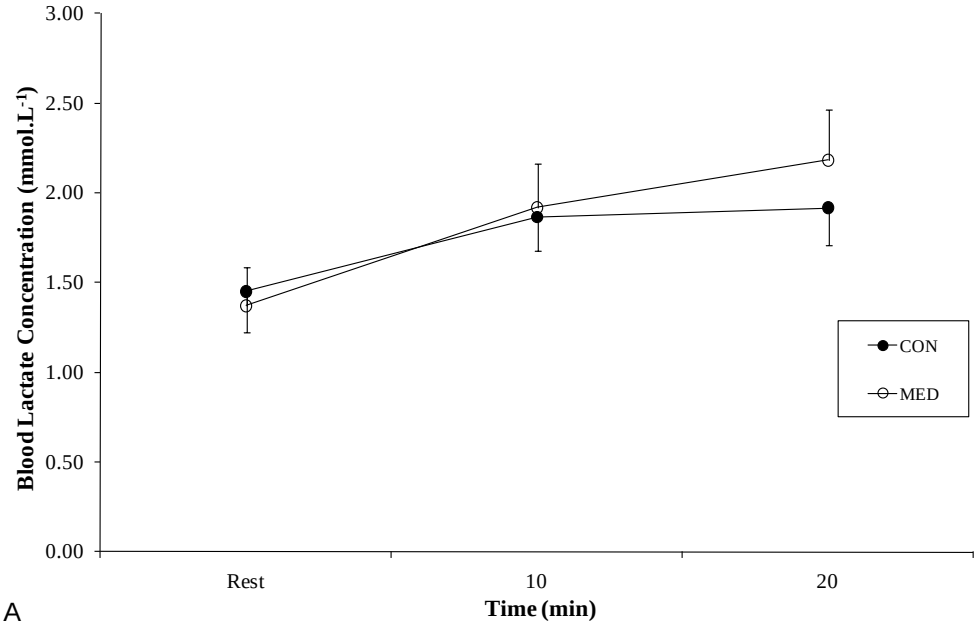


Figure 5.2: Heart rate response (mean ± SEM) to CON and MED during work and recovery phases at 5, 10, 15 and 20 min during exercise in CHF and controls.

Lac values increased significantly above baseline at 10 min ($P < 0.001$) and 20 min ($P = 0.002$). There was no difference between CON and MED ($P = 0.383$), or between controls and CHF ($P = 0.863$). There was a significant interaction between time (rest, 10 min and 20 min) and exercise protocol (CON and MED) ($P = 0.030$). However, follow-up tests showed that, although Lac increased to a greater extent in MED at 20 min (Figure 5.3), the difference did not reach statistical significance ($P = 0.079$).



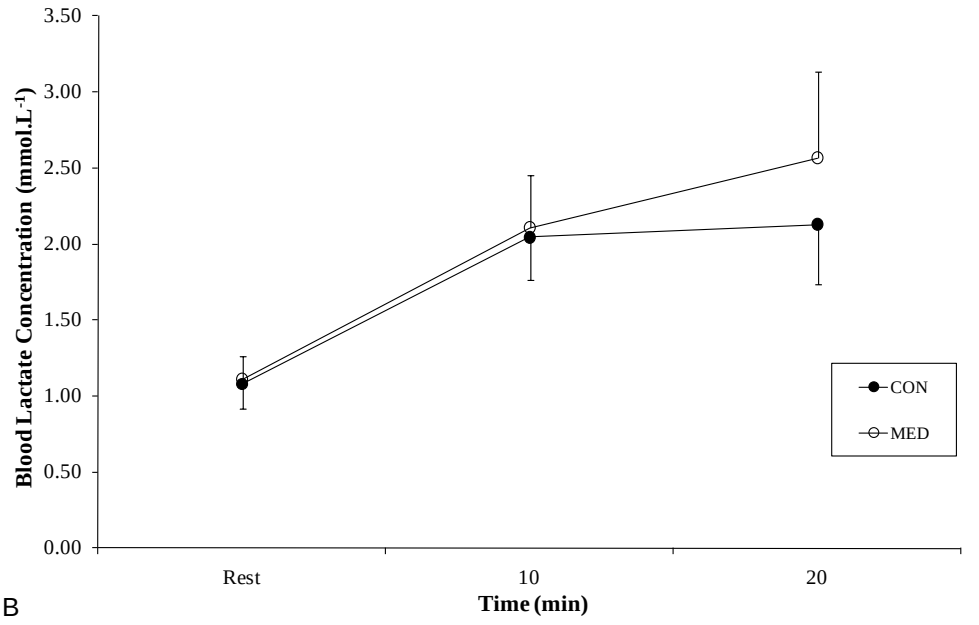


Figure 5.3: Blood lactate concentration (mean ± SEM) in CON and MED in CHF Patients (A) and Controls (B).

5.3 Discussion

Intermittent training allows individuals to exercise at high work loads and, when compared with continuous training, can result in greater improvements in peak exercise capacity than continuous exercise, both in healthy individuals (Gorostiaga et al., 1991) and in CHF (Meyer et al., 1996c). When compared to continuous exercise of the same total work done, short intermittent work bouts appear to impose similar cardiovascular and metabolic demands in healthy individuals (Astrand et al., 1960a; Essen et al., 1977; Foster et al., 1999) and similar cardiovascular, but increased metabolic demands in CHF (Meyer et al., 1998a). In this study, there was no detectable difference in respiratory, cardiovascular or metabolic responses, or perception of effort, during a 20 min bout of either moderate continuous or intermittent exercise in CHF or controls, with the exception of V_E, which was higher in MED.

During CON and MED, there was an upward drift in HR, but no significant increase in respiratory variables, BP, Lac or RPE from the first to the second half of the exercise bout, apart from an increase in VO_2 in MED in the control group. As CON was set at 90% VT, it was anticipated that a steady state would be achieved, that BP and HR responses would be moderate, and that RPE would indicate a moderate level of exercise intensity (i.e. a score between 12 and 14 on the Borg scale) (Ingle, 2007). In MED, the 30s work phases reached 80-90% of VO_{2peak} work rate, yet the exercise response was similar to CON. Our results agree with previous studies in healthy participants reporting that, at an equal total workload, physiological responses to intermittent exercise with short-moderate work phases are very similar to steady-state exercise. This was first demonstrated by Astrand and Christensen, who found that when cycling work at 98% of VO_2max power in healthy individuals was split into short periods of work and rest, it was transformed into a sub-maximal load, reflected by a VO_2 of 63% max and Lac of 2 $mmol.L^{-1}$ (Astrand et al., 1960a). Reloading of myoglobin stores during the recovery period allows a greater aerobic energy output, giving a higher ATP production per glucose unit compared with lactate formation (Christensen et al., 1960). When the same total amount of work was performed, i.e. 60 min intermittent exercise at a high workload with alternating 15s work and recovery phases and 60 min continuous exercise at half the workload, the overall metabolic response was similar (Essen et al., 1977). Brickley et al (2007) confirmed that muscle metabolic responses to high intensity intermittent exercise were similar to those during continuous

exercise matched for total workload in well-trained athletes. This finding was attributed to three possible mechanisms; the low-intensity recovery phase allowing sufficient recovery of metabolites, a dampening effect of the metabolic responses to low-intensity exercise following the prior high intensity exercise, or a dampening effect on the high intensity exercise due to the prior alternating intermittent exercise phases. The apparent dampening of physiological responses during repeated hard-easy transitions, with a balance in metabolic demand achieved during the recovery period, has also been demonstrated in CHF by Meyer et al (1997) in a study where the workloads were comparatively higher than in this study. Although Lac increased from 1.3 $mmol.L^{-1}$ at 6 min to 1.6 $mmol.L^{-1}$ at 15 min, and RPE from 10.7 to 11.5 for leg fatigue, and 10.0 to 11.2 for dyspnea, these values show that the exercise was easily tolerated (Meyer et al., 1997b). In the current study, V_E was higher in MED than in CON. CHF had lower V_E than controls, and neither group demonstrated abnormally high values. Dyspnea was not assessed separately, but overall RPE was not different between exercise bouts. It has been suggested that patients with a low exercise tolerance might find intermittent training subjectively easier than continuous training (Puhan et al., 2004). In this study mean RPE in both exercise protocols was 12 in CHF, between "light" and "somewhat hard", and within the guidelines of 11-14 for moderate exercise (Ingle, 2007). RPE was significantly lower in controls, and the mean value of 10, "very light" to "light", indicates that they perceived the exercise to be significanty easier than CHF did. It has previously been reported that RPE at VT is 11.0 ± 2.1, and does not differ between cardiac patients taking β-blockers, those not taking β-blockers or younger healthy individuals (McConnell et al., 1993).

In Meyer's study the responses to intermittent exercise were compared to responses measured at 75% VO_{2peak} during an incremental exercise test. Cardiac stress, assessed by rate-pressure product, was lower during intermittent exercise despite the work rate being more than double than at 75% VO_{2peak}, while Lac, catecholamines and RPE did not differ. The authors did not detect any significant differences in variables between the work and recovery periods. Similarly, in the current study only minor changes were observed in CHF in respiratory gas exchange, HR or BP between work and recovery phases. In addition to the dampening of responses typically seen in intermittent exercise, this might also be due to the small VO_2 and HR reserve in CHF patients, the HR and BP moderating effects of medication (β-blockers in particular) or to chronotropic incompetence (Witte et al., 2006). Even if fluctuations do occur, the time

lag for each variable might vary making it difficult to draw specific conclusions from any observed differences. The data from controls showed a distinct fluctuation in VO_2 and HR response to the changes in workload during MED, but the mean values for the duration of exercise were no different to CON. The limited capacity for HR increase during exercise in CHF means that it is difficult to use HR to guide or estimate exercise intensity (Beale et al., 2010), although it does not appear to limit exercise tolerance (Witte et al., 2005) or the benefits of exercise training in CHF (Forissier et al., 2001). However, although the absolute HR values during CON and MED were lower in CHF than controls, the percentages of HR_{peak} and HRR were not different between groups (CHF ~75% HR_{peak} and ~45% HRR; controls ~71% HR_{peak} and ~47% HRR). Similarly, the VO_2 during CON and MED relative to VO_{2peak} was slightly, but not significantly, higher for CHF than for controls (CHF ~65% VO_{2peak}; controls ~57% VO_{2peak}). This indicates that, when exercise is prescribed at 90% VT, the average relative intensity in terms of HR and VO_2 will be similar for CHF and controls.

Exercise practitioners may questions whether patients with low VO_{2peak} can practically participate in moderate intensity activity, either in a CR setting or during activities of daily living. This study demonstrates that patients are able to perform 20 min cycling at an intensity just below VT while maintaining a steady-state in VO_2, HR and Lac, at an RPE of 11. This lends further support to the usefulness of identifying VT via CPET for exercise prescription. Six CHF had a VO_{2peak} < 15 $ml.kg^{-1}.min^{-1}$, and VT in these patients ranged from 55-76% VO_{2peak}, and work rate at VT from 17-50 W. Clearly, for patients who reach their VT at work rates as low as 20W, many daily activities will be higher than moderate intensity.

There was no difference in the oxygen cost of exercise between modes of exercise, although CHF did have higher values than controls (11-12 vs 9-10 $ml.W^{-1}$), or in the recovery VO_2. This is in agreement with previous research suggesting that CHF consume more VO_2 than control subjects for the same unit of work during exercise. Levy et al (2004) reported that, at the same submaximal steady-state workload of 35W, CHF patients consumed 14.9 ± 1.2 ml/W compared with 9.7 ± 0.7 ml/W in control subjects. The authors hypothesised that this is due to the decrease in Type I oxidative fibres, oxidative enzymes and mitochondrial density, plus chronic sympathetic activation, reported in CHF (Clark et al., 1996). VO_2 kinetics are slower in CHF than in healthy controls, both at the same constant and relative work rates, meaning that

patients take longer to reach a steady state for VO_2 due to impaired oxygen delivery to the exercising muscles (Sietsema et al., 1994). Recovery of VO_2 to baseline values is also reportedly higher in CHF than in controls, possibly to compensate for the slowed attainment of steady state and consequent oxgyen debt that is repaid following completion of exercise (Sietsema et al., 1994; Levy et al., 2004). In the current study there was no difference in VO_2 during 3 minutes of recovery. However, in Levy et al's (2004) study CHF were exercising at a relatively higher intensity (67% VO_{2peak}) than in the current study, with 11 of the 15 patients above VT, where the oxygen cost of exercise is increased, while control subjects were exercising at a relatively lower intensity (32% VO_{2peak}). Mitchell et al (2003) reported that during maximal incremental exercise CHF may appear to be "economical" by having a low VO_2 per Watt, but that in fact they accumulate a large oxygen debt (Mitchell et al., 2003). The same study also found that CHF became less "economical" above VT. By contrast, the current study demonstrates that, when exercising below VT, CHF use more oxygen per unit of work when compared with controls, but that their early recovery is not delayed in either continuous or intermittent exercise. The additional oxygen cost, and thus the lower economy of energy expenditure in CHF might be partly explained by lack of skill or technique. It is not clear to what extent economy can be improved following training in CHF through optimisation of technique as well as improvement in oxidative capacity. This adaptation in healthy individuals results in the ability to maintain exercise for a longer time at the same intensity, or at an increased intensity for the same period of time (Cooke, 2001). Future studies should address this issue, using appropriate measurements for economy, i.e. VO_2 at a given work rate (Cooke, 2001), and aerobic work "efficiency" (Levy et al., 2004; Wasserman et al., 2005).

Meyer et al (1998) reported that intermittent exercise appeared to be more strenuous than continuous exercise of matched total work, as HR was higher, and Lac continued to increase whereas it was stable in continuous exercise. However, as shown in Study 1, the 16 min exercise bouts were performed at a higher relative intensity than in this study, as the continuous exercise workload was matched to the total intermittent exercise workload, calculated from a steep test, rather than being set below VT as in this study. Lac at the end of exercise was 3.5 $mmol.L^{-1}$ for continuous and 4.1 $mmol.L^{-1}$ for intermittent exercise, compared with values of 1.9 and 2.2 $mmol.L^{-1}$ respectively in this study. The authors estimated that the intensity was likely to be close to maximal lactate steady state (MLSS)

(Meyer et al., 1998a), that is the highest work rate that can be maintained over time without continual blood lactate accumulation (Billat et al., 2003). The work rate at MLSS is assumed to correspond to the work rate at RCP, although in trained individuals RCP occurrs at approximately 10% VO_{2max} higher than MLSS (RCP: 85% VO_{2max} vs MLSS: 74% VO_{2max}) (Dekerle et al., 2003). In the current study, Lac tended to be higher during intermittent exercise than during continuous exercise at 20 min, but not at 10 min. Although there was no statistically significant difference, it is possible that even small increases in Lac could influence exercise tolerance over a longer period. A limitation of this study was that the exercise duration was limited to 20 min. In addition, no lactate threshold measurement was performed, hence it is not possible to interpret Lac values in relation to the lactate threshold, an alternative demarcation for moderate intensity exercise.

5.4 Conclusion

This study investigated the cardiovascular, respiratory, metabolic and RPE responses to continuous and intermittent exercise of matched total workload. The results support the hypothesis that there is no difference in cardiovascular and respiratory responses between continuous and intermittent exercise in CHF. However, the results do not support the hypothesis that metabolic and RPE responses are higher during intermittent exercise than during continous exercise in CHF. The hypothesis that, in control participants, there is no difference in cardiovascular, respiratory, metabolic or RPE responses between continuous and intermittent exercise is supported.

The results of this study complement previous research in this area and show that both continuous and intermittent exercise of matched total work, equal to 90% VT, elicit similar responses in respiratory, cardiovascular and metabolic variables and RPE in both CHF patients and control participants.

CHAPTER 6: THE EFFECT OF VOLATILITY ON ACUTE RESPONSES TO INTERMITTENT EXERCISE IN CHF AND HEALTHY CONTROLS

6.0 Introduction

Intermittent exercise allows both healthy individuals and cardiac patients to exercise at a higher intensity than it would be possible to maintain continuously (Christensen et al., 1960; Meyer et al., 1997b; Billat et al., 2000; Astrand et al., 2003). It may be possible to enhance the training adaptation by increasing the intensity of the work phases to impose a greater exercise stimulus, while still allowing a balance in metabolic demand to be achieved during the recovery phases. In coronary bypass patients, intermittent training resulted in a greater increase in physical performance than continuous training, even though the mean total workload over 20 minutes was lower in the intermittent training condition (Meyer et al., 1990). The authors concluded that improvement in patients with impaired capacities appears to be due to the higher intensity of work in the intermittent training. Subsequent studies by the same group in CHF patients demonstrated that intermittent exercise was more strenuous than continuous exercise, as RPP, La and RPE were all higher, despite the average workload being the same for both types of exercise (Meyer et al., 1998a). Chapter 5 illustrated that the acute responses to intermittent exercise where the 30s work intervals reached 80-90% of VO_{2peak} power did not differ to those during moderate continuous exercise of matched total work load. Other studies of CHF patients have used 30s work intervals of 100% of the workload achieved at VO_{2peak}, or 50% of that achieved in a steep ramp test which, as demonstrated in Chapter 4, is likely to be similar to 100% VO_{2peak} work rate in CHF.

It is not known if manipulating the intensity of the work and rest phases while maintaining the same total workload alters cardiovascular, respiratory and metabolic responses or perception of effort. Only one previous study has investigated the effects of manipulating the intensity of the work intervals in CHF. Meyer et al. (1996a) compared the response to work intervals of 50%, 70% and 80% of steep ramp test WR_{max}, with work phase durations of 30s, 15s and 10s respectively, interspersed with 60s recovery at 15W, thereby decreasing the duration of the work phase to compensate for the increase in intensity (Meyer et al., 1996b). There were no differences in cardiovascular or metabolic responses between the different intermittent protocols, and although the highest work rate induced greater leg fatigue, and an upward drift in HR and BP during the exercise, the exercise was well tolerated. Rate-pressure product

remained within acceptable levels, and VO_2 and Lac did not increase during the course of exercise in any of the 3 protocols.

The aim of the current study was to examine the effect of volatility on cardio-respiratory and metabolic responses to exercise by comparing a high volatility exercise bout (HIGH), where the amplitude of the work phases above the mean (i.e. the volatility) was increased, with a low volatility exercise bout (LOW), where the amplitude of the work phases was decreased, whilst maintaining the same total work by adjusting the workload of the recovery phase. As described in Chapter 5, a continuous bout of moderate intensity exercise (90% VT) was set, and the total workload of the intermittent exercise bouts was matched to this. The work phase for HIGH was set in the extreme exercise intensity domain, while the work phase for LOW was set in the heavy exercise intensity domain.

Hypothesis: High volatility intermittent exercise will elicit higher cardiovascular, respiratory, metabolic and RPE responses than low volatility intermittent exercise or continuous exercise of matched total workload in CHF and control participants.

6.1 Methods

6.1.1 Participants

Ethical procedures and patient inclusion and exclusion criteria were adhered to as detailed in the General Methods. Nine CHF and 5 controls from those described in Study 1 (Chapter 4) participated.

6.1.2 Experimental design

General methods were followed as described in Chapter 3. Participants performed CON, LOW and HIGH, as described in Section 3.4. The same methods for data and statistical analysis described in Study 2 (Chapter 5) were used, i.e. variables during LOW and HIGH were measured and analysed in the same way as those during MED.

6.2 Results

Participant characteristics are shown in Table 6.1

Table 6.1: Characteristics (mean ± SD) of CHF patients and healthy controls

Characteristic	CHF (n=9)	Controls (n=5)
Age (years)	75 ± 9	63 ± 2
Male/ Female	8/1	3/2
Height (cm)	176 ± 11	174 ± 11
Body Mass (kg)	85 ± 17	79 ± 16
NYHA Class II/III	7/2	-
Ejection Fraction (%)	36 ± 9	70 ± 7
Aetiology (ischaemic/dilated cardiomyopathy)	5/4	-
Co-morbidities		
COPD	1	-
Diabetes	1	-
Hypertension	1	-
Medication		
ACE inhibitor	3	-
Angiotensin II receptor blocker	4	-
Anti-arrhythmic	3	-
β blocker	8	-
Calcium channel blocker	2	-
Diuretic	7	-

Table 6.2 describes the maximum exercise capacity measured during CPET, and the derived work rates for CON, LOW and HIGH. In order to maintain equality of total workload in all three exercise bouts, 2 CHF with low functional capacity rested without pedalling during the recovery phase in HIGH. Exercise was well-tolerated by all CHF patients and control participants (RPE$\leq$ 13). Seven out of 9 CHF patients and all 5 controls completed all three 20 minute exercise bouts. One CHF stopped CON after 17 minutes, and another stopped HIGH after 13 minutes, due to leg fatigue. In these cases, the respiratory data from 11-16 min and 5-10 minutes respectively, instead of 15-20 min, were used to compare values across all 3 exercise bouts. All CHF achieved 20 minutes of exercise in LOW.

Table 6.2: Maximum exercise capacity and training work rate (mean ± SEM)

	CHF	Control
Maximum exercise capacity		
VO_{2peak} (ml.min^{-1})	1,363 ± 150	2,034 ± 232
VO_{2peak} (ml.kg^{-1}.min^{-1})	15.9 ± 1.5	25.5 ± 1.6
Peak work rate (W)	86 ± 10	150 ± 17
Exercise training work rate		
CON (W)	36 ± 4	58 ± 5
LOW (W): work phase	58 ± 8	85 ± 10
HIGH (W): work phase	95 ± 10	148 ± 17
LOW (W): recovery phase	26 ± 3	46 ± 4
HIGH (W): recovery phase *	11 ± 3	18 ± 2
* recovery phase for 2 CHF = rest		

The Q-Q plots of normality and Kolmogorov-Smirnov tests showed that the assumption of normality had been met in all variables except RPE, where non parametric tests were therefore selected. The assumption of sphericity was violated for the change in Lac and HR over time, hence the Greenhouse Geisser adjustment was applied.

Table 6.3 presents the data for CON, LOW and HIGH for CHF and controls. There was no significant difference in respiratory variables or in HR or BP between exercise protocols in CHF or controls ($P > 0.05$). Lac was significantly higher in HIGH than in CON ($P = 0.002$) and LOW ($P = 0.023$) in CHF and controls. RPE was not significantly different between exercise protocols, or between CHF and controls, with the exception of LOW, where RPE was significantly higher in CHF than controls ($P = 0.012$).

Figure 6.1 illustrates Lac over time for the 3 exercise protocols. Lac values increased significantly above baseline at 10 min ($P < 0.001$) and 20 min ($P < 0.001$) in all exercise protocols. There was no significant difference between controls and CHF ($P = 0.286$). There was a significant difference in Lac between CON, LOW and HIGH ($P = 0.004$), with a moderate effect size ($\eta^2 = 0.341$), and a significant interaction between time and exercise protocol ($P = 0.001$). Follow-up tests (Bonferroni adjustment: α level

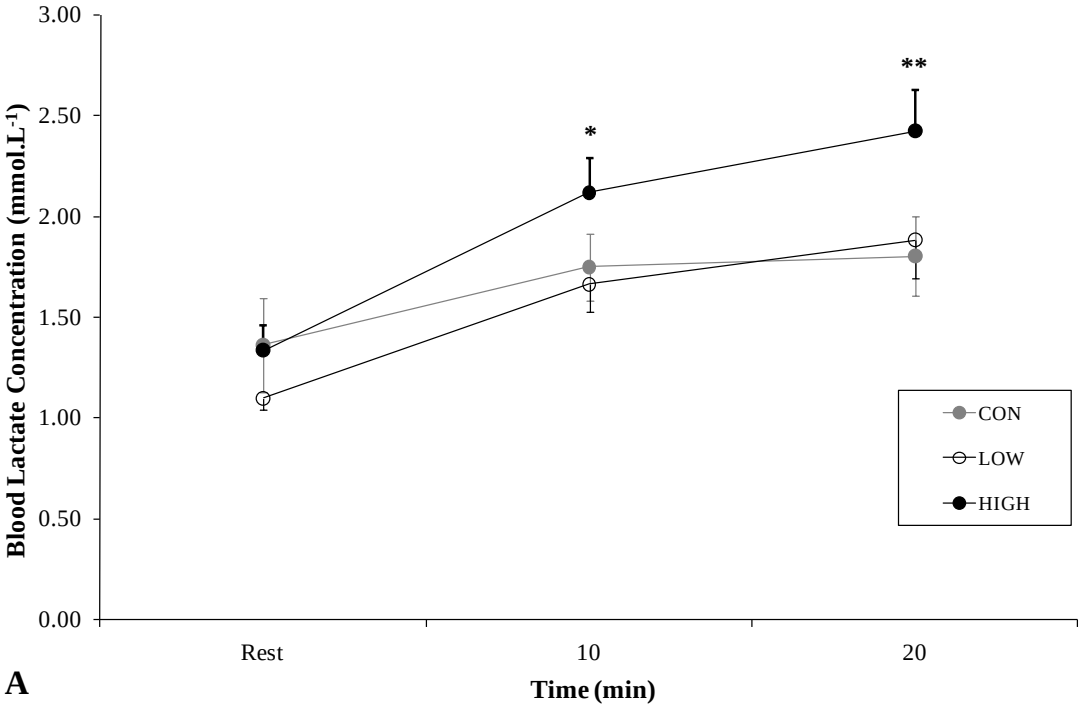
$P \leq 0.0167$) showed that in CHF Lac at 10 min and 20 min was greater in HIGH than LOW ($P < 0.001$ and $P = 0.012$ respectively). In controls Lac was significantly greater in HIGH compared to CON at 20 min ($P = 0.011$) .

Table 6.3: Responses to continuous (CON), low volatility (LOW) and high volatility (HIGH) intermittent exercise in CHF patients and controls

Values for Ventilation, RER, Heart Rate, Blood Pressure, Blood Lactate Concentration and Rating of Perceived Exertion are mean values for the 20 min exercise bout.

	CHF			**CONTROL**			
	CON	**LOW**	**HIGH**	**CON**	**LOW**	**HIGH**	
Resting VO_2 ($ml.min^{-1}$)	260 ± 14	268 ± 18	274 ± 19	304 ± 38	331 ± 42	307 ± 48	
Unloaded VO_2 ($ml.min^{-1}$)	449 ± 30	434 ± 34	437 ± 36	598 ± 99	596 ± 89	602 ± 103	
Average exercise VO_2 ($ml.min^{-1}$)	859 ± 92	837 ± 97	858 ± 115	1,201± 92	1,252 ± 142	1,233 ± 138	†
Total net exercise VO_2 (ml) (work-rest)	11,820 ± 1,656	11,548 ± 1,767	11,675 ± 1,992	17,940 ± 1,103	18,400 ± 2,034	18,508 ± 1,741	†
% VO_{2peak}	67 ± 3	65± 5	66 ± 4	57 ± 3	59 ± 2	58 ± 3	
Average 15-20 min net VO_2 ($ml.min^{-1}$)	457 ± 91	435 ± 95	457 ± 94	682 ± 60	757 ± 104	756 ± 60	†
Exercise economy (VO_2/W)	11.7 ± 1.3	11.8 ± 1.6	11.2 ± 1.7	10.1 ± 1.1	10.8 ± 0.8	10.4 ± 0.7	
Recovery VO_2 (3 min) (ml)	1,037 ± 192	1,159 ± 222	1,028 ± 173	1,030 ± 102	1,088 ± 175	1,147 ± 158	
Ventilation ($L.min^{-1}$)	27 ± 2	27 ± 3	28 ± 3	35 ± 4	39 ± 5	39 ± 5	†
RER	0.93 ± 0.02	0.93 ± 0.02	0.93 ± 0.01	0.91 ± 0.03	0.94 ± 0.04	0.93 ± 0.04	
Heart Rate (beats. min^{-1})	78 ± 3	78 ± 2	78 ± 3	115 ± 9	115 ± 8	116 ± 8	†
% Peak Heart Rate	75 ± 3	74 ± 3	75 ± 3	73 ± 3	71 ± 2	75 ± 3	
% Heart Rate Reserve	46 ± 3	44 ± 3	45 ± 4	47 ± 4	49 ± 3	50 ± 5	
Blood Pressure (systolic) (mmHg)	125 ± 6	122 ± 6	123 ± 5	151 ± 7	147 ± 5	159 ± 6	†
Blood Lactate Concentration ($mmol.L^{-1}$)	1.8 ± 0.2	1.9 ± 0.2	2.4 ± 0.2 *	2.2 ± 0.5	2.5 ± 0.3	3.1 ± 0.6 *	
Rating of Perceived Exertion	11.8 ± 0.2	12.3 ± 0.3	11.5 ± 0.6	10.9 ± 0.3	11.0 ± 0.3	10.3 ± 0.5	††

Difference between exercise bouts: * P < 0.05 HIGH vs CON and LOW
Difference between groups † *P* < 0.05 CHF versus Controls; †† P < 0.05 CHF versus Controls in CON and LOW



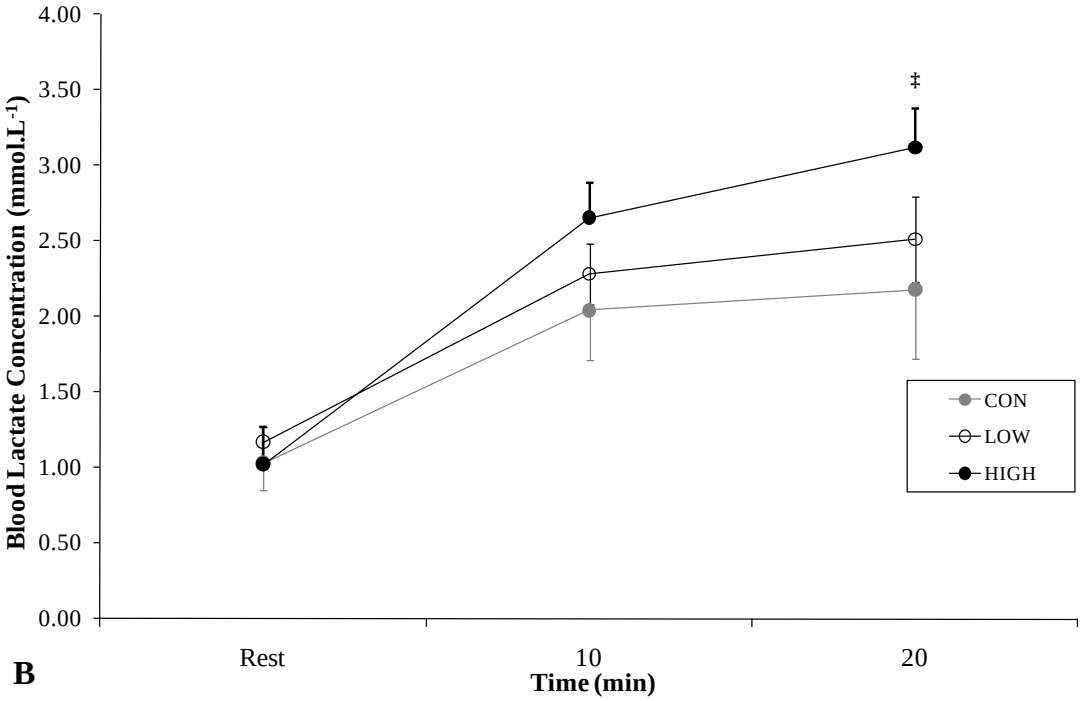


Figure 6.1: Blood lactate response (mean ± SEM) to CON, LOW and HIGH in (A) CHF and (B) Controls

* $P < 0.05$ HIGH vs LOW in CHF at 10 min

** $P < 0.05$ HIGH vs LOW in CHF at 20 min

‡ $P < 0.05$ HIGH vs CON in controls at 20 min

Analysis of variables at 5, 10, 15 and 20 min did not reveal any significant difference between CON, LOW and HIGH. There was an upward drift in HR in both groups, but there was no significant difference in HR at 5, 10, 15 and 20 min between exercise protocols once the rest and recovery phase values were averaged ($P > 0.05$). Figure 6.2 illustrates the HR response during CON LOW and HIGH. HR was significantly lower ($P<0.05$) in CHF than controls, and CHF demonstrated a blunted HR response between work and rest phases compared with controls.

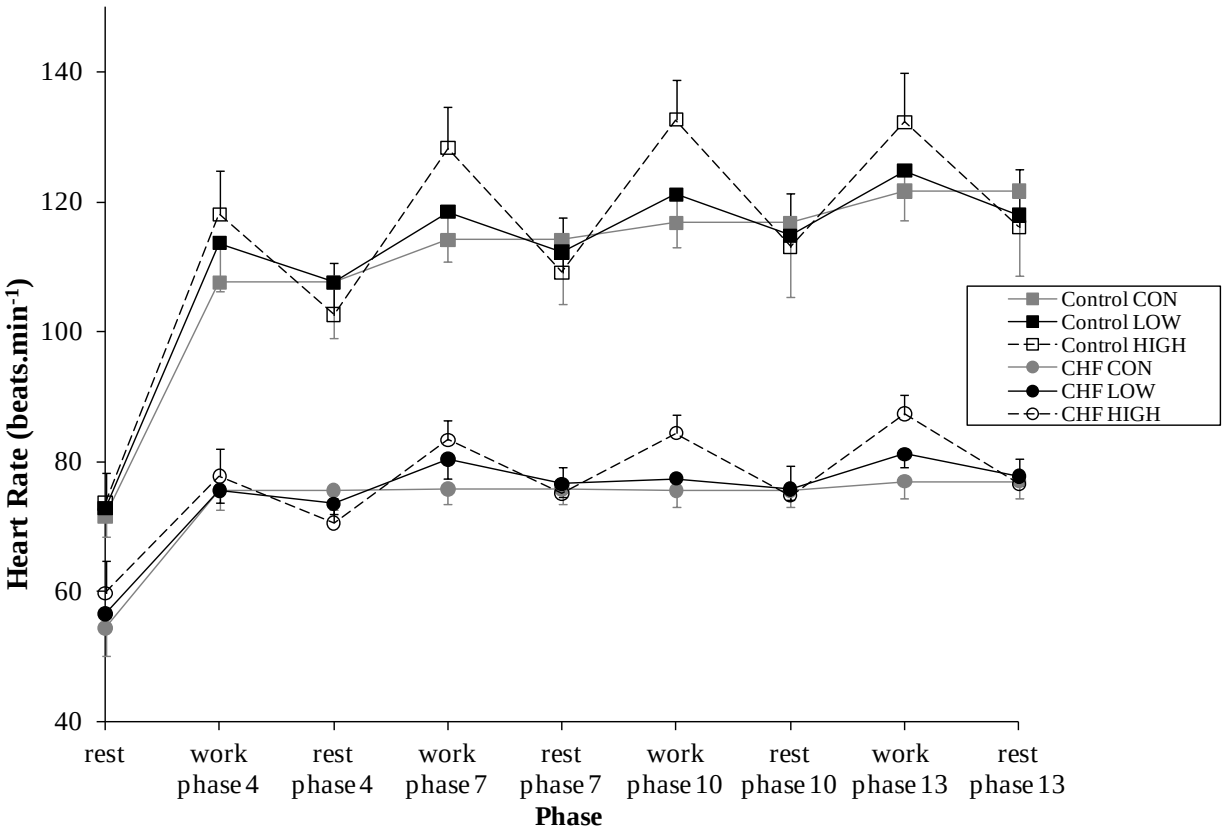


Figure 6.2: Heart rate response (mean ± SEM) to CON, LOW and HIGH during work and recovery phases at 5, 10, 15 and 20 min during exercise in CHF and controls

6.3 Discussion

The current study demonstrates that, if the total workload is kept equal, respiratory and cardiovascular responses, and RPE, are not different in continuous exercise at 90% VT, high or low volatility intermittent exercise. However, high volatility exercise induces a significantly greater increase in Lac, suggesting that the exercise stimulus to the peripheral muscles is greater in this condition.

It has been reported that, in healthy individuals, high intensity work phases of 60s or more produce a different metabolic response to shorter work phases, with Lac values continuing to increase, whereas in shorter work phases and continuous exercise it remains stable (Astrand et al., 1960a; Foster et al., 1999). The data in the current study suggest that, in CHF patients and older individuals, even in 30s work phases, when the work load is increased beyond a certain level the increased metabolic demand cannot be fully compensated during the recovery phases, even if these impose minimal work or rest. One CHF was unable to continue HIGH after 13 minutes due to self-reported leg fatigue. Imposing too high a work rate in the work phase can lead to localised peripheral fatigue which ultimately compromises exercise tolerance, although this was not seen in the other 8 CHF. A recent review paper suggests that lactate plays a role in the detection of severe exercise stress, signalling to nerve cells, and ultimately leading to reduction or cessation of exercise (Philp et al., 2005). The same reviewers also propose that the presence of lactate mimics hypoxic conditions, and triggers adaptive responses in the muscle, including angiogenesis and oxidative defence mechanisms, thus supporting the idea that HIGH applies a greater training stimulus than LOW or CON.

The response to high volatility intermittent and continuous exercise agree with those reported by Meyer et al (1990) in coronary bypass patients, where high intensity intermittent exercise induced significantly greater increases in Lac than continuous training, although cardiovascular responses were similar. A study in trained athletes also demonstrated that average HR, VO_2, energy cost and RPE were the same in response to continuous and intermittent cycling of the same average intensity, but Lac was higher during intermittent training (Palmer et al., 1999). Left ventricular function is similar in continuous and intermittent exercise, in both healthy individuals and CHF,

and there appears to be a dampening in haemodynamic response similar to the dampening in VO_2 (Meyer et al., 1998a; Foster et al., 1999).

Only one study in CHF has previously manipulated the workload of intermittent exercise bouts, by comparing three protocols with work bouts set at different percentages of steep test WR_{max}: 50% for 30s duration, 70% for 15s and 80% for 10s, interspersed with 60s recovery (Meyer et al., 1996b). As discussed in Chapter 4, Meyer et al's 30s intermittent work rate was higher than the high volatility work rate for CHF in the current study. Even at these higher work rates, Meyer et al reported no significant difference, or increase during exercise, in VO_2, VCO_2, V_E, RPP or catecholamines, suggesting that increased intensity can be compensated for by reducing duration. In contrast to the results in the current study, Lac in Meyer et al's study did not differ between exercise protocols. Values remained close to resting levels, and were between 1.2 ± 0.1 and 1.3 ± 0.1 $mmol.L^{-1}$ lower than in the current study. However, Meyer et al sampled capillary blood from the ear lobe whereas forearm venous blood was sampled in the current study. Different sampling sites and methods may influence lactate values, with finger capillary blood taken during cycle and treadmill exercise showing higher values that venous or ear lobe samples (Dassonville et al., 1998).

HR increased by a maximum of 5 $beats.min^{-1}$ in LOW and 9 $beats.min^{-1}$ in HIGH in CHF, but there was no difference in average values between exercise protocols, nor was there a difference in BP. In Meyer et al's study HR and BP were also stable throughout the 50 and 70% intensities, and, although they increased towards the end of the 80% intensity, RPP was only 83-88% of the value reached at 75% VO_{2peak}. Leg fatigue was also higher at the end of the 80% intensity indicating that very high work loads may induce local fatigue and perception of effort. Nevertheless, the highest value of 12.4 was similar to the results of the current study, where there was no difference in RPE between exercise protocols, and mean values were between 11.5 and 12.3. These values indicate a moderate level of effort, and correspond RPE values previously reported at VT (McConnell et al., 1993). As described in Chapter 5, RPE values for controls were lower than for CHF in CON and LOW, indicating that they perceived the exercise to be easier, even though the relative intensity was set at the same level for both groups. However, there was no difference in RPE between controls and CHF in

HIGH. It is interesting that, despite the higher Lac, this was the only exercise protocol in which CHF did not rate the exertion higher than controls did.

A further study by Meyer et al (1998) compared 16 min intermittent exercise at 50% steep ramp for 30s and 60s recovery phases of 10W with continuous exercise set at the same mean work load. Intermittent training appeared to be more strenuous than continuous exercise, reflected by a higher HR, and a continuing increase in Lac compared with a stable Lac response in continuous exercise. Once again, the mean work load was higher than in the current study, and the continuous exercise was matched against the intermittent exercise, rather than being set below VT. This is reflected by the higher Lac levels (intermittent: 4.1 ± 0.4, continuous: 3.5 ± 0.4 $mmol.L^{-1}$). The authors estimated the intensity to be at or below maximum lactate steady state (Meyer et al., 1998a). The values were obtained from arterialised blood, compared with capillary blood in their earlier study, and the differences in the method of blood sampling might explain why the values were considerably higher in the second study, although the 30s work load was set at the same intensity (Yoshida et al., 1982).

In the current study it was not straightforward to match the total workload in HIGH to CON and LOW, particularly in patients with a low exercise capacity. The average workload for CON, i.e. 90% VT, was 36W, thus the range of adjustments to the amplitude below the mean for the recovery phases is very limited in CHF. The two CHF with the lowest exercise capacities stopped pedalling during the rest phase in order that the total work done for all 3 protocols was equal. Active recovery from intermittent exercise is recommended rather than rest in order to facilitate blood flow and lactate removal (McLellan and Skinner, 1982). For the purpose of this study, i.e. to compare the acute responses to intermittent versus continuous exercise, and to examine the effects of volatility, we ensured that the total work done was equal across CON, LOW, and HIGH. In practice, it may be better to perform an active recovery with unloaded pedalling, even if this results in a greater total amount of work done. In fact, greater training adaptations are reportedly achieved after high intensity intermittent training compared with continuous training because it allows a greater amount of work to be achieved. Meyer et al (1997) noted that the amount of work achieved during high intensity intermittent training, with recovery phases set at 15W, was much greater than would be achieved by exercising continuously at 75% VO_{2peak}.

As reported in Chapter 5, although the absolute values for HR were lower in CHF than controls, presumably due to the effect of β-blockers and chronotropic incompetence, there was no significant difference in relative exercise intensity, in terms of % HR, % HRR or % VO_{2peak}, between CHF and controls during CON, LOW or HIGH. In the current study there was no difference in exercise "economy" between CHF and controls. This is in contrast to the higher oxygen cost of work in CHF reported in Chapter 5. Observation of the VO_2 response to intermittent exercise in these studies shows minor fluctuations in CHF in response to the work and rest phases, whereas in controls the fluctuations are more pronounced (Figure 5.1). It is beyond the scope of these studies to assess VO_2 kinetics during intermittent exercise, but future studies should investigate whether slowed VO_2 kinetics explain the blunted VO_2 responses between work and rest phases, and how this relates to the underlying pathophysiology. Methodological issues as well as physiological determinants and clinical relevance of VO_2 kinetics measurement are discussed in a recent review (Kemps et al., 2009). It is possible that a greater oxygen "debt" accrued during the work phase is repaid during the recovery phase, resulting in the minimal changes in VO_2 between phases. Although slowed VO_2 kinetics have been reported in CHF during incremental exercise (Cohen-Solal et al., 1997), and patients may show a prolonged VO_2 kinetics response compared to controls at the same absolute work rate, the response appears to be similar at the same relative work rate (Sietsema et al., 1994; Hepple et al., 1999). Future work could assess the effect of a longer active recovery on the VO_2 response, and the implications for exercise training.

6.4 Conclusion

The aim of this study was to investigate the effect of adjusting the volatility of intermittent exercise, while maintaining the same total work (equal to continuous exercise at 90% VT), on cardiovascular, respiratory, metabolic and RPE responses. Lac was significantly higher in HIGH compared to LOW and CON, supporting the hypothesis that high volatility intermittent exercise elicits higher metabolic responses than low volatility intermittent exercise or continuous exercise of matched total workload in CHF and control participants. However, the hypothesis that high volatility intermittent exercise also elicits higher respiratory, cardiovascular and RPE responses

than low volatility intermittent exercise or continuous exercise of matched total workload is not supported.

A 20 minute intermittent exercise bout with work phases set in the extreme exercise intensity domain, 10% above the highest work rate reached during a standard maximal incremental exercise test, was well tolerated by CHF patients, and would be an appropriate protocol for a training programme. The increased Lac in these high volatility work phases suggests that the challenge to cellular homeostasis was higher than when the volatility was reduced, which could theoretically induce greater adaptations after a period of training by this method. Previous studies have reported that intermittent exercise training results in greater increases in aerobic exercise performance than continuous training in healthy individuals (Gorostiaga et al., 1991), in patients after coronary bypass surgery (Meyer et al., 1990) and in CHF patients (Meyer et al., 1997b).

CHAPTER 7: COMPARISON OF HIGH INTENSITY INTERMITTENT TRAINING TO CIRCUIT-BASED AEROBIC TRAINING AT IMPROVING FUNCTIONAL CAPACITY, VENTILATORY EFFICIENCY, BNP AND QUALITY OF LIFE IN CHF

7.0 Introduction

Despite the growing body of evidence in favour of exercise training for CHF, there is less evidence that study findings are transferable to clinical practice. Firstly, it has been reported that the exercise dose in randomised controlled trials of CR is more than four times greater than is usual UK practice (Taylor et al., 2007). Secondly, the majority of studies are not representative of the total population of CHF patients. Older patients, females, individuals with implantable devices and those with more severe heart failure and/or co-morbidities tend to be excluded (Rees et al., 2004). More than half of the exercise training studies in CHF have been published since 2000, with the greatest proportion appearing in the past 5 years (Figure 7.1), i.e. post-dating the start of this thesis in 2004. The majority of these studies have focussed on aerobic training at a steady-state intensity expressed as a percentage of VO_{2peak} (range 50-80%), of HR_{max} (range 60-80%) or of HRR (range 60-80%) (van Tol et al., 2006). More recent studies have included different methods to achieve training adaptations, including intermittent and resistance as well as aerobic training. Details of exercise training studies in CHF are presented in Appendix 1 (Tables A1 and A2), and several of these have been discussed in the Review of Literature.

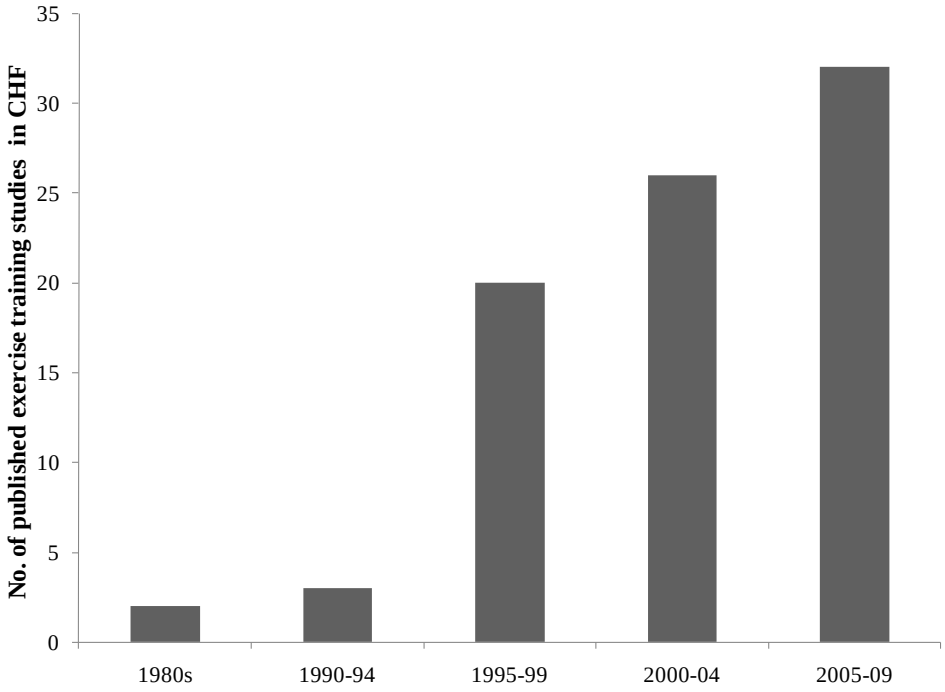


Figure 7.1: Estimation of number of studies on exercise training in CHF patients published between 1980 and 2009

Meyer's landmark study in 1996 suggested that short-term intermittent exercise training is more effective at improving cardio-respiratory fitness than longer-duration moderate intensity exercise for CHF patients as it provides a greater stimulus to the peripheral muscles (Meyer et al., 1996b). ESC and AHA guidelines suggest that intermittent exercise, based on Meyer et al's protocols, may be appropriate for CHF (Giannuzzi et al., 2001; Pina et al., 2003). Studies 1-3 of this thesis demonstrate that the traditional method of setting intermittent work intensity at 100% workload achieved at VO_{2peak} is based on sound physiological principles, is reproducible and achievable by CHF. Since Meyer's study a handful of other studies have investigated the effectiveness of intermittent training for CHF. These include one observational (Meyer and Laederach-Hofmann, 2003) and one cross-over study (Meyer et al., 1996c), two RCTs comparing intermittent with no training (Willenheimer et al., 1998; Sabelis et al., 2004), three RCTs comparing intermittent with continuous training (Dimopoulos et al., 2006; Roditis et al., 2007; Wisloff et al., 2007) and one comparing intermittent with continuous and with no training (Nechwatal et al., 2002). The latter 4 studies have been published since the current series of studies. A variety of intermittent protocols have been employed, including 50% WR_{peak} in Meyer's steep ramp test, 100% WR_{peak} in a maximal CPET, or a percentage of maximal HR in studies where the work phases are $\geq$ 90s. Table 7.1 summarises the studies applying intermittent work phases of $\leq$ 90s.

Although they demonstrate the benefits of intermittent training compared with usual care, these studies offer conflicting information about whether it has any benefits over moderate continuous training. A short-duration RCT reported that intermittent and continuous training improved maximal and sub-maximal exercise capacity to a similar extent, but that intermittent improved central haemodynamics to a greater extent, while continuous had a more beneficial effect on psychological well-being (Nechwatal et al., 2002). Although the duration of this study was only 3 weeks, training frequency was high at 5-6 times per week, similar to Meyer's study. When training was applied 3 times per week for 12 weeks, high intensity intermittent training resulted in similar increases in VO_{2peak} and VT compared with continuous training (Dimopoulos et al., 2006; Roditis et al., 2007). However, longer work phases of 4 minutes, performed at a lower intensity, were more effective than continuous training at increasing VO_{2peak} and LV and mitochondrial function as well as reducing BNP, a marker of LV stress

Table 7.1: Summary of intermittent exercise training studies (with work phases of 30s -90s) in CHF patients.

Study	Design	Sample	Exercise Intervention	Outcome Variables	Results
Dimopoulos et al (2006)	RCT parallel two-group study comparing continuous (C) to interval (I) training	Randomised n=29 CHF; completed n=24 (C/I) 14/11, Age (C/I) 61 ± 10/62 ± 7 yrs; Men/ women (C vs I)14/0 vs 9/1; NYHA I/II/III 4/9/1 vs 3/6/1, LVEF (C/I) 31 ± 10/ 35 ± 11 %; aetiology (C/I) ischaemic 5/14, DCM 8/6, valvular 1/1; medication (C/I): ACE inhibitors 13/10, diuretics 11/10, digitalis 6/4, β-blockers 12/8	3 x 40 min sessions per week for 12 weeks. C: 50% peak work rate, increased by 5% every 4 weeks; I:30s @ 100% peak work rate, increased by 10% every 4 weeks, alternated with 30s rest	CPET on cycle ergometer, chronotropic response, heart rate recovery at 1 min	Significant improvement in VO_{2peak} (C 6% ,I: 8%) and VT (C 10% I: 6%). Only C showed significant improvements in chronotropic response (26%) and heart rate recovery (61%)
Roditis et al (2006)		Randomised n=21 CHF (C/I) 11/10		Oxygen uptake kinetics	Significant increase in phase I oxygen uptake kinetics in both groups. Only C showed significant improvements in phase II oxygen uptake kinetics
Meyer et al (1996)	Crossover RCT comparing combined aerobic interval and resistance training with usual care	Randomised n=18 male CHF NYHA II/III (8/10), Age (mean ± SEM) 52 ± 2 yrs; LVEF 21 ± 2 %; aetiology: ischaemic 9, dilated cardiomyopathy; medication (E/C): ACE inhibitors 16, diuretics 16, digoxin/digitalis 14, β-blockers 7	5 x 15 min cycle ergometer (30s work @ 50% steep ramp test peak work rate: 60s @ 15W) 3 x 10 min treadmill (60s work: 60s low speed) 3 x 20 min flexibility, strength + inspiratory exercises per week for 3 weeks	CPET on cycle ergometer (12.5 $W.min^{-1}$)	Significant improvement in VO_{2peak} (20%) & VT (24%) after exercise compared with activity restriction
Meyer et al (2003)	Observational study measuring improve-ments in quality of life after cardiac rehab.	n=51 CHF NYHA I/II/III 3/26/22, Male/female 43/8, Age 59 ± 11 yrs; LVEF (E/C) 30 ± 13/32 ± 15 %; aetiology: ischaemic 28, dilated 19, valvular heart disease 4; medication: ACE inhibitors, diuretics, β-blockers, angiotensin II inhibitors	3 sessions per week (30 min cycle ergometer interval training, 30-45 min calisthenics, resistance and respiratory training and 1 hour/week multidisciplinary education for 12 wks	CPET on cycle ergometer (12.5 $W.min^{-1}$), 6 min walk distance, and QoL via SF-36 and MLHFQ	Significant improvement in VT (12%), VO_{2peak} (11%), SF-36 physical functioning, role physical and mental health and MLHFQ sum (29%) and physical scores (37%)

Study	Design	Sample	Exercise Intervention	Outcome Variables	Results
Nechwatal et al (2002)	RCT comparing interval and continuous training	Randomised E1 (continuous: n=20) E2 (interval n=20) E3 (control: n=10) CHF NYHA I-III ; LVEF (E1/E2/C) 27/29/27 %; aetiology: ischaemic/DCM, 9 evaluated for heart transplant	E1: 6 x 15 min cycle ergometer sessions @ 75% HR_{max} for 3 weeks; E2: 6 x 15 min cycle ergometer sessions with intervals @ 50% Steep ramp test peak work rate for 3 weeks	CPET on cycle ergometer, haemodynamic measurements and QoL via SF-36	Significant increase in VO_{2peak} (E1: 14%; E2: 14%) and VT (E1: 9%; E2: 8%). No difference between groups. No change in central haemodynamics in E1, but significant improvement in cardiac index, stroke volume index, and peripheral resistance in E2. QoL improved significantly in both groups; psychological sum factor improved more in E1.
Sabelis et al (2004)	RCT comparing exercise with usual care	Randomised n=77 CHF NYHA II-III LVEF < 35% age 40-70 years, completed n=61 (E/C) 36/25; male/female (E vs C) 25/11 vs 20/5 aetiology (E/C): ischaemic 53/52%, dilated 47/48%; medication (E/C): ACE inhibitors 75/84%, diuretics 53/60%, digoxin 13/31%, β-blockers 50/52%	2 x 60 min supervised sessions/week (warm-up, interval training 30s work @ 50% steep test peak work rate/60s recovery plus strength and endurance exercises @ 70% steep test HR_{max}) and 2 x 11 min home-based sessions for 6 months	CPET on cycle ergometer (20W every 3 min), insulin sensitivity (euglycaemic hyperinsulinaemic clamp)	Significant increase in VO_{2peak} (6%) in E vs C. No significant effect of training on insulin sensitivity, although change in insulin sensitivity correlated positively with change in VO_{2peak}
Willenheimer et al (1998)	RCT comparing interval exercise training with usual care	Randomised n=54 CHF; completed n= 49 (E/C) 26/23 ; Age (E/C) 64 ± 9/ 64 ± 5 yrs; NYHA I/ II/III (E/C) 3/8/16 vs 3/11/8; LVEF (E/C) 36 ± 11/35 ± 11 %; ischaemic aetiology (E/C) 78/73; medication: ACE inhibitors 100/100 %, diuretics 93/95 %, digitalis 30/50%	3 x 15-45 min sessions per week interval training (90s @ 80% VO_{2peak} HR ± 5 $beats.min^{-1,}$ or RPE 15, for as long as possible, 30s rest) for 16 weeks	CPET on cycle ergometer (30W start, 10 $W.min^{-1}$ increments), LV function via echocardiography, dyspnea-fatigue index, QoL and habitual physical activity	No significant improvement in VO_{2peak} or VT in E (5%) vs C, despite significant increase in exercise duration (7W, 6%) and global QoL. Men with ischaemic aetiology (n=11) improved significantly more than non-ischaemic aetiology and women.

Abbreviations: ACE angiotensin converting enzyme; CPET cardiopulmonary exercise test; C control group; E exercise group; HR heart rate; LVEF left ventricular; MLHFQ Minnesota Living with Heart Failure Questionnaire; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold

(Wisloff et al., 2007). When the intermittent work phases were lower in intensity and duration, neither VO_{2peak} or VT increased (Willenheimer et al., 1998).

An observational study reported increases in QoL as well as cardio-respiratory fitness following intermittent training (Meyer and Laederach-Hofmann, 2003). Sabelis et al (2004) reported that intermittent training twice per week, a frequency more in line with UK current practice, increased VO_{2peak} compared with no training, but the 6 month study duration is considerably longer than current UK programme duration. Furthermore, in all these studies, with the exception of Wisloff et al (2007), the patients' mean age was approximately 60 years, younger than the majority of CHF who might benefit from exercise training.

Many UK CR exercise classes comprise circuit-training where patients move around a series of different work stations to perform aerobic and muscular strength and endurance exercises for a pre-determined period, usually 1-2 min. The British Association for Cardiac Rehabilitation (2006) recommends an intensity for aerobic exercise of 60-80% HR_{max} or 40-70% HRR and an RPE of 12-15, although, it is unlikely that these targets can be accurately adhered to in practice (Beale et al, 2010, Appendix 7). Circuit training is, arguably, a form of intermittent training in that there are periods of aerobic exercise interspersed with active recovery and/or muscular strength and endurance exercises. Nevertheless, this differs from high intensity intermittent exercise because the intensity of the work phases is intended to be moderate. There is some evidence confirming that circuit-training is appropriate for CHF, and that it induces a similar oxygen and haemodynamic demand to continuous cycle ergometer exercise at 70-80% HR_{max} (Green et al., 2001). However, given the low frequency and duration of UK CR programmes (~ 1.6 sessions per week for 7 weeks) (Taylor et al., 2007), high intensity intermittent exercise might compensate for this low exercise dose.

Given the compelling body of evidence supporting the benefits of exercise training for CHF patients, and the recommendation that clinically stable patients should undertake exercise training, it would not be ethical to have a control group from who exercise training is withheld. CR programmes are increasingly inclusive of this population, and "usual care" now includes an optional short-term exercise programme, based on moderate intensity exercise which is commonly circuit-based. In the light of previous

studies that have demonstrated either no change or a decline in health in CHF who are inactive for several weeks (Hambrecht et al., 1995a; Meyer et al., 1996c; Maiorana et al., 2000), this study proposes to investigate differences in response to different types of training, rather than between training and no training. Evidence-based practice is now mandatory, supporting the need to compare new treatment strategies with current therapy (Beckers et al., 2008), in this case comparing a novel training method with existing CR exercise training.

Aim

The aim of this study is to investigate whether high intensity intermittent exercise training is different to moderate intensity circuit-based training at improving functional capacity, ventilatory efficiency, BNP and QoL in chronic heart failure patients in a short-term twice-weekly CR programme.

Hypothesis

There will be no difference between traditional circuit-based and high intensity intermittent exercise training in improving functional capacity, ventilatory efficiency, BNP and quality of life in CHF on a 6 week CR programme.

7.1 Methods

7.1.1 Participants

The study population was obtained by screening all clinically stable patients with CHF under the care of the Specialist Heart Function Nurse at Eastbourne District General Hospital. Patients who met the inclusion criteria (described in the General Methods) were approached by telephone to establish initial willingness to participate. Full study details were sent to those who indicated this willingness. A minimum of one week later, these patients were contacted by telephone and those who volunteered to participate were invited to a familiarisation exercise testing session. Provided that there were no reasons to exclude these patients following this initial session, they were enrolled in the study. Ethical approval and participant informed consent was obtained as described in the General Methods.

Fifty CHF were screened as meeting the inclusion criteria. Of these, 32 patients agreed to take part in the study. 26 of these met the inclusion criteria, and were enrolled in the study. Patients were evaluated at baseline and after 12 sessions of exercise training performed twice weekly for 6 weeks. Data collection was carried out over a period of 16 months, from July 2008 to October 2009.

7.1.2 Experimental design

The study involved baseline testing, randomisation to one of two exercise training groups for 6 weeks, and follow-up testing. It was not possible to blind either the patients or the assessors to the group assignment. A schematic of the experimental design is shown in Figure 7.2.

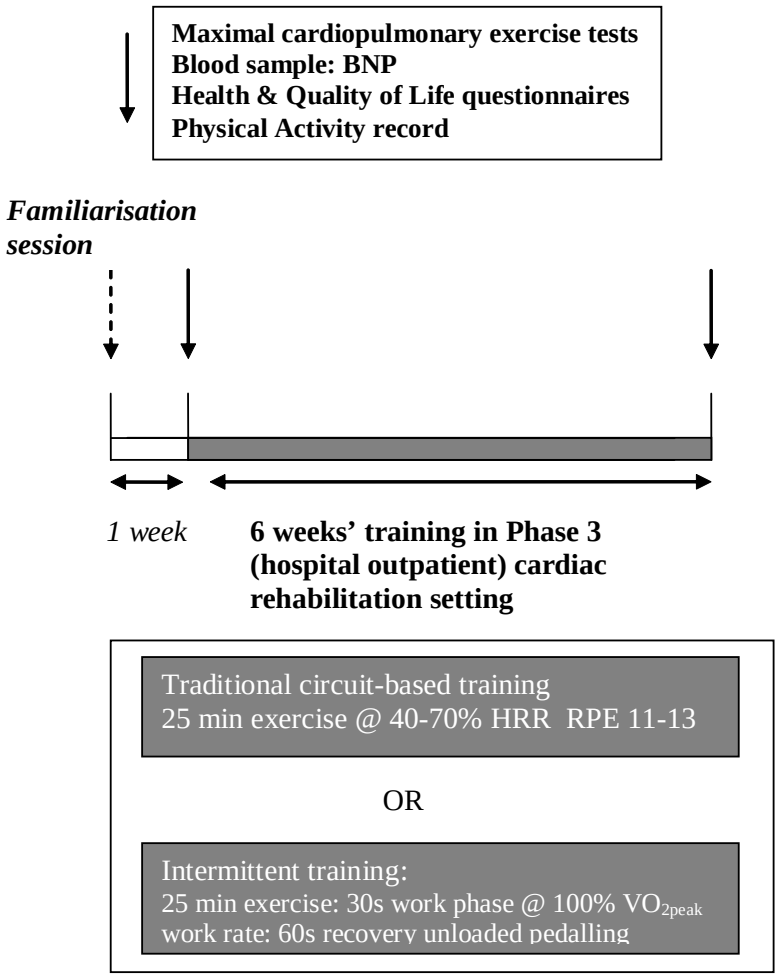


Figure 7.2: Schematic of experimental design

7.1.3 Cardiopulmonary exercise test

Standardisation procedures, as described in the General Methods were followed. Based on the findings in Chapter 4, which demonstrated a learning effect between the first and second attempts at a maximal exercise tests, the current study included familiarisation tests for patients who had not previously performed a maximal test on a cycle ergometer.

The equipment used in this study differed from studies 1-3. The ergometer was a semi-recumbent cycle (semi-couch Schiller, Baar, Switzerland, safety ergometer 911 BP/LS, including ergosana measuring system, ergosana Ganshorn Medizin Electronic (GmbH), Bitz, Germany). The initial resting phase was 3 minutes, followed by a starting workload of 10 W, with increments of 10 $W.min^{-1}$ as recommended by the ESC (Tavazzi et al., 2001). Patients were asked to maintain a pedal cadence of approximately 60 rpm, and were verbally encouraged to exercise to exhaustion, as defined by intolerable leg fatigue or dyspnoea. Patients stopped pedalling when exhaustion was reached. During the recovery period, patients were advised to pedal with no added resistance at a self-selected cadence in order to avoid venous pooling in the legs and subsequent hypotension.

Ventilatory expired gases were obtained at rest and during exercise via a face mask using a breath-by-breath respiratory gas analysis system (Schiller ergo-spirometry unit with Ganshorn Power Cube gas analysis). Respiratory gas exchange variables were produced automatically over a 10s average. VT was identified by computerised V-slope method (Katz et al., 1992), and this was cross-checked and confirmed by an experienced observer, in conjunction with plots of ventilatory equivalents and end tidal gas tensions for VO_2 and VCO_2, as recommended in the literature (Meyer et al., 2005b; Myers et al., 2010). VO_{2peak} and V_E/VCO_2 slope were analysed according to the methods described Chapter 4 (paragraph 4.1.3).

Respiratory gas measurements were not continued beyond 60s into the recovery period since feedback from patients during the familiarisation sessions indicated that wearing the mask while recovering from maximal exertion caused intolerable discomfort.

7.1.4 Cardiac rehabilitation

In Eastbourne, the majority of patients attend twice weekly CR sessions for a period of 6 weeks. This is similar to the frequency (~1.6 sessions per week) and duration (~ 7 weeks) of other UK CR programmes, but lower than the average 2.8 sessions per week for 18 weeks reported in clinical trials of CR (Taylor et al., 2007). Many of the clinical studies in CHF also comprise higher frequencies and duration of training. However, several studies have, like the current study, specifically investigated the benefits of exercise programmes in current practice, including once or twice weekly sessions (Owen and Croucher, 2000; Austin et al., 2005b; Van Laethem et al., 2007; Nilsson et al., 2008b).

Due to lack of resources exercise training for high risk patients, including CHF, and those limited by orthopaedic limitations and/or with a very low functional capacity is limited to once weekly sessions. As part of this study, an additional session was added to the CR programme for these "high risk" patients, so that they too could attend twice weekly. The sessions were run by specialist cardiac nurses and included educational sessions on anatomy and physiology, surgical procedures, medication, monitoring and interpreting symptoms, stress reduction, dietary behaviour and physical activity. Patients were encouraged to perform regular daily moderate physical activity in addition to the exercise sessions.

7.1.5 Exercise training

Patients were supervised during exercise sessions by CR specialist nurses, exercise physiologists and specialist heart function nurses at a staff:patient ratio of 1:4. BP and HR were measured prior to exercise to check for contraindications. All patients performed a gradual warm-up and cool-down prior to and following the circuit or intermittent training, in accordance with current guidelines (British Association for Cardiac Rehabilitation, 2006; Association of Chartered Physiotherapists in Cardiac Rehabilitation, 2009). HR was monitored throughout via telemetry, and was recorded at 5s intervals (Polar Electro 610, Polar Electro, Finland) for each individual during their final exercise session, and downloaded for analysis by Polar Precision Performance Software (S-Series Precision Toolkit) accessed using a Polar USB IR

interface. Minimum, maximum and average values were calculated for the 25 min circuit or intermittent section.

Patients were randomly assigned, in blocks of 4 patients at a time, to circuit or intermittent training.

The circuit training protocol followed the existing format for the exercise component of Phase III CR at Eastbourne DGH, based on the guidelines from the British Association for Cardiac Rehabilitation (2006) and the Association of Chartered Physiotherapists in Cardiac Rehabilitation (2009). Following the warm-up component of the exercise class, circuit training comprised 10 x 2 min aerobic stations (e.g. walking, cycling, stepping, arm ergometer) interspersed with active recovery stations (upper body muscular exercises, e.g. biceps curls and chest press, using light hand weights or therabands). All patients started with a ratio of 1 aerobic station to 1 active recovery station. Target HRs for the aerobic stations were 40-70% HRR, according to current standards and guidelines, with an adjustment in the calculation of 20-30 beats.min^{-1} reduction for patients on β-blockers (British Association for Cardiac Rehabilitation, 2006; Association of Chartered Physiotherapists in Cardiac Rehabilitation, 2009). In addition to target HR, or in cases where patients were unable to achieve target HR, or HR values could not be obtained by telemetry, patients were instructed to exercise at RPE 11-13. Depending on individual progress, patients progressed from arm ergometry to rowing, and then increased the ratio of aerobic stations to active recovery stations.

High intensity intermittent training was performed on a cycle ergometer following the warm-up component of the exercise class. Following a 2 minute phase of unloaded cycling, patients performed 10–15 repetitions of 30s work phases @ 100% work rate achieved in the maximal CPET, interspersed with 60s of unloaded pedalling at a self-selected cadence. This protocol was chosen after Studies 2 and 3 demonstrated that it was achievable for CHF, but induced a higher Lac than lower intensity work phases, suggesting that the stimulus to the peripheral muscles was higher.

If training sessions could not be attended for various reasons (e.g. public holidays), extra sessions were added until 12 sessions were completed, within a maximum duration of 8 weeks.

7.1.6 Blood sampling and analysis

Blood samples were taken from 15 CHF (circuit n = 7, intermittent n = 8) for analysis of B-type Natriuretic Peptide (BNP). At the same time of day at baseline and post-training, after 30 min seated rest, a 5ml venous sample was drawn from the ante-cubital vein into a sterile syringe by a trained phlebotomist. The whole blood was then immediately analysed for BNP by The Triage® BNP Test (Biosite Ltd, Belfast, or Biosite Diagnostice Inc, San Diego, California), a rapid point-of-care fluorescence immunoassay, a sensitive and specific test used to diagnose CHF in a point-of-care setting (Dao et al., 2001). This test is reported to be reproducible, with an interassay coefficient of variation (n=10) of 8.4% and 8.0% at concentrations of 19.3 ng/l and 392 ng/l, respectively (r=0.998, from 5 pg/ml to 818 pg/ml) (Vogeser and Jacob, 2001). In the current study, duplicate testing was carried out on two different samples, with coefficients of variation of 4.8% for a mean value of 176 pg/ml and 3.6% for a mean value of 277 pg/ml.

The BNP test kit includes built in controls to check that the control value results are within the limits set during manufacturing. Two external liquid control solutions were used to calibrate the test meter with each new lot of test devices. The Quality Control Device was used before each testing session to verify instrument performance, and it was ensured that each parameter passed this calibration test before analysis of blood samples.

7.1.7 Quality of life measures

7.1.7.1 Minnesota Living with Heart Failure Questionnaire

At baseline and at the end of the training programme, QoL was assessed with the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (Rector et al., 1987a; Rector et al., 1987b; Rector, 2005) (Appendix 6), according to current guidelines (Rector and Cohn, 2004). This self-administered disease-specific questionnaire consists of 21 items recording patients' perceptions of how CHF affects their physical, psychological and socioeconomic lives. Using a Likert scale, answers are given a score from 0 (no effect) to 5 (severe effect), resulting in a total scoring range from 0 to 105, with lower scores indicating a better QoL. Separate physical and emotional dimension

scores may also be identified to further characterize the effect of heart failure on a patient's life. Patients were asked to mark zero for any items that did not apply to them, to avoid the problem of missing data affecting within-patient scores.

7.1.7.2 Medical Outcomes Study Short Form Health Survey (SF-36)

At baseline and at the end of the training programme, QoL was assessed with the Medical Outcomes Study Short Form Health Survey (SF-36) (Appendix 6). This self-administered questionnaire consists of 36 items recording patients' perceptions of their health, with higher scores indicating a better health state. After data entry, according to the manual and interpretation guide (Ware et al., 1993), 10 items were re-coded, scale scores were computed by summing items in the same scale, and raw scale scores were transformed to a 0-100 scale. Normative scores from the general population are provided for reference.

7.1.8 Physical activity record

Patients completed a physical activity record for the 8 week study period by making a note of any physical activity undertaken (for a period of ≥ 5 minutes), and listing the type and intensity of activity (e.g. 10 minutes weeding and pruning, light intensity). From the information provided, the metabolic equivalent values (METs) were estimated from the Compendium of Physical Activities (Ainsworth et al., 2000), and number of minutes of light (< 3 METS) or moderate (3-6 METS) activity were classified, and the total duration calculated for each week (Macfarlane et al., 2006).

7.1.9 Statistical analysis

The Kolmogorov-Smirnov and Levene tests were used to test for normality of distribution and homogeneity of variance of the data between the circuit and intermittent training groups. Where the assumptions of normality were violated, a non parametric test was used to compare the difference between groups and effect of training. Where the data was normally distributed, but the variance was significantly different between groups, the "equal variances not assumed" t test statistic was used to test for differences between groups at baseline. At baseline, after randomisation, group differences were compared using independent samples Student's t-tests or Mann-

Whitney U tests as appropriate. Two way repeated measures analyses of variance were used to calculate the effect of training and any interaction (difference in the effect of training between groups). The Mann-Whitney U test was used to compare the difference between groups in changes in QoL from pre- to post-training. The relationship between changes in cardiorespiratory fitness and QoL following training was determined by Pearson's correlation coefficient, or, where data was not normally distributed, by Spearman's correlation coefficient.

7.2 Results

7.2.1 Participants

The flow chart in Figure 7.3 describes the participant recruitment process. Twenty six CHF (19 men and 7 women, age 73 ± 7 years) in NYHA class II (n=20) or III (n=6) commenced the study. Patients were classified as having ischaemic cardiomyopathy if they had experienced a myocardial infarction or had angiographic evidence of coronary heart disease. If they did not meet these criteria, they were classified as having idiopathic dilated cardiomyopathy. The aetiology was ischaemic heart disease (n=18) or idiopathic dilated cardiomyopathy (n=8), and the following co-morbidities were present: hypertension (n=3), diabetes (n=3), intermittent claudication (n=1), COPD (n=3). 8 CHF were in atrial fibrillation, 8 had cardiac resynchronisation devices with implantable cardioverter defibrillators (CRT-D), and 3 had biventricular pacemakers. Mean LVEF as determined by echocardiography was < 40%. All patients had been in a stable condition for the preceding 4 weeks and were on optimal medication doses: ace inhibitor (15), angiotensin receptor antagonist (9), anti-arrhythmic (11) [amiodarone 6/ digoxin 5], beta-blocker (21), diuretic (17), statin (18), calcium-channel blocker (1), alpha-blocker (1), aldosterone antagonist (1) and potassium channel activator (3). 20 patients (14 men and 6 women, age 73 ± 7 years) completed the study and their data is included in the statistical analysis.

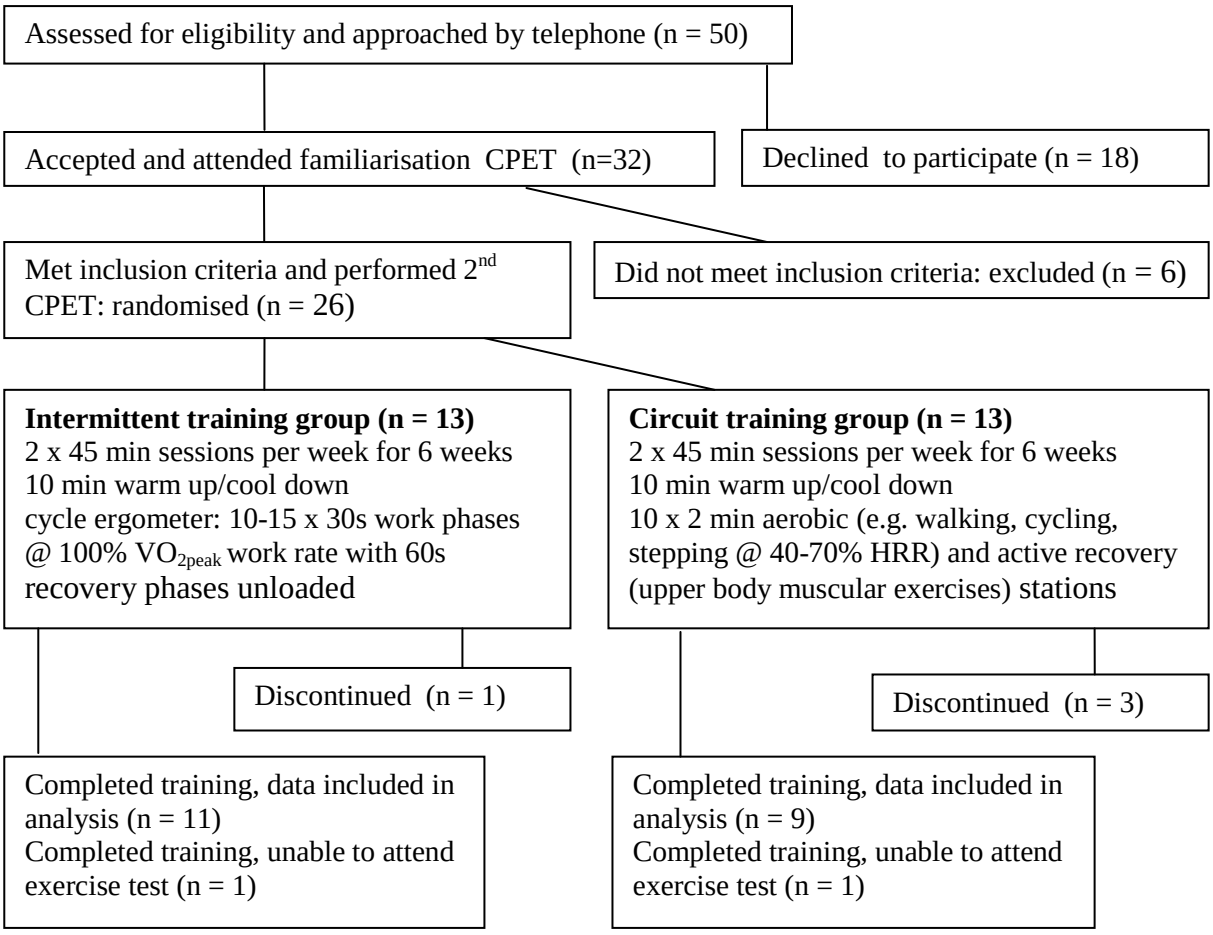


Figure 7.3: Participant recruitment flow chart
CPET cardiopulmonary exercise test; HRR heart rate reserve

Table 7.2: Baseline characteristics of CHF who did and did not complete the study (mean ± SD)

Characteristic	Completed (n = 20)	Did not complete (n = 6)
Age (years)	73 ± 7	76 ± 7
Male/female	14/6	5/1
Height (m)	1.71 ± 0.09	1.73 ± 0.06
Body mass (kg)	83 ± 21	82 ± 6
NYHA class II/III	18/2	2/4
Ejection fraction (%)	29 ± 10	35 ± 6
Aetiology (ischaemic/DCM)	13/7	5/0
VO_{2peak} ($ml.kg^{-1}.min^{-1}$)	13.84 ± 4.08	12.87 ± 2.97
Peak RER	1.11	1.12
Peak work rate (W)	69 ± 19	58 ± 19
VO_2 at VT ($ml.kg^{-1}.min^{-1}$)	9.07 ± 2.33	8.85 ± 1.06
V_E/VCO_2 slope	30.42 ± 3.6	33.8 ± 1.6
BNP (pg/ml)	346 ± 295	665 ± 456
MLHFQ Total score	29 ± 16	44 ± 11
Physical	15 ± 9	22 ± 5
Emotional	7 ± 6	14 ± 3*

DCM: idiopathic dilated cardiomyopathy; BNP: B-type natriuretic peptide; MLFHQ: Minnesota Living with Heart Failure Questionnaire
* $P < 0.05$ different from Completed

Patients who did not complete the study tended to be older, were more likely to be in NYHA class III and have CHF of ischaemic aetiology, and achieved a lower peak work rate, a lower VO_2 at peak exercise and at VT, a higher V_E/VCO_2 slope and BNP value, and a poorer QoL, as measured by the MLFHQ. However, only the emotional component MLFHQ score was significantly different between groups ($P = 0.016$) (Table 7.2)

There were no significant differences between the circuit and intermittent groups in baseline measures (Table 7.3). The data was normally distributed and homogenous in variance, unless stated otherwise below.

Table 7.3: Baseline characteristics of CHF in the circuit and intermittent training groups (mean ± SD).

There were no significant differences between groups.

Characteristic	Circuit group (n=9)	Intermittent group (n=11)
Age (years)	73 ± 7	73 ± 7
Male/female	7/2	7/4
NYHA class II/III	8/1	10/1
Ejection fraction (%)	27 ± 9	32 ± 9
Resting heart rate (beats.min^{-1})	68 ± 11	67 ± 15
Systolic blood pressure (mm.Hg^{-1})	114 ± 19	120 ± 22
Diastolic blood pressure (mm.Hg^{-1})	69 ± 13	72 ± 12
Aetiology (ischaemic/DCM)	5/3	7/4
Medication:		
α-blocker	1	0
ACE inhibitor	5	6
Aldosterone antagonist	0	1
Angiotension II receptor blocker	4	5
Anti-arrhythmic (amiodorone/digoxin)	2/3	2/1
β-blocker	8	10
Calcium channel blocker	1	0
Diuretic	5	9
Potassium channel activator	0	1
Statin	6	8
BNP (pg/ml)	420 ± 136	274 ± 45
MLHFQ Total score	25 ± 5	32 ± 5
Physical component	13 ± 3	16 ± 3
Emotional component	6 ± 2	8 ± 2

ACE: angiotensin converting enzyme; DCM: idiopathic dilated cardiomyopathy; BNP: B-type natriuretic peptide; MLHFQ: Minnesota Living with Heart Failure Questionnaire

7.2.2 Medication

At baseline medication was similar between groups (Table 7.3). During the intervention period there were minor changes in medication in some patients; in two patients, one of whom did not complete the final exercise test, the β-blocker dose was increased. In one patient, the dose of diuretics was increased, and in another the brand of angiotensin II receptor blocker was changed.

7.2.3 Safety

There was one case of post-exercise hypotension resulting in syncope and admission to hospital for 24 hours' observation in a patient with an ICD in the intermittent group. Clinical investigations revealed no effects beyond the brief period of hypotension, but it was recommended that the patient withdraw from the study as a precaution. No other adverse events occurred during exercise training.

7.2.4 Compliance

In addition to the patient described above, 3 further patients withdrew from the study within the first 2 weeks of training, 2 from the circuit and 1 from the intermittent group, for medical reasons unrelated to cardiac health (removal of ingrown toenail, incapacitating arthritis and newly diagnosed Pagett's disease). One patient in the intermittent group and 1 patient in the circuit group were not well enough to participate in the post-training exercise test (due to worsening breathlessness in both cases). Twenty patients randomly assigned to the circuit (n=9) or intermittent (n=11) training attended > 80% of the sessions (mean attendance 96 ± 2% of sessions) and were included in the analysis of baseline and post-testing values.

Patients in the circuit group exercised for 20-25 min (10 exercise stations, 2 min per station plus 30s change-over time) at a mean HR of 97 ± 6 beats.min^{-1}. All patients started with 2 min aerobic exercise:2 min active recovery. Seven patients progressed to 4 min aerobic exercise:2 min active recovery. Patients in the intermittent group exercised for 20-25 at a mean HR of 106 ± 7 beats.min^{-1} and performed 10-15 30s work intervals at 100% WR_{peak} achieved on the CPET. Seven patients started with 10 work intervals and progressed to 15 by the end of the programme. Patients (n = 4) who were

unable to complete 10 work intervals in succession were permitted a 2-4 min recovery period of low-intensity walking and/or arm ergometer exercise half way through the intermittent exercise session. All of these patients were able to complete 10 work intervals on the cycle ergometer by the end of the 6-week training programme. All patients maintained a RPE between 11 and 14 during the training sessions.

7.2.5 Effect of exercise training on CPET variables

CPET results at baseline and after 6 weeks' training in the circuit and intermittent training groups are shown in table 7.4. There was a significant main effect of training on VT (P = 0.010) and on WR_{peak} (P = 0.023) but no interaction (P = 0.573 and P = 0.368 respectively) and no difference between the circuit and intermittent groups (P = 0.540, P = 0.717 respectively). There were no significant differences in any other variable. Further details of statistical results are included in Appendix 5. The effect size was moderate for VT (partial $\eta^2 = 0.545$) and small for WR_{peak} (partial $\eta^2 = 0.256$).

Table 7.4: Cardiopulmonary exercise data in the circuit and intermittent training groups at baseline and after 6 weeks' training

Exercise test variables	Circuit Group (n=9)			Intermittent Group (n = 11)			*P* value		
	Baseline	**Post-Training**	**% change**	**Baseline**	**Post-Training**	**% change**	main effect	inter-action	between subjects
Test duration (s)	413 ± 22	428 ± 35	3 ± 5	408 ± 39	440 ± 41	9 ± 5	.084	.509	.950
Peak work rate (W)	68 ± 4	71 ± 6	4 ± 5	69 ± 7	76 ± 7	14 ± 6	.023*	.368	.717
VO_{2peak} ($ml.min^{-1}$)	1,054 ± 65	1.157 ± 107	8 ± 5	1,167 ± 114	1,206 ± 104	6 ± 6	.081	.418	.569
VO_{2peak} ($ml.kg^{-1}.min^{-1}$)	13.5 ± 1.2	15.0 ± 1.5	11 ± 4	14.1 ± 1.4	14.4 ± 1.2	5 ± 6	.064	.205	.976
Peak RER	1.08 ± 0.03	1.11 ± 0.02		1.14 ± 0.03	1.09 ± 0.03				
VO_2 at VT ($L.min^{-1}$)	0.716 ± 0.045	0.803 ± 0.052	13 ± 7	0.738 ± 0.070	0.871 ± 0.078	19 ± 5	.008*	.893	.747
VO_2 at VT ($ml.kg^{-1}.min^{-1}$)	9.27 ± 0.72	10.24 ± 0.92	11 ± 6	8.90 ± 0.77	10.55 ± 0.98	18 ± 5	.010*	.573	.540
V_E/VCO_2 slope	31.8 ± 1.5	31.7 ± 1.8	0 ± 3	29.6 ± 1.4	28.7 ± 1.4	-2 ± 4	.614	.880	.174

*$P < 0.05$

7.2.5.1 Inter-individual variation

Inter-individual variation was seen in changes in VT and VO_{2peak} in response to training (table 7.5)

Table 7.5: Inter-individual variation in change in VT and VO_{2peak} in response to training

Change from baseline to post-training	Circuit (n = 9)		Intermittent (n = 11)	
	VT	VO_{2peak}	VT	VO_{2peak}
Decrease 0-9%		2	1	2
Decrease ≥ 10%	1			2
Increase 0-9%	5	3	2	4
Increase 10-19%	2	2	2	
Increase 20-29%		1	4	3
Increase 30-39%		1	1	
Increase 40-49%				
Increase 50-59%	1			

Two patients in the intermittent group showed decreases of 21% and 30% in relative VO_{2peak} following training, despite no change in body mass. They were aged 66 and 75 years respectively, both had ICDs. One had ischaemic and the other had non-ischaemic heart failure.

The relationship between VO_{2peak} and change in VO_{2peak} in the 2 groups is illustrated in Figure 7.4. There was a moderate negative correlation in the intermittent group but this was not statistically significant (circuit group: r = .365, *P* = 0.334; intermittent group: r = - .428, P = 0.189).

The relationship between VT and change in VT in the 2 different groups is illustrated in Figure 7.5. There was a moderate correlation in the intermittent group but this was not

statistically significant (circuit group: r = .146, *P* = 0.708; intermittent group: r = .410, P = 0.210).

The relationship between baseline VO_{2peak} and change in VO_{2peak} in CHF with ischaemic and non ischaemic aetiology is illustrated in Figure 7.6. There was a weak positive correlation between change in VO_{2peak} relative to baseline VO_{2peak} in patients with CHF of ischaemic aetiology (r = .354, *P* = 0.259). By contrast, in patients with CHF of non-ischaemic aetiology there was a strong and significant negative correlation (r = -.885, *P* = 0.004), indicating that a higher baseline value were associated with a lower, possibly negative, training response.

The relationship between baseline VT and change in VT in CHF with ischaemic and non ischaemic aetiology is illustrated in Figure 7.7. There was a moderate non-significant correlation between change in VT relative to baseline VT in patients with CHF of ischaemic aetiology (r = .553, *P* = 0.062). In patients with CHF of non-ischaemic aetiology there was a weak negative correlation (r = -.145, *P* = 0.731).

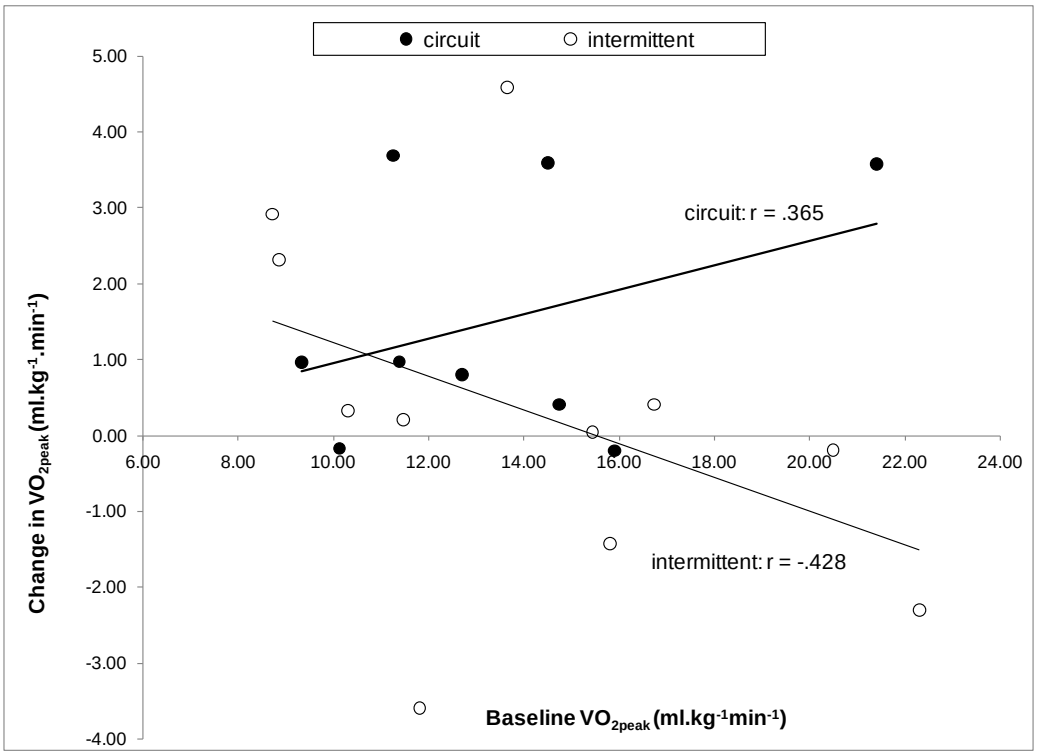


Figure 7.4: Change in VO_{2peak} following exercise training versus baseline VO_{2peak} in circuit and intermittent groups

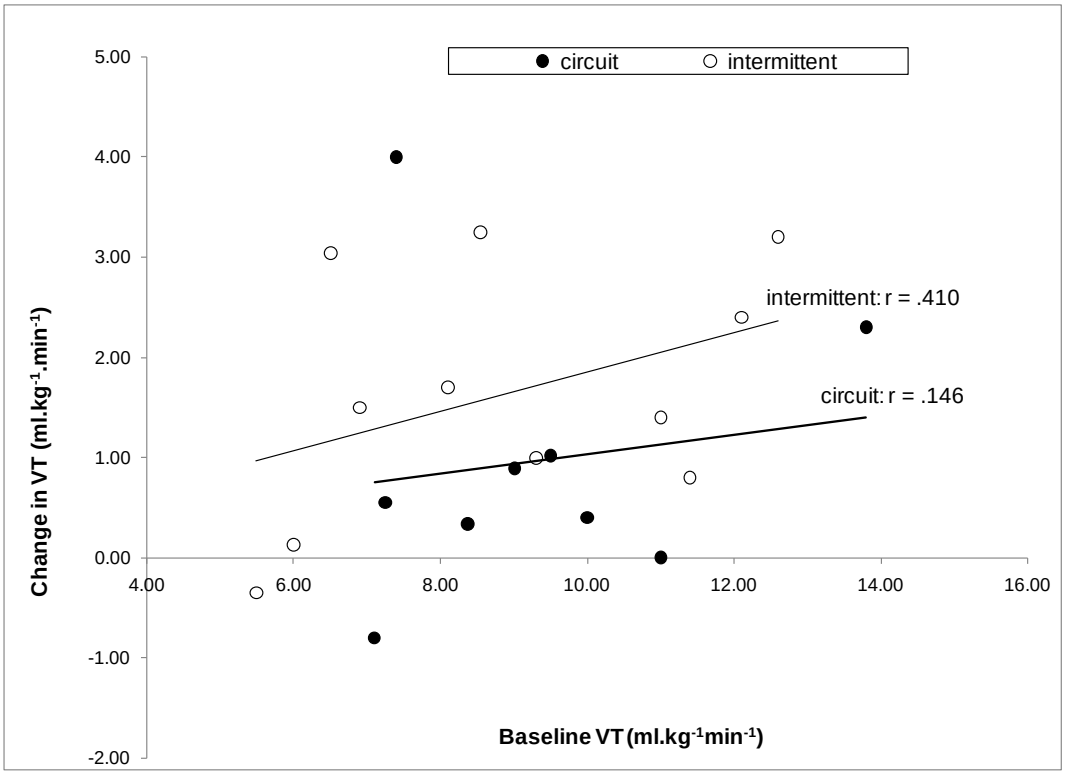


Figure 7.5: Change in VT following exercise training versus baseline VT in circuit and intermittent groups

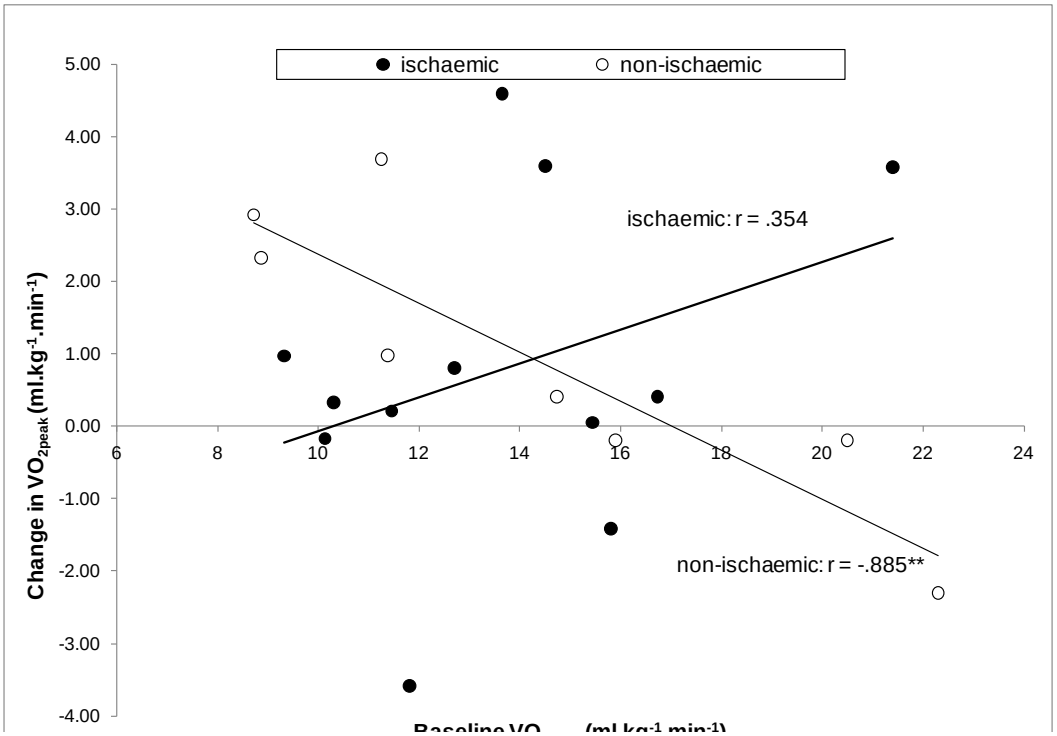


Figure 7.6: Change in VO_{2peak} following exercise training versus baseline VO_{2peak} in patients with ischaemic and non-ischaemic aetiology
** $P < 0.01$

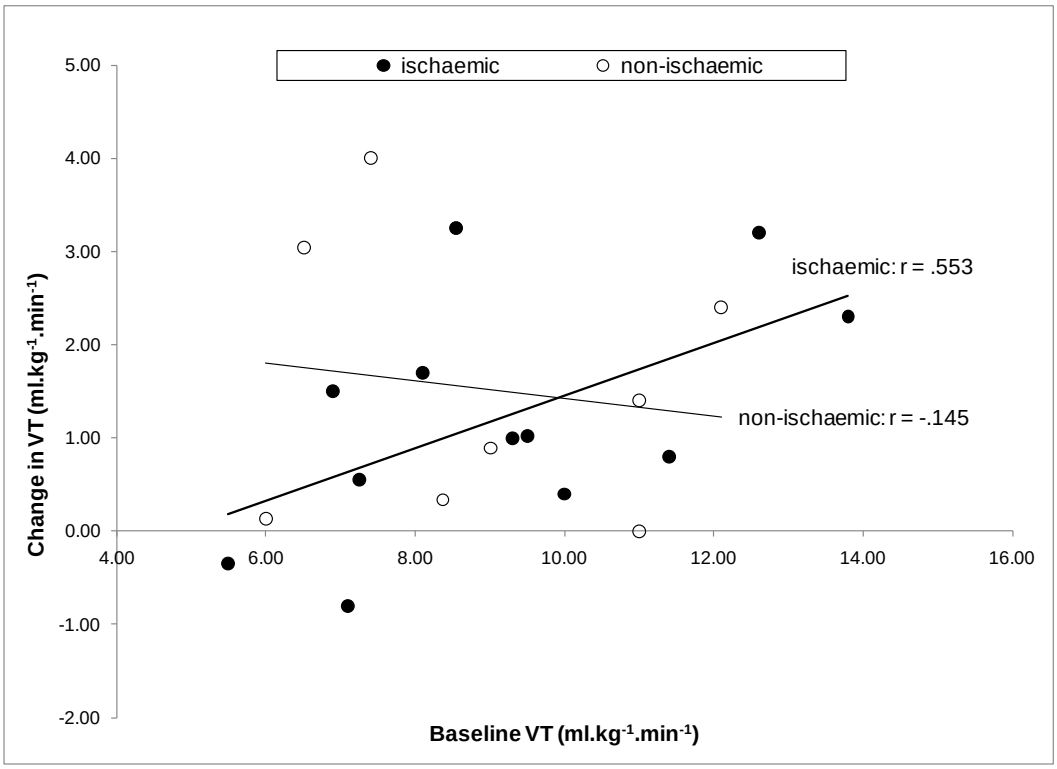


Figure 7.7: Change in VT following exercise training versus baseline VT in patients with ischaemic and non-ischaemic aetiology

7.2.6 BNP

BNP decreased from 420 ± 136 to 383 ± 86 pg.ml^{-1} in the circuit group (n=7) and increased from 274 ± 45 to 307 ± 50 pg.ml^{-1} in the intermittent group (n=8). There was no main effect from training (P = 0.738), and no interaction (P = 0.355) or difference between groups (P = 0.565). The range of values was large (circuit group 78 – 1210 pg.ml^{-1}; intermittent group 103 – 508 pg.ml^{-1}) and the change following training was > 10%, both positive and negative, in 10 out of 14 patients.

7.2.7 Heart rate

Measurement of HR_{peak} was compounded by interference to the ECG signal by muscular movement during peak exercise. In addition, accurate HR measurements could not be taken during exercise for the 8 patients in atrial fibrillation. HR data during exercise training is presented in section 7.2.10.

7.2.8 Quality of life

7.2.8.1 Minnesota Living with Heart Failure Questionnaire (MLHFQ)

The MLHFQ data was not normally distributed. The non parametric Mann Whitney U test showed that there was no significant difference in total MLHFQ scores between groups at baseline (P = 0.235), nor in physical or emotional component scores (P = 0.487 and 0.265 respectively).

MLHFQ scores for the circuit and intermittent groups, and for individuals within the groups, are illustrated in Figures 7.8-7.11. The Wilcoxon Signed Ranks test showed a significant improvement in total MLHFQ score in both groups following training (circuit P = 0.017, intermittent (P = 0.050). Physical component score improved significantly in the circuit group only (P = 0.038) , while emotional component score improved significantly in the intermittent group only (P = 0.024). Seven out of ten patients in the circuit group and six out of ten in the intermittent group showed a reduction in total MLHFQ of ≥ 5 points which is considered to be clinically relevant. There was no significant difference between groups in changes in MLHFQ scores.

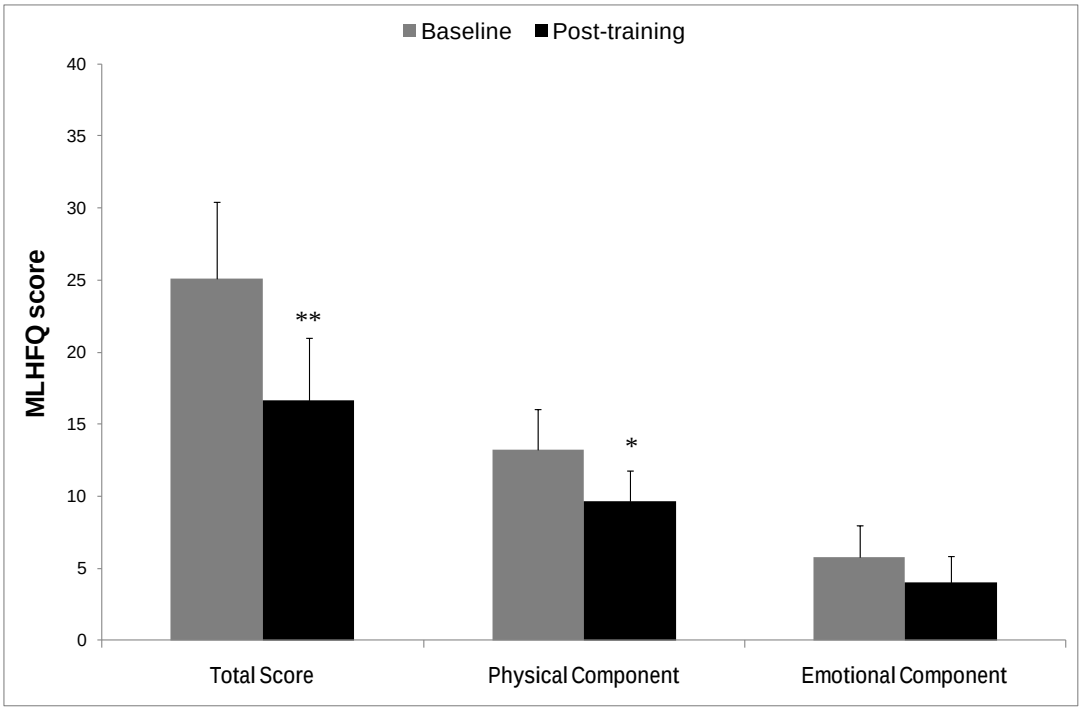


Figure 7.8: Minnesota Living with Heart Failure Questionnaire total and component scores before and after training in the circuit group (mean ± SEM). ** $P = 0.017$, * $P = 0.038$

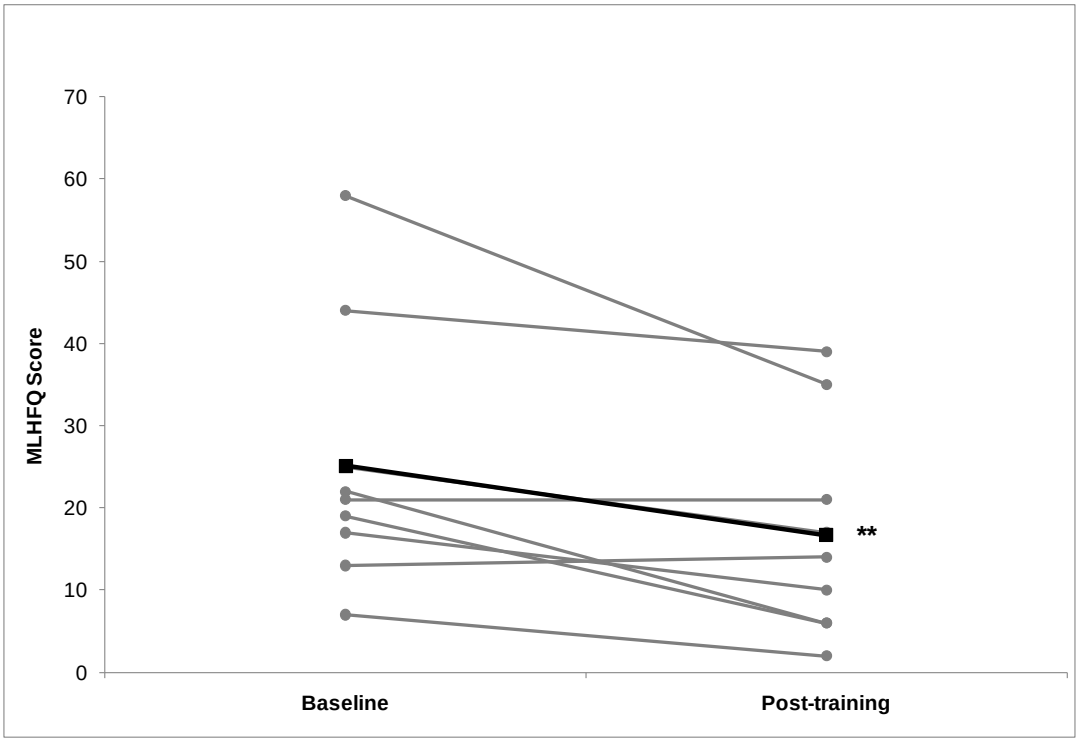


Figure 7.9: Minnesota Living with Heart Failure Questionnaire total scores for individual patients before and after training in the circuit training group.
The squares and black line denote the mean values. ** $P = 0.017$

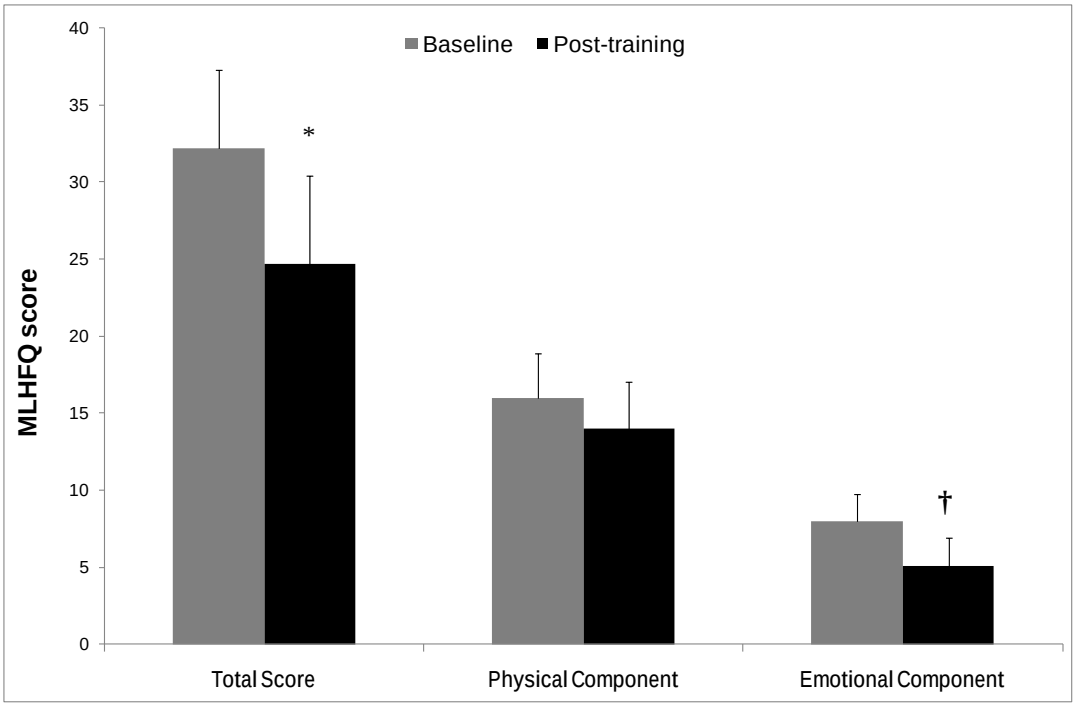


Figure 7.10: Minnesota Living with Heart Failure Questionnaire total and component scores before and after training in the intermittent group (mean ± SEM).
* $P = 0.050$, † $P = 0.024$

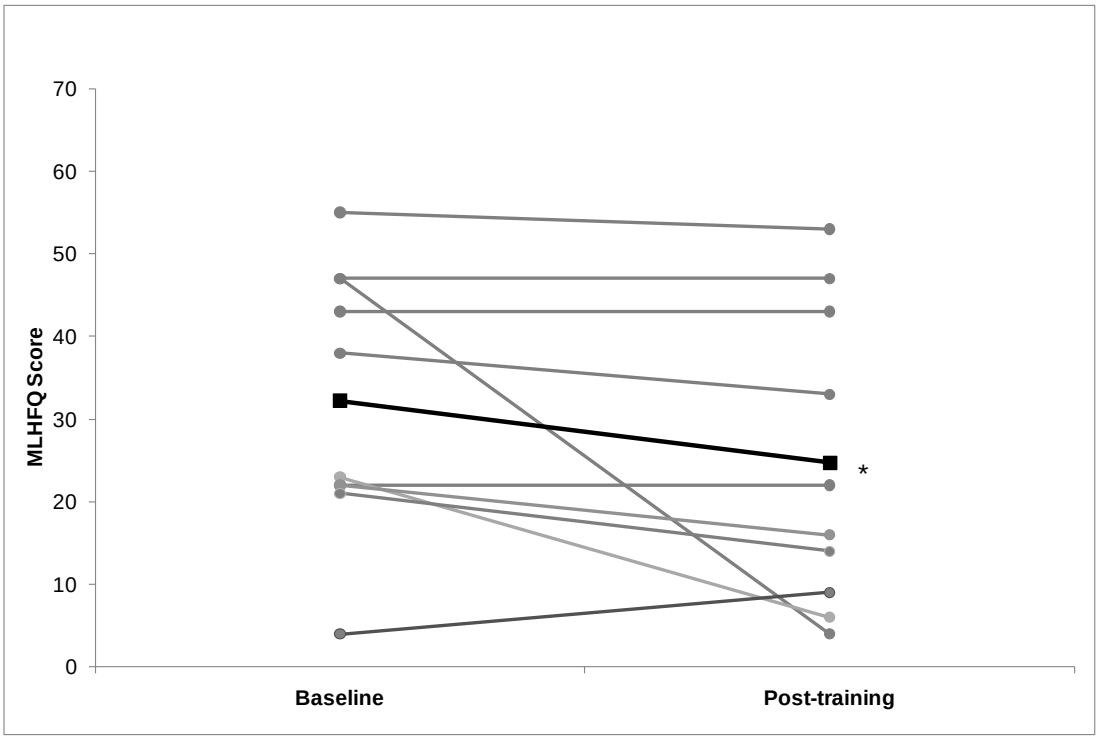


Figure 7.11: Minnesota Living with Heart Failure Questionnaire total scores for individual patients before and after training in the intermittent group.
*The squares and black line denote the mean values. * P = 0.050*

7.2.8.2 Short-Form 36 (SF-36)

SF-36 scores for the intermittent and circuit groups are illustrated in Figures 7.12 and 7.13. The Kolmogorov-Smirnov test showed that the data for 5 of the 8 scales were not normally distributed in one or both groups, therefore non-parametric tests were used. The Mann Whitney U test showed no significant difference in SF-36 scales between groups at baseline, with the exception of Bodily Pain ($P = 0.02$)

The Wilcoxon Signed Ranks test showed no significant difference in baseline and post-training scores in any of the SF-36 scales (Table 7.7). The Mann Whitney U test showed no significant difference in change in SF-36 between the two groups.

Table 7.6: SF-36 scores at baseline and after training in the circuit and intermittent groups

	Circuit Group (n=9)				**Intermittent Group (n=10)**				
SF-36 Scale	**Baseline**	**Post-Training**	**Change in score**	***P* value**	**Baseline**	**Post-Training**	**Change in score**	***P* value**	**Normative scores**
Physical Functioning	61 ± 15	64 ± 16	**3 ± 10**	0.343	53 ± 23	59 ± 22	**6 ± 14**	0.233	85 ± 23
Role-Physical	53 ± 44	64 ± 40	**11 ± 20**	0.157	43 ± 50	60 ± 41	**18 ± 31**	0.102	81 ± 34
Bodily Pain	31 ± 8	31 ± 9	**0 ± 10**	1.000	20 ± 11	24 ± 11	**4 ± 7**	0.102	76 ± 24
General Health	56 ± 24	59 ± 24	**2 ± 19**	0.723	48 ± 16	59 ± 21	**11 ± 18**	0.109	72 ± 20
Vitality	54 ± 18	65 ± 20	**11 ± 19**	0.091	41 ± 26	51 ± 21	**10 ± 20**	0.072	61 ± 21
Social Functioning	83 ± 26	89 ± 16	**6 ± 24**	0.892	81 ± 14	83 ± 16	**1 ± 15**	0.750	84 ± 22
Role-Emotional	56 ± 47	74 ± 36	**19 ± 31**	0.109	70 ± 37	80 ± 36	**10 ± 27**	0.257	81 ± 33
Mental Health	78 ± 24	77 ± 18	**-1 ± 14**	0.461	69 ± 21	75 ± 15	**6 ± 18**	0.396	75 ± 18

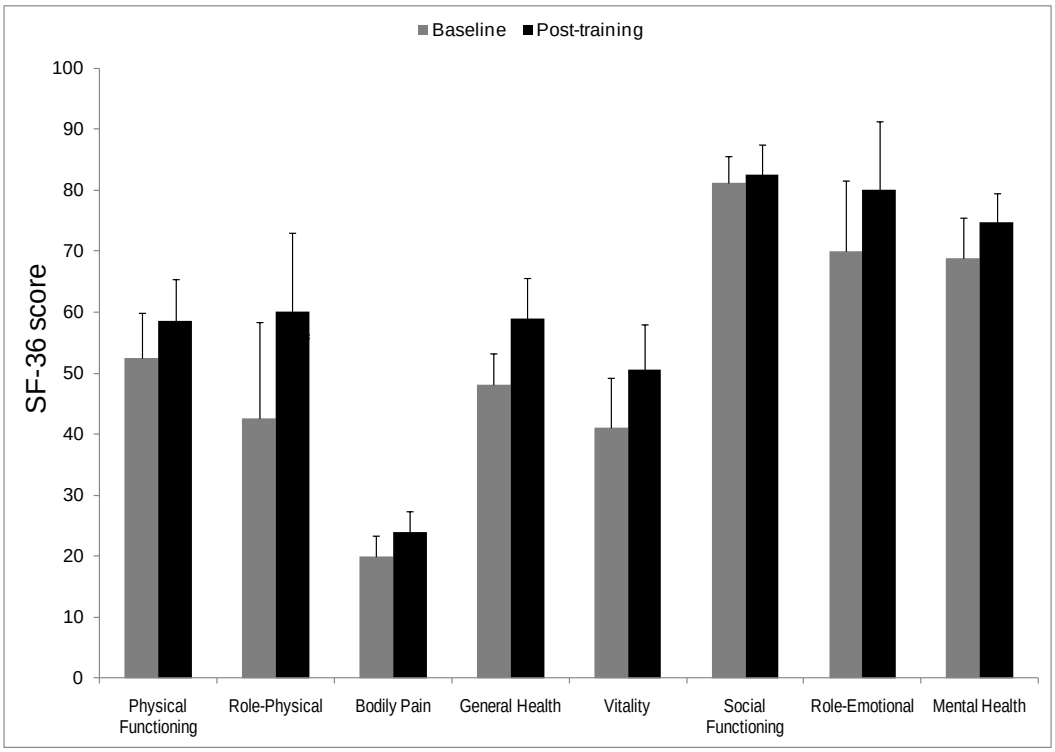


Figure 7.12: SF-36 scores before and after training in the circuit group (mean ± SEM).

No significant differences were found

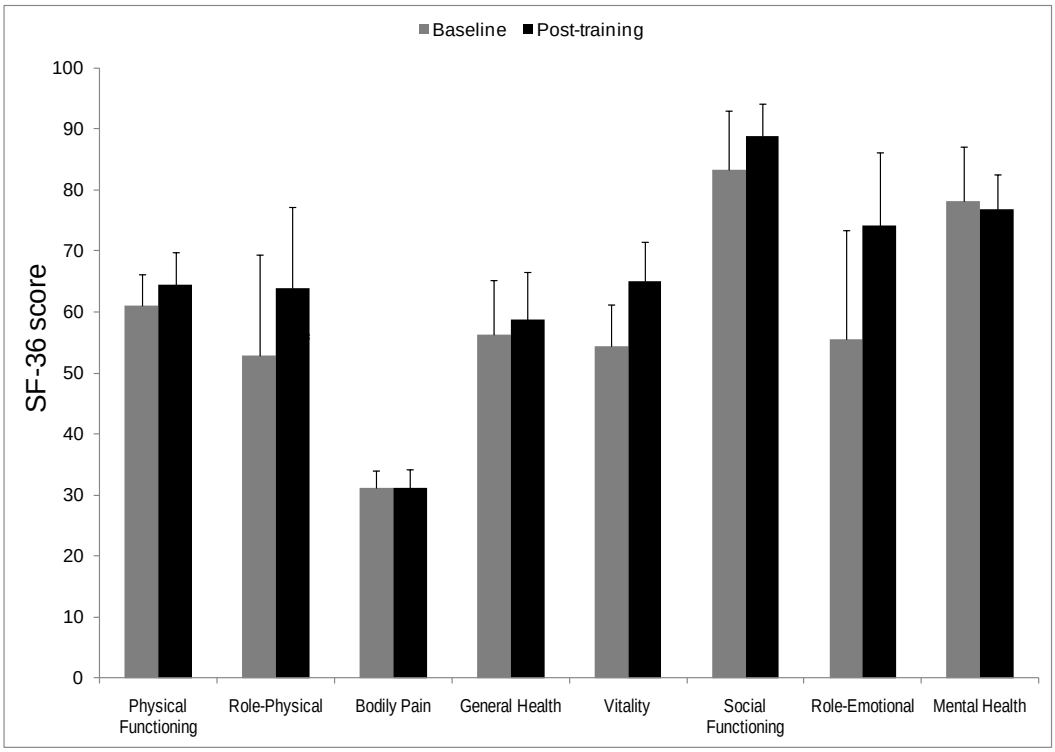


Figure 7.13: SF-36 scores before and after training in the intermittent group (mean ± SEM).

No significant differences were found.

7.2.9 Relationship between change in functional capacity and quality of life in the circuit and intermittent groups

There were no significant correlations between changes in VO_{2peak}, VT and QoL after training, nor were changes in these variables significantly correlated with age (Table 7.8).

Table 7.7 Correlations between change in functional capacity, quality of life and age in the circuit and intermittent groups

			Change in VT ($ml.kg^{-1}.min^{-1}$)	Change in MLHFQ score	Age
Circuit n=9	Change in VO_{2peak} ($ml.kg^{-1}.min^{-1}$)	Correlation‡ *P* value	.644 0.061	-.502 0.168	.140 0.720
	Change in VT ($ml.kg^{-1}.min^{-1}$)	Correlation‡ *P* value		-.628 0.070	.296 .440
	Change in MLHFQ score	Correlation‡ *P* value			-.059 0.881
Intermittent n=11	Change in VO_{2peak} ($ml.kg^{-1}.min^{-1}$)	Correlation‡ *P* value	-531 0.093	.129 0.723	.195 0.565
	Change in VT ($ml.kg^{-1}.min^{-1}$)	Correlation‡ *P* value		.190 0.599	-.157 0.645
	Change in MLHFQ score	Correlation‡ *P* value			.464 0.177
‡ Pearson's for parametric data and Spearman's for non-parametric (MLHFQ) data					

7.2.10 Training data

Mean ± SD work phases in the intermittent group, set at 100% WR_{peak}, were 70 ± 25 W (range 40 - 90 W). RPE for both groups during training was maintained at 11-13. In patients in AF, and in some patients with implantable devices, HR could not be accurately recorded during exercise. Although theoretical HR training zones were calculated at the beginning of the programme for patients in the circuit training group, in practice it was not useful to use these to monitor the intensity of training due to

inability of patients to achieve exercising HR that corresponded to prescribed HR in the minority of patients for whom accurate HR telemetry data could be obtained.

Values for average, minimum and maximum HR during the final training session for patients, excluding those in AF, or with non-rate responsive pacemakers, are shown in Table 7.9. The Mann Whitney U test showed no significant differences between groups in resting HR, average HR during exercise or average, minimum and maximum HR expressed as % HR_{peak} ($P > 0.05$). In both groups the mean HR (averaged over the 20 min session) exceeded 90% of the HR_{peak} achieved during CPET, and the highest HR during training was close to, or higher than HR_{peak}. The larger HR range during training in the circuit group (77 ± 5 - 103 ± 7% HR_{peak}) compared with the intermittent group (85 ± 4 - 99 ± 4% HR_{peak}) reflects the different types of exercises performed in this group, e.g. active recovery exercises with light hand weights and stepping. Figures 7.15 and 7.16 show examples from one patient in each group.

Table 7.8: Heart rate during the "aerobic" component of training in the circuit and intermittent groups.

Patients in AF or with non rate-responsive pacemakers are excluded.

Heart Rate (beats.min^{-1})	**Circuit group (n=4)**	**Intermittent group (n=6)**
Average	97 ± 6	106 ± 7
Expressed as % peak heart rate achieved during CPET		
Average	91 ± 6%	92 ± 3%
Minimum	77 ± 5%	85 ± 4%
Maximum	103 ± 7%	99 ± 4%

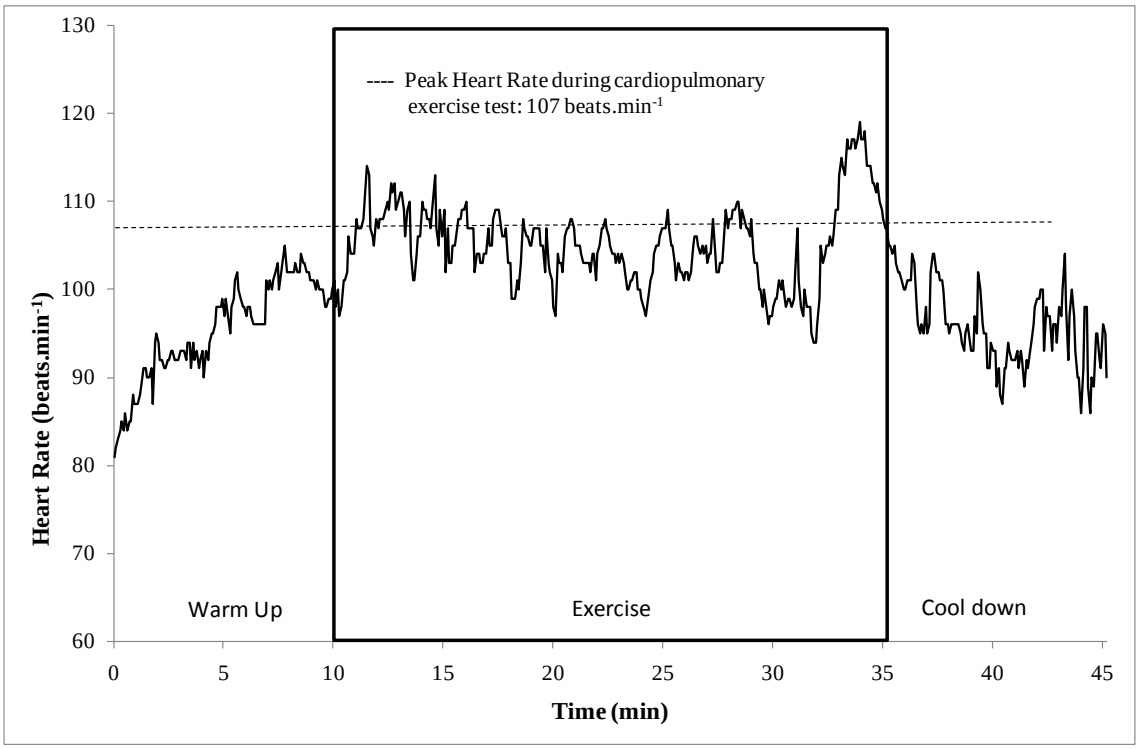


Figure 7.14: Exercise session heart rate data for patient in intermittent group (female, aged 70 years).

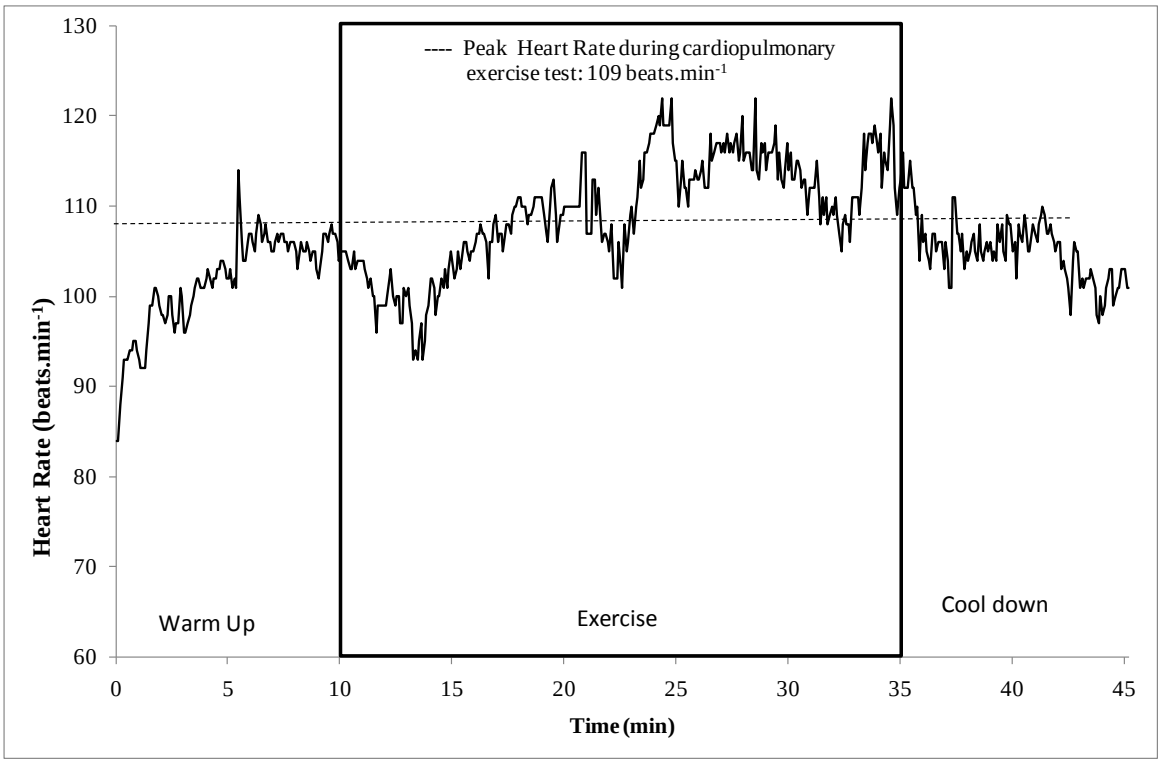
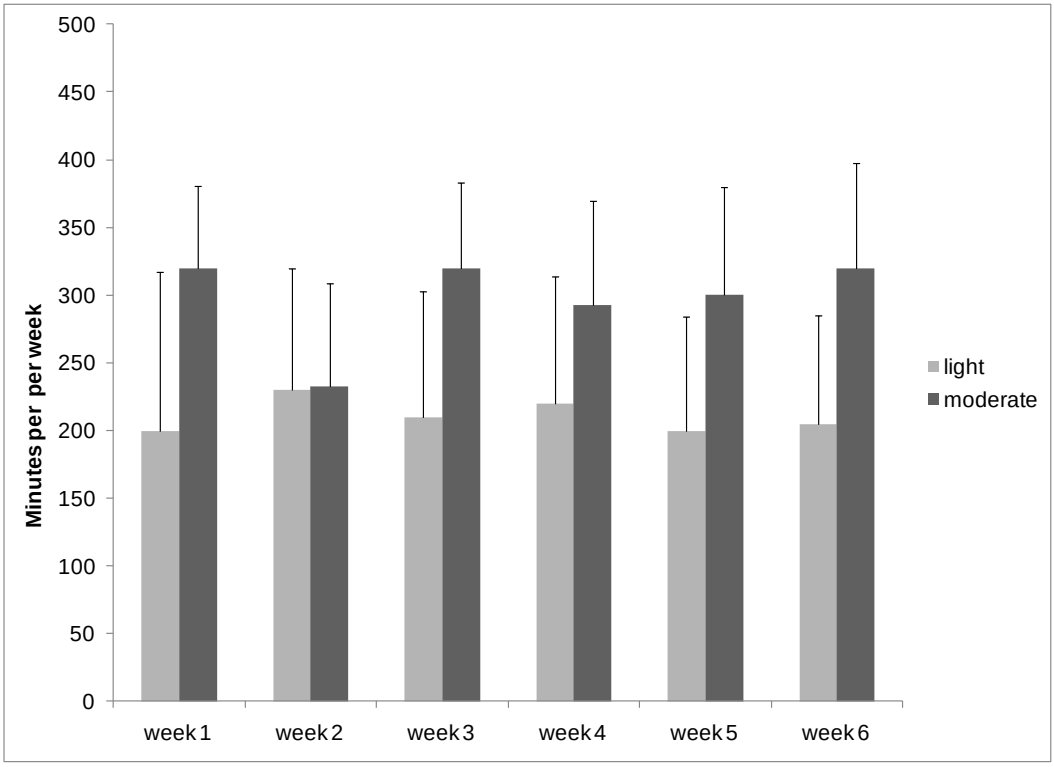


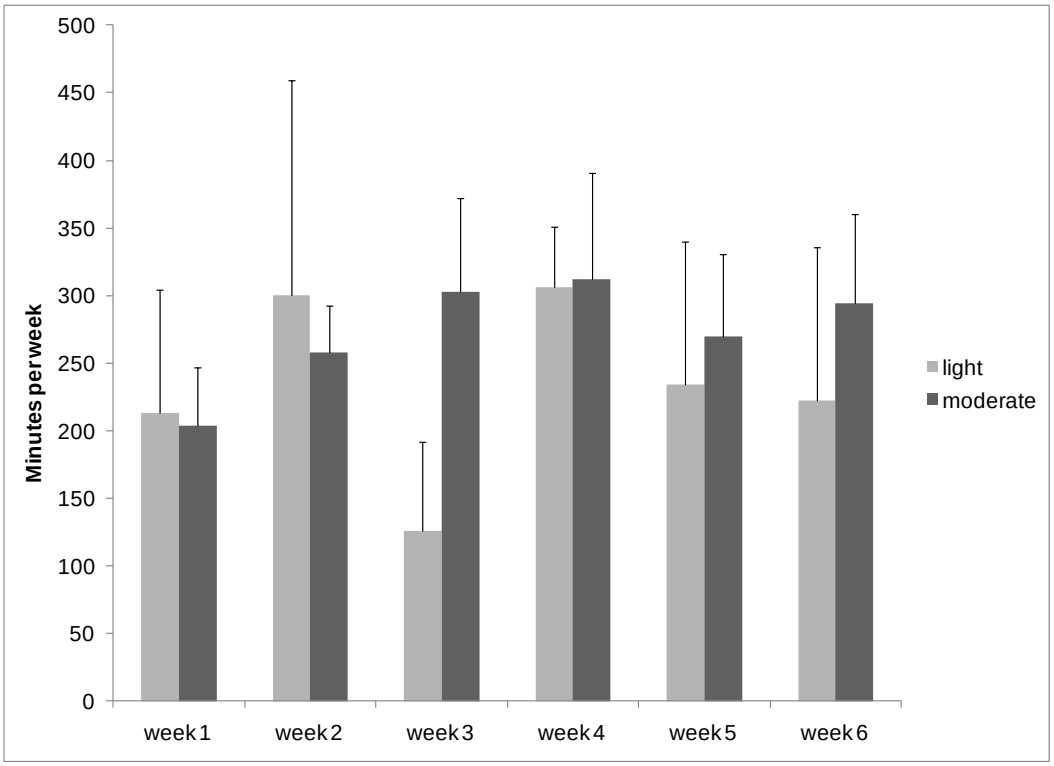
Figure 7.15: Exercise session heart rate data for patient in circuit group (female, aged 62 years).

7.2.11 Physical activity record

Time spent in physical activity outside the CR classes is shown Figure 7.17. There was substantial intra-individual variability; minutes spent in light (< 3 METS) activity ranged from 0 – 720 min (circuit: 211 ± 93, intermittent: 274 ± 59) and moderate (3-6 METS) activity from 60 to 600 min in different patients (circuit: 298 ± 72, intermittent: 234 ± 97). There was evidence of differences in subjective interpretation of what constitutes light or moderate physical activity. Some patients listed housework & meal preparation as light activity, others did not consider it to "count" as activity, so did not include it. Nevertheless, the data collected indicates that physical activity habits did not change significantly during the 6 week training intervention ($P = 0.617$), and that there were no significant differences in physical activity levels between the circuit and intermittent groups ($P = 0.742$).



A



B

Figure 7.16: Minutes (mean ± SEM) spent in light (< 3 METS) and moderate (3-6 METS) physical activity each week in the circuit (A) and intermittent (B) groups

7.3 Discussion

This study is the first to compare a high intensity intermittent training programme with traditional circuit-based training in a UK CR hospital-based outpatient setting in a representative sample of the general CHF population. In agreement with previous studies of longer duration, this study demonstrates that both circuit training, set at moderate intensity, and high intensity intermittent training significantly improve sub-maximal exercise capacity and disease specific QoL in CHF after only 6 weeks. However, neither training method resulted in the 10-30% increase in VO_{2peak} commonly reported following exercise interventions, nor in a reduction in BNP, V_E /VCO_2 slope or generic QoL.

7.3.1 Recruitment and compliance

The recruitment and compliance of participants to exercise training studies can be challenging, and particularly so in an elderly population with chronic disease. This study provides interesting information on patient recruitment for exercise training studies in a clinical setting. 64% of eligible patients volunteered to participate, which is higher than the 40-45% reported in similar studies (Jolly et al., 2007; Prescott et al., 2009). Although 64% of the 50 patients invited to participate agreed to do so, 52% actually started the study, and 40%, or 77% of those who started, completed. Adherence to supervised exercise training has previously been reported as 75% in a 16 week study (Willenheimer et al., 1998) to > 80% for shorter studies (Wielenga et al., 1999; Dimopoulos et al., 2006). In a UK CR programme, 12 patients out of 100 withdrew from the exercise intervention due to onset of severe co-morbidity or anxiety about exercise, typical reasons for non-compliance in an elderly population with physical and psychological frailty (Austin et al., 2005b). The reasons for non-completion in the current study were worsening heart failure and other co-morbidities. Only one patient stopped training due to an adverse reaction (hypotension). Patients with ischaemic rather than non-ischaemic CHF are more likely to "drop out" of exercise training studies (44% vs 17%) (Keteyian et al., 1996), and all 6 non-completers in the current study had ischaemic CHF. Interestingly, non-completers had a significantly higher emotional component MLFHQ score than completers, which might have affected their confidence to continue training. Alternatively the poorer

emotional QoL could reflect that they were more affected by their CHF and co-morbidities. In general, non-completers did tend to be older, in a higher NYHA class, and have poorer functional capacity and higher BNP values, as well as poorer QoL.

7.3.2 Exercise performance

A recent systematic quantitative review reports a 13% significant increase in VO_{2peak} (+2.06 $ml.kg^{-1}.min^{-1}$) , with a pooled effect size of 0.60 and 95% confidence intervals of 0.42–0.79 $ml.kg^{-1}.min^{-1}$ (van Tol et al., 2006). In the current study the increase in VO_{2peak} did not reach statistical significance (circuit: 1.53 ± 0.54 $ml.kg^{-1}.min^{-1}$ (11± 4 %), intermittent 0.30 ± 0.70 $ml.kg^{-1}.min^{-1}$ (5 ± 6%), although the WR_{peak} was significantly higher after training. Several previous studies have also reported small increases in VO_{2peak} alongside significant increases in WR_{peak} (Kiilavuori et al., 1996; Willenheimer et al., 1998; Wielenga et al., 1999; Larsen et al., 2001; Conraads et al., 2004; Jonsdottir et al., 2006).

VO_{2peak} is the most commonly reported outcome measure in exercise training studies in CHF, and has prognostic value, but day-to-day limitations in function are more likely to be related to VT. van Tol et al's systematic quantitative review reports a 17.4% significant increase in VT (+1.91 $ml.kg^{-1}.min^{-1}$), with a pooled effect size of 0.84 and 95% confidence intervals of 0.48 –1.20 $ml.kg^{-1}.min^{-1}$. The current study demonstrates improvements of a similar size (circuit: 0.97 ± 0.47 $ml.kg^{-1}.min^{-1}$ (11± 6 %), intermittent 1.64 ± 0.40 $ml.kg^{-1}.min^{-1}$ (18 ± 5%), with no significant difference between groups. The implication is that both modes of exercise training will enable patients to achieve routine daily activities with fewer symptoms, but that high intensity intermittent training offers no advantage.

This finding is contrary to the view that short-term high intensity intermittent exercise training is particularly effective at increasing VO_{2peak} and VO_2 at VT (Meyer et al., 1996c). A more recent 6 month intervention using Meyer's intermittent training protocol, but during twice weekly sessions rather than Meyer's five sessions per week, and supplemented with home-based strength and endurance training, reported a smaller increase in VO_{2peak} (6%) (Sabelis et al., 2004). Both studies compared intermittent training with no training, rather than with an alternative mode of training.

Other studies have specifically compared high intensity intermittent with moderate continuous cycle training, and have reported no advantage of intermittent training in improving maximal or sub-maximal exercise capacity. Dimopoulos et al (2006) reported significant increases in WR_{peak} of 20% and 30%, in VO_{2peak} of 6% and 8%, and in VT of 10% and 6% after 12 weeks' continuous and intermittent training (Dimopoulos et al., 2006). A 3 week intervention resulted in improvements in VO_{2peak} of 14% in both the continuous and the intermittent group, and increases in VT of 9% and 8% respectively (Nechwatal et al., 2002). However, some exercise interventions, including moderate continuous (Keteyian et al., 1999) and intermittent (Willenheimer et al., 1998) exercise have failed to improve VT, despite being considerably longer in duration and including more frequent training sessions.

One study comparing intermittent to continuous training, in CHF with similar baseline exercise capacity to those in the current study, has reported greater improvements in VO_{2peak} following intermittent exercise (46% vs 14%) (Wisloff et al., 2007). The larger improvements may be explained by the increased duration of the intermittent work phases (4 min at 90-95% HR_{max}) as well as the additional training session per week and the 12 week study duration. This exercise stimulus resulted in substantial improvements in exercise capacity, and these were matched by improvements in LV diameters and volumes, myocardial contractile function, endothelial function and BNP, suggesting that haemodynamic and myocardial abnormalities were particularly responsive to this stimulus and contributed to the improvement in VO_{2peak}.

The current study set out to compare high intensity intermittent training with circuit training in which the intensity was intended to be moderate (Association of Chartered Physiotherapists in Cardiac Rehabilitation, 2009). However, the HR data recorded during the circuit training suggests that the intensity is variable, and is not necessarily moderate. Although the exercise intensities of the two different training interventions were pre-determined, in practice it is difficult to ensure that this intensity is maintained, and to measure the total amount of work achieved. The intensity of the intermittent training was set (30s at 100% WR_{peak}), although the number of repetitions performed depended on individual capabilities. The intensity of the circuit training was, in theory, set at 40-70% HRR. HR was recorded throughout the final exercise session as an indicator of the intensity of exercise performed. After excluding patients in AF and those with non-rate responsive pacemakers, data was only available for 4 patients in the

circuit group and 6 in the intermitent group. In both groups, the mean training HR exceeded 90% HR_{peak} achieved during CPET, and the highest training HR was close to, or higher than this HR_{peak}. This was possibly due to the difference in haemodynamics between semi-recumbent cycling in the CPET and upright cycling and/or weight bearing exercise performed during the training session, and is discussed further in Chapter 8 (Section 8.4). Alternatively, the short duration of the CPET (7 ± 2 min) compared with the 20 exercise session, which was preceded by a 10 min warm-up, might not have allowed adequate time for the chronotropic response. Average HR was not different between groups, but HR was more variable in the the circuit group, ranging from 77-103% HR_{peak} compared to 85-99% HR_{peak} in the intermittent group. This is probably a reflection of the different types of exercises performed in this group, e.g. active recovery exercises with light hand weights and weight-bearing exercises, such as walking or stepping, engaging a greater active muscle mass than cycling. One small study of 6 CHF has previously reported no differences in VO_2, HR, BP or RPE between circuit training and continuous cycling exercise at 70-80% HR_{max} (Green et al., 2001). Interestingly, in patients performing continuous exercise on a cycle ergometer, HR correlated with VO_2, but not with RPE, whereas in the circuit group HR correlated with RPE, but not with VO_2. This highlights the practical difficulties of setting and monitoring exercise intensity in this population, where the relationship between percentages of HR_{peak} and VO_{2peak}, HRR and VO_2R, and RPE do not conform to those observed in the general population (Coplan et al., 1986; Brawner et al., 2002; Mezzani et al., 2007). Existing guidelines based on estimated HR_{max} are unlikely to provide a meaningful guide to exercise intensity (Beale et al., 2010), and the current study indicates that even if HR_{peak} is measured the exercising HR may bear little relationship to it. In future, a comprehensive analysis of circuit and intermittent training, using measurements of VO_2, HR, Lac and motion analysis should be undertaken to describe the physiological intensity of each type of exercise.

7.3.3 Changes in ventilatory response to exercise

The current study did not find any change in V_E/VCO_2 slope after either circuit or intermittent training. Previous studies have reported mixed findings on the effect of exercise training on V_E/VCO_2 slope. The current study agrees with others that have reported no change (Keteyian et al., 1996), including studies of older patients

(Brubaker et al., 2009) and those on optimal medication (Passino et al., 2006b). Similarly Dimopoulos et al's study (2006) comparing continuous and intermittent exercise reported no change in either group, despite improvements in VO_{2peak} and VT. By contrast, one older study (Coats et al., 1992a) and two more recent studies of CHF on optimal medical therapy (Klecha et al., 2007; Van Laethem et al., 2007) have reported improvements in V_E/VCO_2 slope following 2–6 months' training. Reductions in V_E and V_E/VCO_2 during sub-maximal exercise have also been reported, most likely due to an increase in VT, meaning that, at a given intensity, a reduced amount of CO_2 is required for buffering, therefore reducing the drive to increase ventilation (Kiilavuori et al., 1996).

It is possible that the benefits of current medical therapy limit the additional benefits of exercise training on ventilatory efficiency. β-blockers improve the ventilatory response in CHF, due to a combintaion of attenuated β-adrenergic response to catecholamines, alterations in muscle metabolism that decrease ergoreflex stimulation, and improved ventilation-perfusion matching (Wolk et al., 2005). Piepoli et al. (1996) argue that the improvement in symptoms following exercise training, or other treatment, in CHF is dependent on the resolution of skeletal muscle abnormalities and the associated exaggerated ergoreflex response (Piepoli et al., 1996). They demonstrated that training reduced the ergoreflex contributions (diastolic pressure, ventilation and leg vascular resistance) more in CHF than in control subjects. The lack of improvement in V_E/VCO_2 slope in the current study could be due to an inadequate training stimulus to reduce the ergoreflex response. Although the study duration of 6 weeks was the same, the exercise dose in Piepoli et al's 1996 study was higher, comprising 2-3 sessions per day, specifically targeting the forearm muscles. The exercise dose in other studies reporting an improvement in V_E/VCO_2 slope was also higher, in terms of frequency and/or duration, than the current study (Coats et al., 1992a; Klecha et al., 2007; Van Laethem et al., 2007).

Another issue for consideration is the report that the ventilatory response to exercise and V_E/VCO_2 slope are higher in weight-bearing, i.e. treadmill protocols, which appear to increase the ergoreflex activation to a greater extent than weight-supported exercise (Witte and Clark, 2005). It is possible that, by imposing a greater stimulus on the

erogreflex response, weight-bearing exercise training might be more effective at improving ventilatory efficiency. This is speculative, and requires further investigation.

7.3.4 Inter-individual response to training

Experts in the field have highlighted the importance of reporting the individual variation in responses to exercise training as well as the mean change, and investigating the personal characteristics which influence inter-individual variation in dose-response (Haskell, 2001). Despite significant mean increases in VO_{2peak} in the majority of studies, not all patients respond to exercise training (Coats et al., 1992a; Belardinelli et al., 1995a). Some studies have reported "responders" and "non-responders" to training. Although CR failed to improve mean VO_{2peak} in older CHF, it increased by > 10% in 6 out of 30 patients, and by 0 – 10% in another 9 patients, whereas it decreased in 8 patients (Brubaker et al., 2009). Similarly, in the current study there was evidence of inter-individual response to training in both groups. In 2 CHF in each group, VO_{2peak} showed small decreases, whereas in 2 further patients in the intermittent group VO_{2peak} decreased by 20-30%. Both these patients were fitted with an ICD and it is possible that the severity of heart failure influenced the training response. However, VO_{2peak} increased by 25% and 33% in 2 CHF with ICDs in the circuit group, suggesting that the mode of exercise might have played a part. The heterogeneity of CHF patients prevents any conclusions being drawn as to the reasons for finding "responders" and "non-responders". Further studies comparing different modes of training in patients with ICDs may clarify this.

There is conflicting information in the literature about whether aetiology, specific limitations or age affect the outcome of exercise training. It has been suggested that patients with ischaemic aetiology are more responsive to exercise training (Willenheimer et al., 1998), although non-ischaemic aetiology has also been associated with a positive training response (Forissier et al., 2001). Neither the aetiology of CHF nor age was associated with the response to training in the current study. The few studies that have, like this one, focussed on older CHF with co-morbidities, suggest that training effects are less pronounced in the wider CHF population than in the earlier studies restricted to homogenous samples of younger CHF (Owen and Croucher, 2000; McKelvie et al., 2002). Exercise training was less effective at increasing VO_{2peak}

in CHF patients over 65 years, with reported average improvements of 0.5 $ml.kg^{-1}.min^{-1}$ compared with 1.2 $ml.kg^{-1}.min^{-1}$ in patients under 65 years (Wielenga et al., 1998). Lack of improvement in inflammatory and endothelial function, and NT-pro BNP after exercise training in older CHF has also been reported, although an inadequate exercise dose might have been a contributing factor here (Prescott et al., 2009). Patients exercised twice weekly for 8 weeks at an intensity of 70-80% VO_{2peak}, a slightly higher dose than the current study.

Alternatively, the severity of CHF rather than aetiology or age might play a role. In mildly symptomatic CHF, the major determinant of exercise tolerance is usually cardiac output reserve (i.e. VO_2 delivery) whereas abnormal peripheral mechanisms play a greater role with increasing severity of CHF (Tavazzi et al., 2001). Therefore, patients with moderate and severe CHF have a greater potential to benefit from exercise training. Hambrecht et al (1995) reported that the greatest improvements in exercise capacity and muscle oxidative capacity were reported in those patients with the most severe exercise intolerance and/or LV dysfunction. Jette et al (1991) reported that post myocardial infarction CHF with poor LV function (EF < 30%) significantly improved VO_{2peak} following a 4 week exercise programme compared with a decline in the non-training control group, whereas patients with low-moderate LV function (EF 31-50%) showed no change in either the exercise or control group (Jette et al., 1991). In Meyeret al's study, patients had a mean EF of 22%, and half were awaiting heart transplantation. The greatest improvements were demonstrated by those whose initial exercise capacity was lowest (Meyer et al., 1996c).

However, Wilson et al (1996) postulated that patients with reduced cardiac output responses are limited by skeletal muscle under-perfusion and would not improve with exercise training whereas patients with preserved cardiac output responses to exercise are limited by deconditioning, and would respond to exercise training. The results of their study support this hypothesis, with improved exercise performance in patients with preserved cardiac output responses, but not in those with severe haemodynamic dysfunction (Wilson et al., 1996). Furthermore, myocardial function at baseline has also been positively related to change in VO_{2peak} following exercise training (Smart et al., 2006).

7.3.5 Potential mechanisms for response to exercise training

The theoretical underlying mechanisms responsible for improvements in exercise capacity are discussed in the Review of Literature (Chapter 2, Section 2.5), and include improvements in cardiac output, oxygen extraction & utilisation, endothelial function, and attenuation of excessive ergoreflex activation. In longer duration studies, improvements in VO_{2peak} and VT are associated with changes in the oxidative capacity of skeletal muscles (Hambrecht et al., 1995a), and reduced total peripheral resistance, enhanced endothelium-dependent vasodilation and peripheral blood flow (Hambrecht et al., 1998; Hambrecht et al., 2000). Further analysis via ultrastructural morphometry reported enhanced oxidative enzyme activity and a characteristic reshift from type II to type I fibres, and these changes were unrelated to changes in peripheral perfusion (Hambrecht et al., 1997). It is possible that the smaller dose of exercise in the current study led to improvements in some of these parameters, accounting for increases in VT and VO_{2peak} in "responders". Studies using 3 x 15 min sessions per week of knee extensor exercise for 8 weeks, a smaller exercise stimulus than in the current study, have reported improvements in oxidative enzyme activity and VO_{2peak} (Gordon et al., 1996; Tyni-Lenné et al., 1996; Tyni-Lenné et al., 1997). In the current study, the lack of improvement in V_E/VCO_2 slope suggests that there was no attenuation of ergoreflex activation.

The majority of studies show that an increase in exercise capacity is achieved without changes to central haemodynamics. van Tol et al's systematic quantitative review reports improvements at rest in diastolic BP and EDV only, with no changes in HR, systolic BP, LVEF or ESV. However, at maximal exercise, HR, systolic BP and cardiac output increased significantly by 2.5, 3.3 and 21.3% respectively, with significant pooled effect sizes**.** Some short-duration studies have reported that cardiac adaptations can be achieved in as little as 8 weeks, but this was in response to an exercise dose of more than 2 hours per day (Dubach et al., 1997). In older CHF, LV volumes, LVEF and diastolic filling, measured by echocardiography, did not change after 16 weeks' CR (Brubaker et al., 2009). MRI is more precise and reproducible for assessing LV function, and two recent studies have used this method. One found no significant changes in LV parameters after 6 months' training, although there was a trend for improvement in EDV, LVEF and wall motion score index (Klecha et al.,

2007). The other, which included 5 training sessions per week, reported improvements in ESV and LVEF after 6-8 months, but not after 2 months (Beer et al., 2008). It therefore seems unlikely that any improvements in exercise capacity achieved in the current study are due to improvements in central haemodynamics.

Previous studies have suggested that exercise training partially reverses chronotropic incompetence Hambrecht et al (2000) reported that 46% of the increase in VO_{2peak} was explained by an increase in HR_{peak}, although it is not clear if the reported increase in HR_{peak} was simply due to improved exercise tolerance. Keteyian et al (1999) reported a 7% increase in HR_{peak}. The authors used an indirect index of sinoatrial node sympathetic responsiveness by determining the ratio of HR reserve to plasma noadrenaline reserve, for which there was no change. They therefore speculated that, rather than an increase in alpha-adrenergic receptor sensitivity, the increase in HR was due to increased leg strength permitting the patients to exercise for longer during the test, thus providing a longer period for chronotropic response to noradrenaline (Keteyian et al., 1999). Myers et al (2007) reported that intensive exercise training induced a more rapid HR recovery, reflecting improved vagal reactivation, after training. However, these patients had a considerably higher baseline exercise capacity than those in the current study, and none were taking β-blockers. 70% of the change in HR recovery was attributable to a widening in HRR (mean 18 beats.min^{-1}), due to an increased HR_{peak} of 7 beats.min^{-1} and a decreased resting HR of 11 beats.min^{-1}. However, these changes are unlikely to occur in patients taking β-blockers, as this medication reduces sympathetic drive and increases in HR, thus would limit the benefits of training on improving autonomic nervous system balance. A significant reduction in central sympathetic neural outflow, measured directly via microneurography, to levels comparable to healthy controls was recorded in 7 CHF after a 4 month training programme (Roveda et al., 2003), but, once again, these patients were not taking β-blockers.

Different physiological responses to continuous and intermittent training have been reported in previous studies despite similar improvements in functional capacity. Dimopoulos (2006) reported that continuous training significantly increased chronotropic reserve (HR_{peak} - resting HR) x100/(220 - age - resting HR) by 26% and HR recovery (61%) at 1 min, whereas there was no change following intermittent training. These patients were on current medication, including β-blockers. The authors

speculated that interval training may not provide an adequate stimulus to the autonomic nervous system. However, the measure of chronotropic reserve used in this study is a crude indirect measure of parasympathetic activity and may be influenced by numerous factors, including posture, blood pooling, recovery activity and heat. HR variability is a more sophisticated tool for assessing autonomic balance (Malfatto et al., 2002). Furthermore comparisons between studies are difficult due to differences in the mode of recovery. Dimopoulos et al (2006) set 30s work phases at 100% WR_{peak}, the same as in the current study, but recovery phases were 30s compared to 60s active recovery in this study, and the authors did not clarify whether the post exercise recovery period consisted of complete rest. Nechwatal (2002) demonstrated improvements in central haemodynamics (cardiac index, stroke volume index and peripheral resistance) after 3 weeks' intermittent but not continuous training. Patients trained 6 times per week in this study, compared to twice weekly in the current study. Wisloff and colleagues are the only group who have demonstrated significantly greater improvements in functional capacity and associated mechanistic parameters, including LV, endothelial and mitochondrial function, and BNP, after intermittent rather than continuous training (Wisloff et al., 2007). However, as discussed previously, the exercise stimulus differed from the current study as the work phases were of a longer duration and lower intensity.

7.3.6 Methodological issues

Differences in the extent of improvement in VO_{2peak} following exercise training may be due in part to methodological issues. In studies reporting increases of approximately 30%, patients did not undergo familiarisation exercise tests (Hambrecht et al., 1995a; Gielen et al., 2003; Klecha et al., 2007). Thus the improvements may be attributed in part to a learning effect, as acknowledged by some authors (Arad et al., 2008). Where a familiarisation maximal exercise test was specifically included, as in the current study, there were smaller improvements (Maiorana et al., 2000), or no improvements in VO_{2peak} (Hambrecht et al., 1995a; Tyni-Lenné et al., 1996; Wielenga et al., 1998; Willenheimer et al., 1998; Gielen et al., 2003; Klecha et al., 2007). Nevertheless, improvements of approximately 20% have also been reported in studies which included a familiarisation test.

Another possible influencing factor on patient effort in the maximal CPET came to light during anecdotal conversations with patients who said that the training programme had increased their confidence to to exercise for longer during the maximal test. Improvements in physical component MLHFQ scores, discussed later in this chapter, might, to some extent, reflect this new-found confidence.

The use of absolute or relative values will also influence the findings. For example, absolute VO_{2peak} increased by 4 ± 5 % in the circuit group and 6 ± 6 % in the intermittent group, whereas increases in relative VO_{2peak} were 11 ± 4 % and 5 ± 6 % respectively. Two CHF in the circuit group decreased their weight by 2 kg whereas 3 CHF in the intermittent group increased their weight by 1-2 kg. It is not clear if these changes in weight were due to fluctuations in fluid retention, muscle mass or fat mass, all of which may influence peak exercise capacity differently.

It could be surmised that the current study has too few participants, is too short in duration, or that the volume of exercise is too low to provide conclusive evidence about the benefits of exercise training. Similar conclusions have recently been drawn about a study on exercise training in elderly CHF (Brubaker et al., 2009; Lavie et al., 2009). Equally, the question of clinical meaningfulness must also be considered. Statistical analysis, particularly on studies with small sample sizes, may not reflect clinical or practical meaningfulness. The HF-ACTION trial, which had a sample size of > 2000 CHF, reported increases in $V0_{2peak}$ of 4% (0.6 $ml.kg.min^{-1}$), lower than the increases in the current study, and these were statistically significant (O'Connor et al., 2009). In common with this study, HF-ACTION patients were on optimal medical treatment, including β-blockers, ACE-inhibitors or angiotensin receptor blockers and biventricular pacemakers and ICDs, which may limit the additional benefits from exercise training. Nevertheless, small improvements in VO_{2peak}, which may not be statistically significant, coupled with improvements in psychological well-being, may translate into a clinically meaningful effect. For example, in coronary heart disease patients completing a CR programme, depressive symptoms were reduced equally effectively, with a subsequent improvement in survival, in those who showed small improvements (0-10%) in VO_{2peak} and those who achieved larger improvements (>10%) in VO_{2peak} (Milani and Lavie, 2007).

7.3.7 BNP

It has been argued that, because there is limited information about the stability or reproducibility of BNP over time in patients who are clinically stable, serial BNP measurements cannot accurately be interpreted to assess the effect of interventions (Packer, 2003). Some authors suggest that therapeutic interventions aimed more clearly at the myocardium are more likely than exercise to elicit changes in BNP and NT-BNP (Meyer et al., 2004b). BNP levels can very over a short period of time due to biological variation, physical activity, and change in medication (Hogenhuis et al, 2006, Smart and Steele, 2009). Although measurements were taken at rest, it is conceivable that increased activity levels resulting from exercise training could increase BNP levels even at rest, thus confounding the issue further (Kjaer et al., 2004; Arad et al., 2008).

However, a recent systematic review, which included 5 trials measuring BNP (Jonsdottir et al., 2006; Passino et al., 2006b; Butterfield et al., 2008; Malfatto et al., 2009), concluded that exercise training does have a favourable effect on BNP (mean difference -79 pg/ml, 95% CI -141 to – 71 pg/ml) (Smart and Steele, 2009). The exercise dose was higher than in this study, with reported training intensities of 50-70% VO_{2peak} for 2-7 sessions per week for duration of 3-9 months, and the authors concluded that a minimum weekly energy expenditure of 400-450 kcal per week was required to elicit changes in this parameter. Wisloff et al (2007) reported that intermittent but not continuous training improved cardiac function and reduced BNP by 40%. It is possible that the frequency and/or duration of training in the present study were too low to elicit changes, or that older CHF are slower to show adaptations in these parameters.

In the current study there was large variability in the point of care BNP measurement, both between patients and between the pre and post-training values. Unpublished data presented at BACR study day (2009) from CR programme at the Heart & Lung Centre, Wolverhampton, also showed a large range of values (mean 1563 ± 664 pre-training, range 37-5525 $ng.L^{-1}$ in 22 CHF. It appears that this technique might not be sensitive enough to detect changes following short-term CR programmes. One small study has assessed the utility of point-of-care BNP measurement in a CR setting (Butterfield et al., 2008). 10 out of 13 CHF patients who completed a 12 week exercise programme

showed a decrease in BNP compared with an increase in 4 of the 6 non-exercising control patients, and this mirrored improvements in 6-minute walk distance, QoL, and stroke volume estimated by non-invasive thoracic impedance cardiography. Future studies should address the reproducibility and thus the value of using this technique to assess changes following therapeutic interventions. In addition, it is important to consider the evidence suggesting that changes in BNP do not reflect changes in clinical status (Spertus et al., 2005).

7.3.8 Daily physical activity

This study did not find any significant change in weekly physical activity levels outside the CR classes, or any difference between the circuit and intermittent groups. This suggests that improvements in VT and physical QoL scales were due to exercise performed in the supervised classes, rather than any home-based increase in physical activity.

Comparison with previous studies of CHF is difficult due to methodological differences, but other authors report that daily energy expenditure or activity, measured by doubly-labelled water and accelerometry, remain unchanged, despite improvements in exercise capacity (Gottlieb et al., 1999; Witham et al., 2005). One study did use patients records of time spent on physical activity, which was classified as low (1 point), moderate (2 points) or high (3 points), and a weekly physical activity score was calculated according to the formula time x intensity^2/100 (Willenheimer et al., 2001). Total activity score only was reported, making it impossible to calculate the time spent in low or moderate activity. In the current study, the majority of patients met UK Government guidelines of 30 minutes of moderate activity on most days of the week, i.e. 150 – 210 min.week^{-1}). It is possible that differences in patient perceptions of what to include as light or moderate activities, as well as inaccuracies when applying generalised MET intensities to the CHF population, might have disguised any changes. For example, for one patient walking at 2 miles per hour might equate to 2.5 METS as listed in Compendium (Ainsworth et al., 2000), but for a patient with very limited exercise tolerance this might be closer to be four times his/her resting metabolic rate.

All patients increased the amount of exercise achieved in the classes, either by progression to a greater ratio of aerobic to active recovery exercises in the circuit group, or by increasing the number of work phases performed in the intermittent group.

7.3.9 Quality of life measures

7.3.9.1 Minnesota Living with Heart Failure Questionnaire

There is mixed evidence as to the effect of exercise training on disease-specific QoL. A systematic quantitative review reports a -9.7 point improvement in MLHFQ score, with a pooled effect size of -0.41 and 95% confidence intervals of -0.6 – -0.22 (van Tol et al., 2006). However, several studies have reported non-significant reductions or no change in MLHFQ scores after training, despite improvements in exercise performance (Gottlieb et al., 1999; Keteyian et al., 1999; Owen and Croucher, 2000; McKelvie et al., 2002; Arad et al., 2008). Improvements in MLHFQ score and global QoL have been reported following intermittent training interventions (Willenheimer et al., 1998; Meyer and Laederach-Hofmann, 2003). Similar improvements in QoL, assessed by the MacNew questionnaire, following intermittent and continuous exercise were reported by Wisloff et al (2007).

The current study supports the finding that exercise training appears to improve QoL regardless of the mode of exercise. There was a significant mean reduction of -8 points in both the circuit and intermittent groups. This exceeds the improvement reported in studies of older CHF similar in age (Austin et al., 2005a; Brubaker et al., 2009). Baseline scores were higher in these studies which, while offering greater potential for improvement, may also have limited the potential benefits of CR. 70% of patients in the circuit group and 60% in the intermittent group exceeded the 5 point reduction considered to be clinically relevant (Rector and Cohn, 1992). Substantial reductions were seen in a few patients, the greatest of which was -23 in the circuit group and -43 in the intermittent group. Both patients had a large improvement in their physical and emotional QoL, illustrating that even a short-term programme can offer sizeable benefits to some patients. Interestingly, both patients had ICDs and while VO_{2peak} improved by 33% in the first, it decreased by 10% in the second patient. An 8 week exercise programme resulted in a mean 22 point improvement in one study, due to improvements in physical capacity as well as patient confidence (Parnell et al., 2002).

On average, CHF in the current study showed small improvements in both physical and emotional scores; in the circuit group improvement in the physical component score was statistically significant, whereas in the intermittent group the improvement in emotional component score was significant.

The current study agrees with previous studies that have failed to demonstrate a significant positive relationship between improvements in cardio-respiratory fitness and QoL, suggesting that QoL is determined by factors other than physical fitness alone (Quittan et al., 1999). Participating in an exercise programme may have a positive effect on health-related QoL in the absence of any improvement in physical capacity owing to the attention, supervision and support offered by staff and peers. In this study both training groups received similar levels of support from the investigator and CR staff, thus precluding the Hawthorne effect seen in studies comparing exercise training with a non-exercising control group. However, the participant information sheet clearly explained the study aims, and included reference to previous work suggesting that intermittent training was more effective than other training methods. It is therefore possible that patients in this group may have perceived that they were more likely to gain benefits, and therefore been more motivated to comply with the exercise prescription, which could have influenced the results. A study comparing two leg training with one leg training as well as a control group reported that improvements in health related QoL, both in the physical and psychological dimensions, were significantly higher in the two leg group, whereas there was no significant difference between one leg training and control (Tyni-Lenné et al., 1996). The authors suggest that this supports that the physical training exerts a beneficial effect over and above any Hawthorne effect from participating in a training programme. Studies showing that home-based training results in similar improvements to supervised group training also indicate that benefits are not due to social support alone (Passino et al., 2006b).

7.3.9.2 SF-36

At baseline, CHF patients demonstrated relatively low scores, (indicating better QoL) in comparison to published norms for a healthy population in all scales apart from social functioning and mental health. This is perhaps surprising given that the British Heart Foundation's statistics that up to 40% of CHF are likely to suffer from depression which would be expected to reduce QoL. However, the SF-36 is not disease-specific

and might not be sensitive to the various factors that contribute to QoL in CHF. Alternatively, the low SF-36 scores could reflect a self-selection bias; CHF with better perceptions of their state of health might be more likely to participate in the study. Although mean scores improved after training, particularly in the role-physical, vitality and role-emotional domains, there was inter-individual variability, and no statistical significance. Nevertheless, mean scores post-training in vitality and role-emotional domains increased from baseline to reach close to normative values.

Other authors have reported significant increases in scores for physical and social functioning, role-physical and vitality and mental health after exercise training compared to usual care (Quittan et al., 1999), and in an observational study after intermittent exercise. However, 6 weeks' CR had no effect on SF-36 scores measured at at 3, 6 or 12 months' follow up in a large sample of cardiac patients, including those with CHF (Zwisler et al., 2008). The authors commented that this generic QoL instrument may be less likely to show an effect, and that the 6 week programme was shorter than the recommended 8-12 weeks. By contrast, 4 weeks' CR, consisting of combined aerobic and resistance training and education sessions, in older CHF did significantly improve physical summary scale score measured by the SF-36v2, but the improvements were not maintained 6 months later despite continued increases in functional capacity (Miche et al., 2009). The SF-36v2 is the newer version of the survey. It includes two summary measurement scales for physical health (physical functioning, role-physical, bodily pain, general health) and psychological health (vitality, social functioning, role-emotional, mental health), which facilitate a simplification of the statistical calculations without losing any of the individual information included within the questionnaire. For licensing reasons, this version was was not used in the current study.

There was no difference in change in SF-36 scores between the circuit and intermittent group in the current study. Nechwatal (2002) reported that SF-36 summary scores improved significantly after continuous and intermittent training, but the improvement in psychological summary scale was more than 3 times higher in the continuous group, although it is not clear why.

7.3.10 Practical implications

This study demonstrates the feasibility of including high intensity intermittent training in an existing hospital-based programme for a heterogeneous group representative of the general CHF population, including the elderly, patients with co-morbidities and on different pharmacological therapies, and those with implantable devices. Despite the fact that these patients may have a poor prognosis, improvements in QoL and sub-maximal exercise performance could translate into an improvement in ability to achieve and enjoy daily activities.

7.3.11 Study limitations

The small sample size in this exploratory study may have resulted in insufficient power to detect significant differences in some outcome measures. The HF ACTION trial recruited 2,331 CHF and reported a 4% improvement in VO_{2peak} (a median increase of 0.6 $ml.kg^{-1}.min^{-1}$), which was statistically significant (O'Connor et al., 2009). An alternative approach in future studies might be to assess whether intermittent training is "not clinically inferior" to existing interventions used in current practice. In this case, the study design should incorporate the recommendations of the extended Consolidated Standards of Reporting Trials (CONSORT) Statement for noninferiority and equivalence trials, and use a sample size appropriate for assessing whether the 95% CIs are above the boundaries of non-inferiority (Puhan et al., 2006).

There was a change of circumstances shortly after data collection began. Limited resources for CR services necessitated that a maximum of 4 study patients could participate in the exercise training sessions at one time, meaning that 4 was the maximum number who could logistically complete the study every 8 weeks. After allowing for public holidays and experimenter/patient availability, the data collection period was 54 weeks, allowing a maximum of 28 patients (i.e. 7 groups of 4 patients). The sample size was also influenced by those who chose to participate, rather than being randomly selected from whole CHF population. However, this study achieved a similar participant number and a similar completion rate per year to numerous published studies subject to the same limitations (Lloyd-Williams et al., 2004).

The high intensity intermittent training protocol used in this study was derived from the study results in Chapters 4-6 in which the characteristics of some of the CHF were different to the current study, which included patients with AF and implantable devices. It is not clear if these patients show the same responses to different volatilities of intermittent exercise. Nevertheless, CPET values for these patients were similar to patients without implantable devices, and those in the intermittent training group were able to perform the prescribed exercise and demonstrated similar ratings of perceived exertion to patients without devices.

It is recognised that a comprehensive exercise programme will include elements of aerobic and resistance/strength training (BACR Core standards). A limitation of this study was that the intermittent training group did not perform any strength training exercises. If intermittent training were to be incorporated into CR exercise classes in the future, it would ideally be combined with resistance, balance and flexibility training.

Due to the nature of the study, it was not possible to blind the intervention allocation to the patient or to the outcome assessor. Intention to treat analysis was not appropriate as only compliant patients attended the follow-up testing session. Those who dropped out did so for medical reasons that prevented them from exercising, and thus from completing follow-up testing.

7.4 Conclusions

This chapter investigated the effect of traditional circuit-based and high intensity intermittent training on functional capacity, ventilatory efficiency, BNP and QoL in CHF patients on a 6 week CR programme. It tested the hypothesis that there would be no difference between the effect of training methods on these variables. The results of this study support this hypothesis. Traditional circuit-based training and high intensity intermittent training are equally effective at improving sub-maximal exercise performance and disease-specific QoL in a short-term twice-weekly exercise programme in a population of elderly CHF of mixed aetiology. Longer-term and/or more frequent training may be required to achieve improvements in maximum exercise capacity and V_E/VCO_2 slope. Neither rapid point-of-care analysis of BNP nor the SF-

36 health questionnaire appears to be an appropriate tool for assessing the effect of a short-term exercise programme.

CHAPTER 8: EXAMPLES OF FURTHER CHALLENGES IN THE EXERCISE TESTING OF CHF PATIENTS

8.0 Introduction

In this thesis, several challenges associated with exercise testing in CHF have already been discussed in detail. These include issues of reproducibility, limited exercise tolerance and the narrow range between the exercise intensity domains. The following chapter explores some further challenges encountered during the exercise testing of CHF in study 4, including testing of patients with implantable devices, and measurement of heart rate and lung function. Where appropriate, case studies will be used to illustrate interesting or unexpected responses to exercise testing. All patients described in the case studies completed the exercise training intervention, and are included in the data presented in Chapter 7.

8.1 Exercise testing in CHF with implantable devices

Pacemakers, cardiac resynchronisation therapy and implantable cardioverter defibrillators are current treatments for the management of CHF (National Collaborating Centre for Chronic Conditions, 2003; Swedberg et al., 2005). There is emerging evidence that exercise training offers additional improvements in functional capacity in patients with these devices, and should be recommended in clinical practice for this population (Conraads et al., 2007; Patwala et al., 2009). However, exercise testing of patients with devices raises certain difficulties, as illustrated below.

Pacemakers may be set in different modes, depending on the aim of the therapy. The North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group (NASPE/BPEG) use codes to describe pacing modes which are set out in Table 8.1. A rate responsive device contains an activity sensor, e.g. an accelerometer in the pulse generator, to detect bodily movement and increase the pacing rate according to a programmable algorithm (Trohman et al., 2004). However, lack of activity of the upper extremities during cycle ergometry may mean that the HR response is not activated. This has previously been reported in a case study in CHF (Nilsson et al., 2008a), and is illustrated in Case Study 1 below.

Table 8.1: NASPE/BPEG pacemaker generic codes

The code to describe various pacing modes usually consists of three, four or five letters *(adapted from Trohman et al, 2004).*

Letter 1	chamber that is paced (A=atria, V=ventricles, D=dual chamber)
Letter 2	chamber that is sensed (A=atria, V=ventricles, D=dual chamber, 0=none)
Letter 3	response to a sensed event (T=triggered, I=inhibited, D=dual - T and I, R=reverse)
Letter 4:	rate responsive features; an activity sensor, e.g. an accelerometer in the pulse generator, in single or dual chamber pacemakers detects bodily movement and increases the pacing rate according to a programmable algorithm (R=rate responsive pacemaker)
Letter 5	Anti-tachycardia facilities

8.1.1 Case study 1: non-activation of heart rate response during cycle ergometer testing

The patient was male, aged 71 years, and measured 182 cm with a body mass of 89 kg. Aetiology was dilated cardiomyopathy and asthma was the only co-morbidity. A cardiac resynchronisation therapy device with a defibrillator (CRT-D) had been fitted 3 years previously, with leads to the right atrium and right and left ventricles. The pacing was rate-modulated in VVI-R mode. Resting BP was 124/80 mm/Hg, and resting HR was 70 beats.min^{-1}. Medication included antiarrhythmic (amiodarone), β-blocker (bisoprolol), angiotensin II receptor antagonist (irbesartan), statin (simvastatin), warfarin and a qvar corticosteroid inhaler.

This patient performed 2 maximal tests one week apart. Figure 8.1 illustrates the VO_2 and HR response to the incremental exercise tests. The test protocol involved 3 minutes at rest, then increments of 10W every minute, as described in the General Methods (Chapter 3). Exercise duration in Test 1 was 9 min 31 s with a WR_{peak} of 100W. Exercise duration in Test 2 was 9 min 15 s with a WR_{peak} of 90W.

In test 1, limited upper body movement failed to activate the movement sensors in the pacemaker at the onset of cycling. At minute 6, the movement sensors were activated by manually tapping on the device. This caused an almost immediate increase in HR of

22 beats.min^{-1}, accompanied by an increase in VO_2. There was no further tapping of the pacemaker, and the HR gradually returned to its pre-determined rate of 70 beats.min^{-1} over a 4 minute period. VO_2 decreased between minute 8 and 9, despite the increase in exercise load, before increasing steadily again until the end of test. In test 2, performed one week later, there was no manual interference to the pacemaker. HR remained constant at 70 beats.min^{-1} and VO_2 increased at a more constant rate until the peak value was reached. VO_{2peak} was ~100 ml lower in test 2.

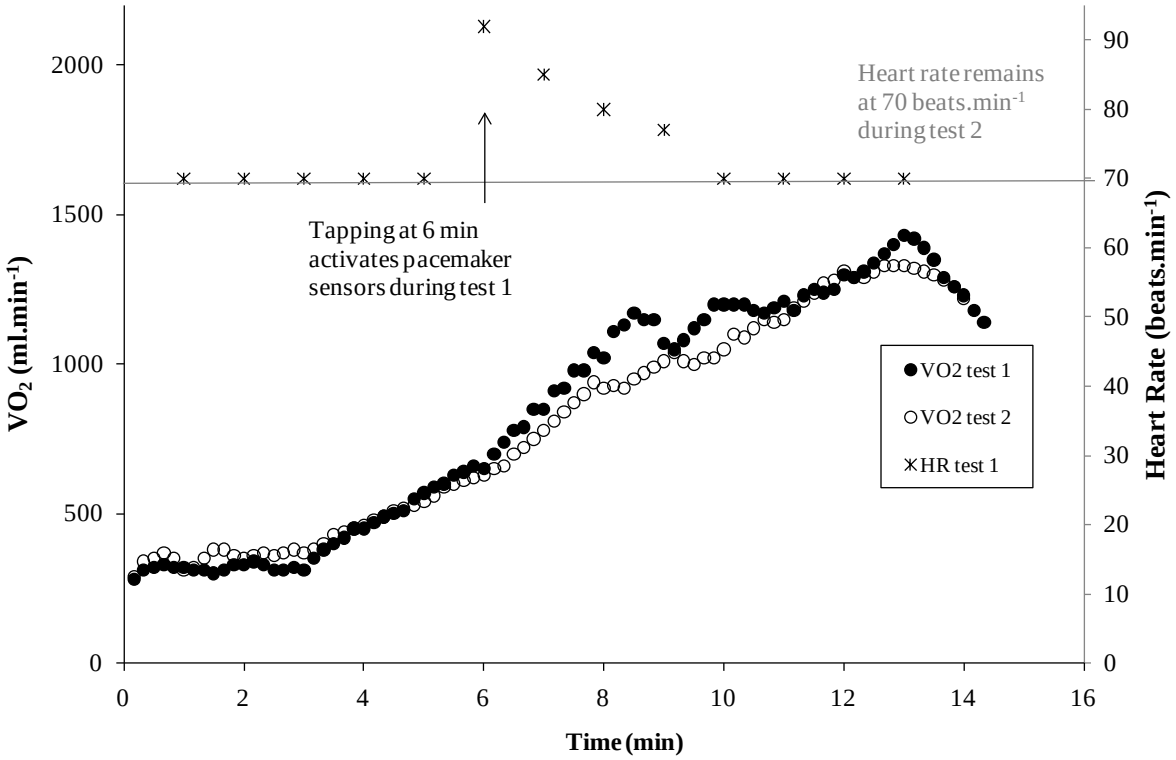


Figure 8.1 : Oxygen uptake and heart rate response to a maximal incremental test in a patient with a rate modulated pacemaker.
In test 1 the pacemaker sensors activated manually. In test 2 the pacemaker sensors were not activated.

It is not clear how exercise responses are affected by the activation or inactivation of the pacemaker HR response sensors, and this is an interesting topic for consideration in the management of CHF with these devices.

8.1.2 Case study 2: Cycle ergometer testing in 2 different pacemaker modes

The patient in case study 2 also performed two tests one week apart. This patient was male, aged 76 years, and measured 168 cm with a body mass of 74 kg. Aetiology was ischaemic, and co-morbidities were Type II diabetes with mild peripheral neuropathy. The patient had suffered a myocardial infarction 10 years previously, had undergone an atrio-ventricular node ablation and CRT-D approximately 1 year prior to participating in the study, but the atrial lead did not function properly. The pacemaker was set in VVI mode. Resting BP was 127/85 mm/Hg, and resting HR was 70 beats.min^{-1}. Medication included, β-blocker (carvedilol), angiotensin II receptor antagonist (candesartan), diuretic (furosemide), statin (atorvastatin), aspirin, warfarin, metformin, anti-convulsant (pregabalin) and H_2 antagonist (ranitidine) for gastro-oesophageal reflux.

Test 1 was performed with the pacemaker in VVI mode (i.e. no HR response). Test 2 was performed with the pacemaker in VVI R mode, i.e. rate responsive (Figure 8.2).

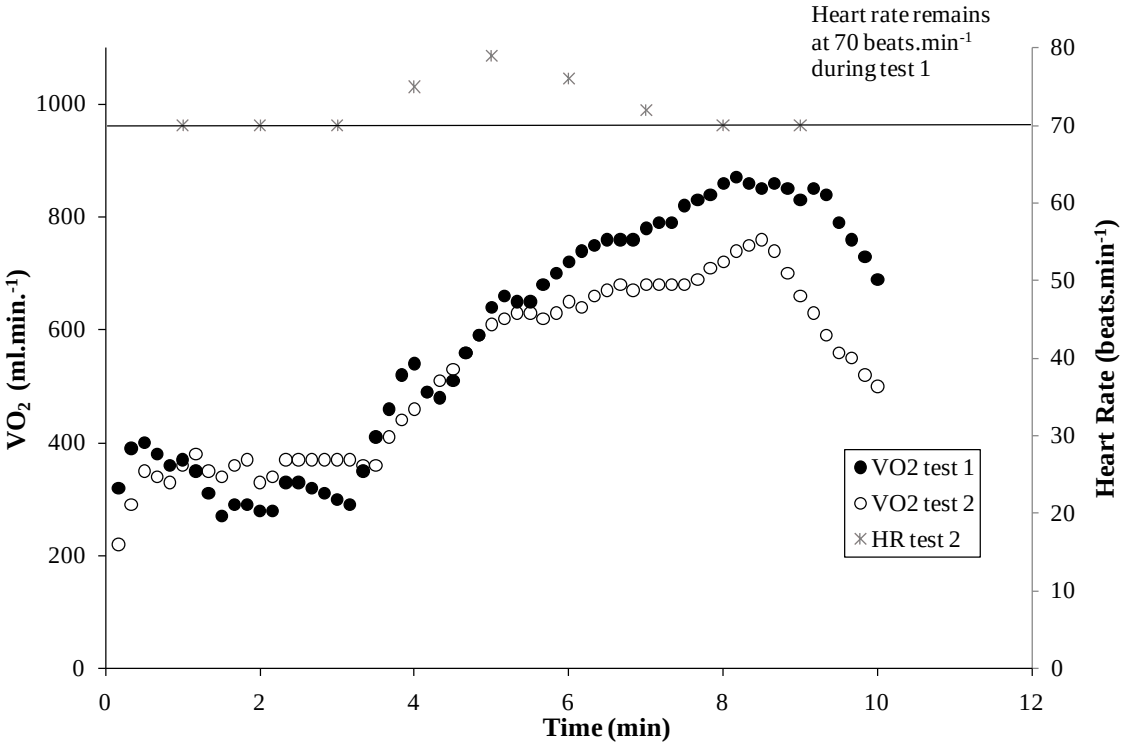


Figure 8.2 : Oxygen uptake and heart rate response to a maximal incremental test in non-rate modulated (test 1) and rate modulated (test 2) pacemaker modes.

Exercise duration in Test 1 was 4 min 55 s with a WR_{peak} of 50W and VO_{2peak} of 870 $ml.min^{-1}$ (11.8 $ml.kg^{-1}.min^{-1}$). Exercise duration in Test 2 was 4 min 11 s with a WR_{peak} of 40 W and VO_{2peak} of 760 $ml.min^{-1}$ (10.3 $ml.kg^{-1}.min^{-1}$). Neither VT nor V_E/VCO_2 slope could be determined in either test. This patient performed better when his pacemaker was in non-rate modulated mode. Case Study 1 illustrated that, even if the pacemaker is rate-modulated, cycle ergometry exercise may not produce enough upper body movement to activate the sensors. Figure 8.2 shows that in Case Study 2, HR does increase at the onset of exercise, but that it starts to decrease towards resting levels after 2 minutes of exercise. The increase in HR was not accompanied by an increase in VO_2, as seen in Case Study 1. It is possible that the initial bodily movement to start turning the pedals was enough to trigger the sensors, but that lack of subsequent movement explains the later decrease in HR. The patient's pacemaker was switched from VVI to VVIR mode shortly after Test 1, meaning that the pacemaker was in the new mode for the week preceding Test 2. The patient reported that he had felt less well than usual this week, although it is not clear whether this was due to the change in mode, or to non-related factors.

An increase in HR during exercise usually contributes to a higher cardiac output, suggesting that rate-modulated pacing is more likely to benefit exercise performance. However, the evidence supporting an improvement in exercise capacity in DDDR-paced patients when compared with DDD-paced patients is inconsistent (Lamas et al., 2004)

The case studies above illustrate potential difficulties of exercise testing in patients with pacemakers. In addition to these, one further issue was experienced in a different patient with an ICD. During the maximal CPET following the training intervention, this patient's HR was approaching (within 5 $beats.min^{-1}$) the threshold for defibrillation; hence the exercise test was terminated prematurely by the experimenters although the patient had not reached volitional exhaustion. However, analysis of the data showed a plateau in VO_2 had been achieved during the final 30s of the test, with an RER of 1.18, and these data were therefore considered valid and included in the results for Study 4.

8.2 Case study 3: Abnormal VO_2 response at peak exercise

Case study 3 was male, aged 70 years, and measured 170 cm with a body mass of 70 kg. Aetiology was dilated cardiomyopathy, with atrial fibrillation and hypertension. Resting BP was 150/71 mm/Hg, and resting HR was 48 beats.min^{-1}. Medication included antiarrhythmic (amiodarone), β-blocker (carvedilol), ACE inhibitor (lisinopril), aldosterone antagonist (eplerenone) and warfarin.

This patient showed an interesting VO_2 response to the maximal incremental exercise test both pre and post training. As illustrated in Figures 8.3 and 8.4, there is a "rebound" in VO_2 on cessation of exercise. This is evident in both tests, but is more pronounced in test 2: VO_2 plateaus during the 90W stage, then decreases in the final stage (100W). An immediate rebound in VO_2 is seen on cessation of exercise that persists for at least 1 min post exercise. It has previously been reported that, due to slowed VO_2 kinetics, VO_{2peak} may be reached in the 30s after exercise (Cohen-Solal et al., 1997), but VO_2 values usually increase steadily until peak is achieved. In this case study, VO_{2peak} measured in recovery was 5% (77 ml or 1.1 ml/kg/min) higher than VO_{2peak} measured during the test, or 12% higher (163 ml or 1.4 ml/kg/min) higher than the average VO_2 value in final 30s of exercise.

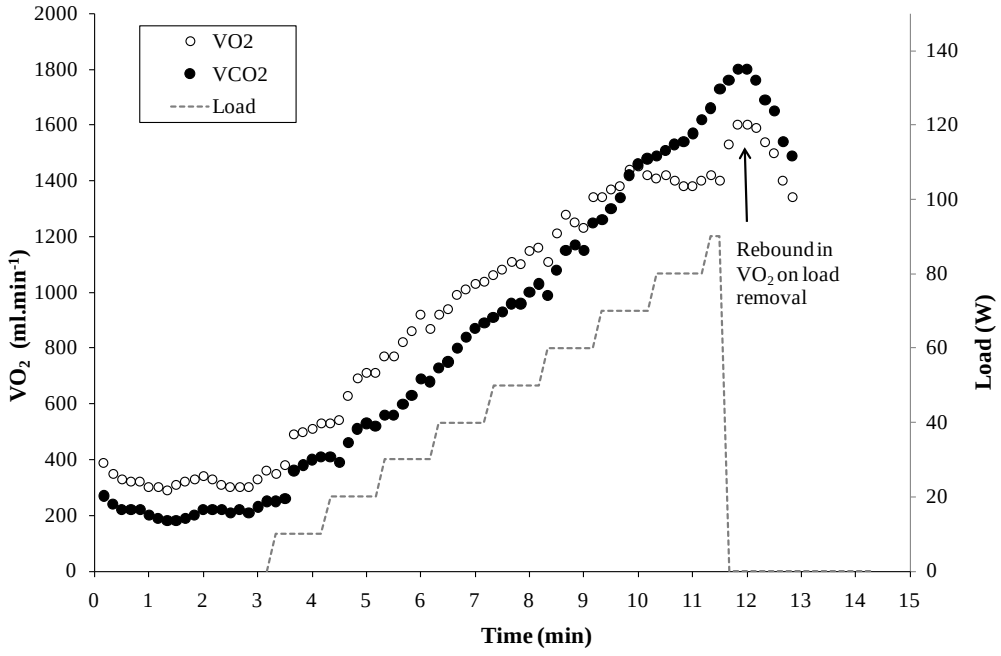


Figure 8.3: Oxygen uptake response to maximal incremental exercise test at baseline

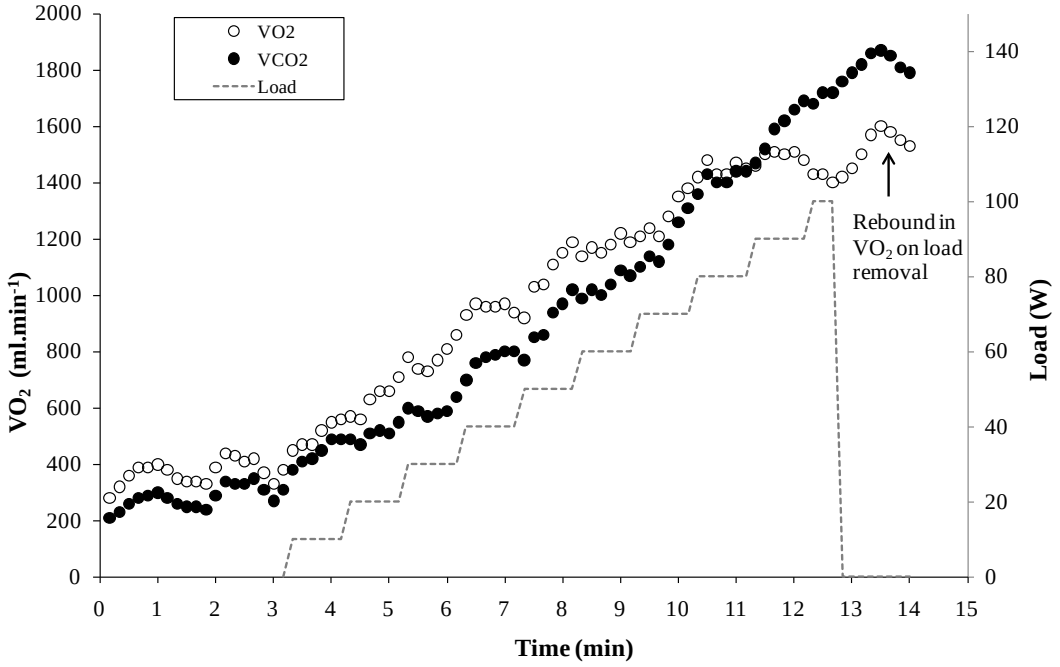


Figure 8.4: Oxygen uptake response to maximal incremental exercise test after 6 weeks' intermittent exercise training

The response in Figures 8.3 and 8.4 is similar to the rebound in LVEF at rapid off-loading of exercise, described by Foster et al (1998), and illustrated in Figure 8.5. When exercise ceases suddenly, there is a significant increase in LVEF, most likely due to decrease in preload. This effect is less apparent in the supine position, where preload remains high (Foster et al., 1998). It is not clear how the semi-recumbent cycle ergometer used in the current study might influence haemodynamics in CHF, but a study comparing upright and semi-recumbent exercise in healthy children found no difference in echocardiographic measure, including LVEF, between the two modes (Chang et al., 2005). Several other mechanisms might contribute to an increase in LVEF on cessation of exercise. Coronary artery disease patients showed a sharp rise in stroke volume during recovery due to a decrease in end systolic volume, probably resulting from an immediate reduction in afterload coupled with a slower decrease in sympathetic activation (Koike et al., 1990). This "rebound" in LVEF on reduction or removal of workload has also been reported in more recent studies using various techniques, including first pass radionuclide ventriculography and echocardiography (Rozanski et al., 2001). The authors report that, in cardiac patients, the regional wall motional abnormalities induced by exercise are resolved rapidly on removal of

workload. These issues are beyond the scope of this thesis, but have implications for the timing of measurement of physiological responses during exercise testing.

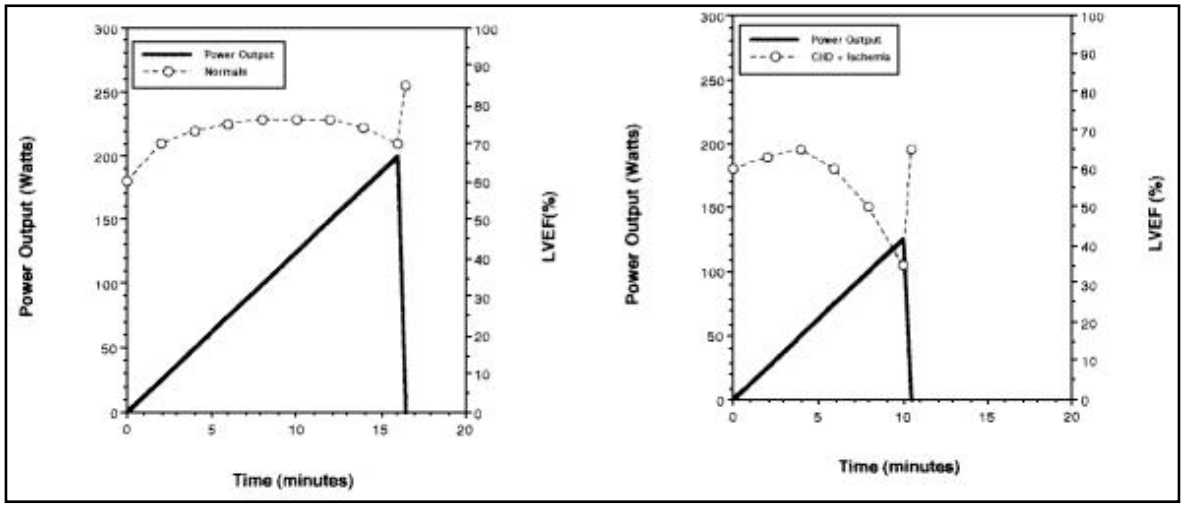


Figure 8.5 : Response of left ventricular ejection fraction to rapid off-loading of exercise in healthy individuals and CHF Patients
(adapted from Foster et al, 1998)

8.3 Heart rate response to exercise in patients with atrial fibrillation

Atrial fibrillation is common in CHF, particular in older patients, yet few exercise training studies have included CHF with atrial fibrillation (Willenheimer et al., 1998; Owen and Croucher, 2000). In the current study, 8 CHF were in atrial fibrillation and HR could not be accurately measured in these patients during exercise, either by 3 lead ECG during exercise testing or by telemetry during exercise. Figure 8.6 shows HR recorded during a training session for a patient in AF.

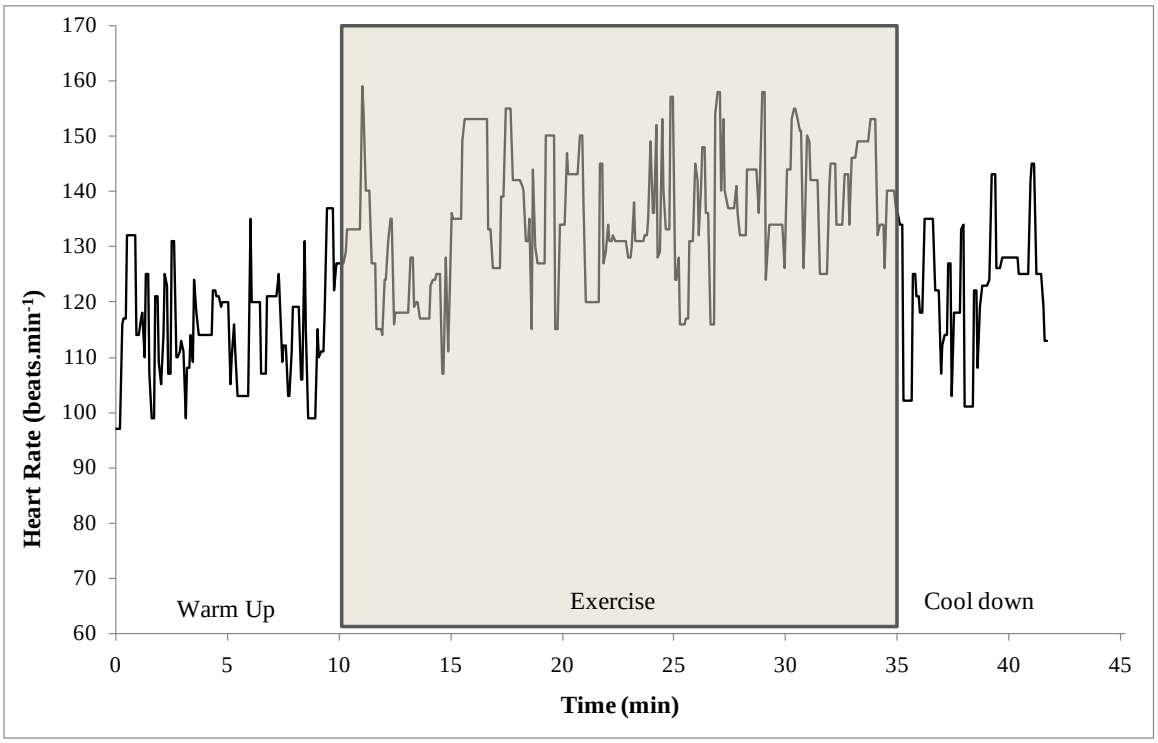


Figure 8.6: Exercise session heart rate data for patient with atrial fibrillation in intermittent group (female, aged 70 years).

8.4 Heart rate guidelines for exercise intensity prescription

Problems with using a percentage of HR_{max} to guide exercise intensity, including a narrow HRR and frequency of atrial fibrillation, have been recently reported (Prescott et al., 2009). In agreement with this, data collected during studies 1-3 of this thesis have been published to emphasise that current HR guidelines for prescribing moderate exercise in CR are likely to overestimate exercise intensity in CHF (Beale et al., 2010) (Appendix 7). HR data measured during Study 4 raises some additional issues. In both the circuit and intermittent training groups, the mean average training HR exceeded 90% of the HR_{peak} achieved during CPET, and the highest training HR was close to, or higher than this HR_{peak}. This might be due to the difference in haemodynamics between recumbent cycling in the CPET and upright cycling and/or weight bearing exercise performed during the training session (Walsh-Riddle and Blumenthal, 1989). The larger HR range during training in the circuit group (77 ± 5 - 103 ± 7% HR_{peak}) compared with the intermittent group (85 ± 4 - 99 ± 4% HR_{peak}) reflects the different types of exercises performed in this group, e.g. active recovery exercises with light hand weights and weight-bearing exercises, such as walking or stepping, engaging a

greater active muscle mass than cycling. Another possible explanation might be that the longer duration of the training session allowed a greater period for the chronotropic response to noradrenaline than the short duration of the CPET.

8.5 Heart rate recovery

HR recovery has been proposed as a simple marker of autonomic function that can be used to assess outcomes during CR (Myers et al., 2007). To provide optimal assessment HR should be recorded for the whole of the recovery period, or for a period of 6 minutes, with workload and pedal cadence controlled if the recovery is active. The protocol for the current study involved an optional active recovery with no added resistance at a self-selected pedal cadence from 90s after exercise cessation (to allow for echocardiography data collection), therefore HR recovery could have been calculated as the difference between HR_{peak} and HR 60s from the end of exercise, as proposed in previous studies (Dimopoulos et al., 2006). However, accurate measurements of both HR_{peak} and/ recovery HR could not be made in 16 out of 26 CHF, due to atrial fibrillation or muscular movement interfering with the ECG HR signal. Therefore this measurement was not included in the study results.

8.6 Lung function

In a clinical setting, it is recommended that, prior to CPET, inspiratory capacity (IC), forced expired volume in 1 s (FEV_1) and forced vital capacity (FVC) are assessed to identify patients with restrictive lung disease (Ingle, 2008). The majority of patients had difficulty performing the lung function test. Although patients were given the opportunity to practise the test, poor technique and patient discomfort limited the validity and usefulness of the tests, hence the results have not been reported. 1 patient participating in studies 1-3 and 1 patient in study 4 had been previously diagnosed with COPD, and 2 patients in study 4 had previously been diagnosed with mild asthma.

CHAPTER 9: GENERAL DISCUSSION & CONCLUSIONS

9.0 Introduction

Exercise training can reduce morbidity and mortality, improve functional capacity and enhance QoL in CHF. Supervised training programmes results in better compliance and the most favourable outcomes in CHF patients in the UK (Jolly et al., 2009), and the multidisciplinary approach offered by CR schemes offers the ideal environment for safe exercise, education and the management of CHF and its co-morbidities (Boudreau and Genovese, 2007). Standardised exercise recommendations for CHF have been published by the ESC, and ACPICR & BACR have published exercise guidelines for UK CR programmes, but experts agree that more research is warranted into the optimal exercise dose for these patients.

The existing body of literature indicates that the benefits of exercise training in CHF are due to a combination of mechanisms. These include improvements in cardiac output and oxygen extraction & utilisation. Underlying these changes are increased skeletal muscle blood flow, capillary density, mitochondrial volume and density and oxidative enzyme activity, improved endothelial function, and attenuation of excessive ergoreflex activation (Lloyd-Williams et al., 2004; Piepoli et al., 2004; Rees et al., 2004; van Tol et al., 2006). The greatest benefits from exercise training are due to peripheral rather than central adaptations in CHF (McConnell, 2005). The aim of exercise training is to apply sufficient stimuli to skeletal muscles without overloading the cardiovascular system (Giannuzzi et al., 2001). However, achieving the optimal exercise dose is not easy. Firstly, patients may not be able to achieve continuous endurance training workloads high enough to have an optimal training effect on the peripheral muscles without experiencing cardiac symptoms or local muscular fatigue. Secondly, the exercise dose used in clinical trials reporting benefits is higher than that in most UK CR settings (Taylor et al., 2007). A possible solution might be to increase the exercise dose by using high intensity intermittent exercise, which allows more work to be accomplished and therefore a greater training response (Christensen et al., 1960; Meyer et al., 1996c). This might compensate for a low frequency and duration of training.

This thesis had two key aims: 1) to examine the methodology for setting intermittent exercise intensity in order to find a reproducible and valid protocol; 2) to assess the

effect of an intermittent exercise intervention compared with an existing exercise intervention used in current practice

9.1 Limitations of maximal CPET for exercise intensity prescription

CPET is useful for aiding diagnosis and prognosis in CHF, for establishing exercise training protocols and for assessing the effect of therapeutic interventions, including exercise training (Ingle, 2007). Chapter 4 demonstrated that, although the mean difference between parameters measured in duplicate tests was < 10%, there appears to be a learning effect between the first and second attempts at a maximal CPET. It agrees with the consensus of opionion on the importance of familiarisation to exercise testing to obtain reproducible results in the general population, and proposes that a familiarisation test should be standard practice in CHF and older individuals, in line with previous opinion (Agostoni, 2006). This is in contrast to recent suggestions, based on data from the HF-ACTION trial, that there is no need to perform more than one baseline cardiopulmonary exercise test (Bensimhon et al., 2008). In this large multicentre trial there was substantial within-subject variability in VO_{2peak}, VO_2 at VT and V_E/VCO_2 slope in repeated tests. The variation appeared to be due to daily haemodynamic and volume status fluctuations, rather than a learning effect, since half of the patients increased and half decreased their VO_{2peak} and VT on the second test. Chapter 4 of this thesis demonstrated that sub-maximal measures, which are less dependent on subject motivation, showed better reproducibility than peak measures, but were still prone to variability between tests. The biological variability of cardiorespiratory measures has implications when using serial assessment to evaluate the effect of therapeutic interventions. Nevertheless, the numerous methodological differences in this thesis make it difficult to compare with other studies. The HF-ACTION trial took place at 83 different clinical sites, where variations in testing conditions could influence the results, and only 12% patients performed cycle ergometer rather than treadmill tests (Bensimhon et al., 2008). Furthermore, it is possible that some of the variability may be eliminated when patients are more familiar with the equipment and testing procedure, which could only be confirmed by a study comparing the results from 3 or more exercise tests.

Chapter 4 shows that the gas exchange thresholds (Meyer et al., 2005b) can be identified in the majority of CHF and older individuals. VT and RCP occurred at 62 ± 9% and 84 ± 6 % of VO_{2peak} in CHF, and 54 ± 6% and 82 ± 6 % in controls, which agrees with values reported in the literature (Simonton et al., 1988; Cohen-Solal et al., 1990; Meyer et al., 1997c; Marburger et al., 1998). Normative values for the percentage of VO_{2peak} at which VT will occur are ~ 58% men and 62% in women aged 70 years, but it is well known that there is considerable variability in both healthy and diseased populations (Wasserman et al., 2005). An interesting finding in Chapter 4 is that it is difficult to accurately prescribe exercise work rates in individual intensity domains in CHF compared to healthy controls because the range of work rate in each domain is very narrow (< 20 W), and the test-retest variability is relatively high.

9.2 Limitations of the steep test (Meyer et al, 1997) for intermittent exercise prescription

For intermittent exercise prescription in CHF, a simple incremental exercise test with large increases in work rate over a short duration (25W every 10s) has been devised (Meyer et al., 1997b). The work phase is set at 50% of the maximum work rate achieved in the test. There is no published literature on the validity or reproducibility of this test. Chapter 4 illustrated that in a repeat test 30% of CHF and 70% controls achieved a difference in WR_{peak} of one or two test stages, i.e. 25 or 50 W. This could translate to an increase in intermittent training workload of 12.5 or 25 W, potentially a substantial increase for CHF patients with a low initial WR_{peak}. Alternatively, it could reduce the workload by the same amount, thus reducing the exercise stimulus. Once again, this illustrates the difficulty of determining precise training workloads in this population, and demonstrates that reproducibility of this test is lower in older healthy individuals than in CHF.

There are no published studies comparing Meyer's intermittent training protocol with the method commonly used by exercise physiologists, which is to set the work phase intensity at VO_{2peak} work rate (Billat, 2001). Chapter 4 addressed this gap in the literature, and showed that intermittent exercise workloads prescribed by the different methods are not significantly different in CHF. However, in healthy older individuals an intermittent work rate set at 100% VO_{2peak} was significantly higher than 50% WR_{peak} in Meyer's steep test.

Although Meyer's steep test was not designed to measure VO_{2peak}, Chapter 4 found that CHF reached similar VO_{2peak} values in this test to values achieved in the standard CPET, and healthy older individuals achieved 91% of standard test VO_{2peak}. The relatively higher performance by CHF in the steep test suggests that these patients are less limited by their symptoms in short duration high intensity exercise. CHF with lower initial functional capacity were more likely to achieve a higher work rate in relation to the standard ramp and a higher VO_{2peak} in a short duration test than in a standard test compared with CHF with higher initial functional capacity and healthy controls. With increasing severity of heart failure, cardiac output response and oxygen delivery to the exercising muscles are increasingly reduced, and peripheral abnormalities reduce aerobic capacity further (Wilson et al., 1996; Tavazzi et al., 2001). Thus it is perhaps not surprising that these patients were more limited during the longer test which imposed a more prolonged stress on the aerobic energy system than the shorter test. The patients in Meyer et al's study (1997), who had severe CHF, reported that VO_{2peak} in the steep test reached only 87% of the standard test value. It is possible that the day-to-day variability and/or familiarisation effect discussed above, or could partly explain the difference between this thesis and Meyer's study.

9.3 Continuous and intermittent exercise of equal total workload elicit similar cardiorespiratory responses in CHF and healthy older individuals

In healthy participants physiological responses to intermittent exercise with short-moderate work phases are very similar to steady-state exercise of an equal total workload (Astrand et al., 1960a; Essen et al., 1977; Brickley et al., 2007). Chapter 5 confirmed that this also applies to CHF, agreeing with a single earlier study in CHF (Meyer et al., 1997b). It appears that there is a dampening of cardiovascular, respiratory and metabolic responses during repeated hard-easy exercise transitions, and that the recovery phases allow sufficient recovery of metabolites. It has been suggested that patients with a low exercise tolerance might find intermittent training subjectively easier than continuous training (Puhan et al., 2004). However, the perception of effort for CHF did not differ between exercise modes. For healthy older individuals RPE was also the same between exercise modes, but was lower than in CHF despite the fact that the workloads were set at the same relative intensity for both groups.

9.4 Changing the volatility of intermittent exercise intensity does not alter cardiorespiratory responses

Prescribing high intensity intermittent exercise for CHF challenges the general principle of exercise training progression for cardiac patients which is to increase the duration and frequency before the intensity. Due to the theoretical increased risk with high intensity exercise, few studies have examined the adaptation to high intensity intermittent training in older & cardiac populations, but those that do have done so safely and with no adverse affects (Meyer et al., 1996c; Wisloff et al., 2007). Chapter 6 demonstrated that manipulating the volatility of the intermittent work and recovery phases, so that they are either closer to or further from the mean exercise workload, while maintaining the same total workload, has no effect on acute cardiovascular and respiratory responses. However, when the intensity of the work phase was increased to $\geq VO_{2peak}$ work rate, Lac increased in comparison to lower volatility intermittent exercise. In theory, this indicates that high volatility intermittent exercise imposes a greater stimulus on the exercising muscles, by eliciting changes in cellular homeostasis, without increasing cardiac workload. This is in line with the aims of exercise training in CHF, namely to apply sufficient stimuli to skeletal muscles without overloading the cardiovascular system (Giannuzzi et al., 2001). CHF perceived high volatility intermittent exercise to be "somewhat hard", which also fits in with current guidelines (British Association for Cardiac Rehabilitation, 2006).

9.5 High intensity intermittent exercise training is an alternative training mode for cardiac rehabilitation programmes

Based on the findings from Chapters 4, 5 and 6, the next stage of this thesis was to assess if high volatility intermittent exercise, derived from a maximal CPET (with a preceding familiarisation test), was an effective method of training in a UK CR programme. Chapter 7 shows that, when transferred to a real-life setting, high intensity intermittent training had a similar effect to current circuit-based training methods at increasing sub-maximal exercise performance and QoL after a 6 week programme. This type of training may therefore offer an alternative and equally effective means of exercise training, which some patients might find easier to achieve and/or more enjoyable. Chapter 7 also demonstrated that neither high intensity intermittent nor

circuit training resulted in the improvements in VO_{2peak} or ventilatory efficiency reported in several exercise training studies in CHF.

9.6 The effect of the total exercise dose on the training response

In the general population, there is a graded dose-response between the total volume of physical activity performed and cardiorespiratory fitness (Oja, 2001). The evidence for a dose-response for activity volume and measures of health is less strong. The short time scale and low frequency of training in Chapter 7, which reflects the situation in current CR practice (Taylor et al., 2007), is likely to explain the limited improvements reported in this thesis. It is difficult to assess how the dose of exercise, in terms of frequency, duration and intensity, influences the training effect. These interrelating factors are discussed below. Although all patients increased the amount of exercise achieved in the classes during the study duration, the daily records indicated that the amount of home-based physical activity did not change. This highlights the importance of achieving an adequate exercise dose during supervised training, and suggests that an additional aim during supervised sessions should be to increase the amount of unsupervised exercise performed.

9.6.1 Frequency and duration

No studies in CHF have compared different volumes of exercise in terms of training frequency and duration. The majority of studies include 3-5 sessions per week, although a few less frequently. There is some evidence that increased frequency and duration of training will result in greater training benefits: an intensive residential training programme involving 2-3 hours of exercise per day increased VO_{2peak} by 26% after only 4 weeks (Myers et al., 2007). Lavie et al (2009) argue that if patients in the HF-ACTION trial had adhered to their exercise prescription of 120 mins per week, rather than completing only half this amount, the higher exercise volume would have been more likely to elicit greater improvements in VO_{2peak}, and reductions in cardiovascular events and mortality (Lavie et al., 2009). This is confirmed by data from the trial showing that the volume of exercise completed each week was directly associated with the magnitude of the increase in VO_{2peak} (Keteyian, 2010).

9.6.2 Intensity

In healthy individuals, the intensity of the the activity appears to be more important than the total volume for increasing cardiorespiratory fitness (Oja, 2001), and "vigorous" intensity activity is associated with a lower risk of cardiovascular disease, and of other chronic diseases (O'Donovan et al., 2010). In studies of CHF, comparison between intensities is hampered by the different methods used to define intensity, e.g. % VO_{2peak}, % HR_{peak}. However, studies where the intensity is higher do not necessarily appear to be more effective. One study concluded that an exercise intensity of 70% HR_{max} was too low to improve VO_{2peak}, but also acknowledged that lack of patient compliance to the home-based exercise, or the short study study duration (6 weeks) could also explain this finding (Harris et al., 2003). By contrast, 6 weeks' low intensity cycle training at$\leq$ 50% VO_{2peak} resulted in a 22% increase in VO_{2peak} (Demopoulos et al., 1997b). Despite the low intensity of training, the frequency was relatively high, with 4 sessions per week, twice as often as the intervention in Chapter 7 of this thesis.

9.6.3 Mode

Previous studies have used various modes, or types, of exercise training, e.g cycling, walking or a combination, aerobic and resistance exercises, but there is a lack of information about how the mode influences the training response. The current evidence suggests that it is beneficial for CHF to participate in an exercise programme, but that the mode is less important. The current thesis is not the only study to address this question and to find no difference between two types of training. Exercise capacity improved equally after either strength training, endurance training or combined strength and endurance training, in 45 CHF compared to a non-exercising control group, but there were no differences between modes (Feiereisen et al., 2007). However, studies comparing intermittent with continuous training suggest that the two different types of exercise might influence the training benefits. The limited evidence to date suggests that intermittent training appears to improve central haemodynamics, LV and mitochondrial function to a greater extent, while continuous exercise results in greater benefits in psychological well-being, phase II VO_2 kinetics and chronotropic response (Nechwatal et al., 2002; Dimopoulos et al., 2006; Roditis et al., 2007; Wisloff et al., 2007).

9.7 Inter-individual difference in training response

The concept of inter-individual differences in response to exercise training across a variety of populations is not new, and is partly due to genetics (Bouchard and Rankinen, 2001). The proportion of individuals who do not show clinically meaningful improvements for a given physiological variable, e.g. VO_{2peak}, is estimated at 10-40%. It is clear that some CHF will not respond to exercise training, and it has been proposed that those who see a $\leq$ 6% improvement in VO_{2peak} after 20 training sessions over 4-8 weeks, have a poorer prognosis for adverse cardiac events (Tabet et al., 2008). It has been reported that older patients show smaller improvements (Wielenga et al., 1998; McKelvie et al., 2002). Some argue that those with better initial myocardial function will respond better to training (Wilson et al., 1996; Smart et al., 2006). However, others propose that CHF with worse LV function have the greatest potential to improve (Jette et al., 1991; Hambrecht et al., 1995b). It is not yet clear if it can be predicted which patients will or will not respond, and current advice is that exercise training should be recommended to all patients who are free from contraindications to exercise (National Collaborating Centre for Chronic Conditions, 2003).

The current study included patients who were representative of the CHF population in general, i.e. older individuals with co-morbidities, and its findings agree with the recent literature suggesting that training effects are less pronounced in the wider CHF population than in the earlier studies restricted to homogenous samples of younger CHF (Wielenga et al., 1998; Owen and Croucher, 2000; McKelvie et al., 2002; Prescott et al., 2009). The Medicare Beneficiaries study indicated that nearly 40% of CHF patients had $\geq$ 5 co-morbidities, and these exacerbated their condition and contributed to preventable hospitalisations (Braunstein et al., 2003). It is likely that exercise training also improves these co-morbidities, and indirectly improves patient outcomes in this way.

9.8 Effect of exercise training on quality of life

CR programmes aim to increase functional capacity, and to improve well-being, which is equally important in this population where QoL is reduced. This appears to be achieved by increasing patient confidence and motivation to exercise, regardless of the mode of exercise or the change in cardio-respiratory fitness. Improvements in disease-

specific QoL, measured with the MLHFQ have been reported by several authors (Belardinelli et al., 1999; Passino et al., 2006b). These benefits can be achieved after a few weeks, and appear to be long term (Nilsson et al., 2008c). After a supervised training intervention, further improvements have been reported after follow-on community-based (Austin et al., 2005b) and home-based (de Mello Franco et al., 2006) exercise. By contrast, several studies report only minor reductions or no change in MLHFQ scores after training, despite improvements in exercise performance (Gottlieb et al., 1999; Keteyian et al., 1999; Owen and Croucher, 2000; McKelvie et al., 2002; Arad et al., 2008). Assessment of generic QoL using the SF-36 has also yielded conflicting results in exercise training studies in CHF (Quittan et al., 1999; Zwisler et al., 2008). Both circuit and intermittent training reduced MLHFQ scores in Chapter 7, but had no significant effect on SF-36 scores.

Conflicting research results may be partly due to the sensitivity of the tool used to assess QoL. The MLFHQ and SF-36 are derived from an expert medical viewpoint, and may not reflect the patient perspective. For this reason, their validity has been questioned, and a patient-centred health related QoL measure is currently being developed for use in every day care (Dunderdale et al., 2007). A qualitative study has identified seven themes for inclusion: changes in physical ability, emotional state, self-awareness and self-perception, changes in relationships, symptoms, maintaining social/lifestyle status and cognitive aspects. While some of these themes are reflected in previous QoL research in CHF, several previously unaddressed topics were revealed. These were: changes in relationships, maintaining social/lifestyle status, forgetting about the condition, and medication issues. It will be interesting to include this new measure in future exercise training studies. In the meantime, this thesis concludes that the SF-36 is not an appropriately sensitive tool for assessing changes in a short-duration CR programme.

9.9 The time-course of benefits from exercise training in CHF

In healthy individuals, the greatest training effects tend to be seen during the initial months of training. In CHF, there is some indication that the maximum benefits are achieved during the first 3-6 months' training (Hambrecht et al., 1995a; Hambrecht et al., 2000) . For example, twice weekly sessions over a 3 month period increased VO_{2peak} by 18% and VT by 20%, and decreased V_E/VCO_2 slope by 6%. After a further

3 months' training, only VT showed a further significant increase of 12% (Van Laethem et al., 2007). This is supported by Kavanagh et al (1996) who reported that VT continued to improve up to 1 year, whereas improvements in $VO2_{peak}$ peaked at 16 weeks (Kavanagh et al., 1996). One study suggests that age might be an influencing factor on the time course of benefits after short-term training. CHF over 70 years increased their VO_{2peak} by a further 13% (in addition to an initial increase of 9%) at a 6 month follow-up from a 4 week CR programme. By contrast, CHF under 70 years increased VO_{2peak} by 17% after 4 weeks, but did not show any further improvements after 6 months (Miche et al., 2009). Therefore, the short-duration of exercise training in the current thesis is a likely explanation for the minimal physiological improvements.

9.10 Conclusion

The aims of this thesis were to determine appropriate methods for intermittent exercise prescription, and to assess the benefits of high intensity intermittent exercise in a UK CR setting.

The response to the thesis hypotheses are set out in table 9.1 In summary, the key conclusions drawn are as follows:-

1. In CHF and age-matched controls, there is a learning effect in a repeated maximal cycle ergometer CPET. Although the difference between tests is < 10%, within-subject variability in VO_{2peak} (LOA bias ± systematic error 1.57 ± 1.88 $ml.kg^{-1}.min^{-1}$) should be taken into consideration when using it to assess the effectiveness of a therapeutic intervention.

2. It is difficult to accurately prescribe exercise in individual intensity domains derived from gas exchange thresholds in CHF compared to healthy controls because the range of work rates in each domain is very narrow (< 20 W), and the test-retest variability is relatively high (LOA between – 13 and 7W for VT, and between -18 and 27 W for RCP) .

3. The steep test for intermittent exercise prescription (Meyer, 1997) will prescribe lower work rates than a standard test for healthy controls, but similar work rates for CHF. CHF with a low exercise tolerance on the standard test will perform relatively better in the steep test.

4. A continuous and an intermittent exercise bout of matched total work, equal to 90% VT, elicits similar cardiovascular, respiratory, metabolic and RPE responses in CHF and healthy controls.

5. If the total workload is kept equal, low and high volatility intermittent exercise elicit similar cardiovascular, respiratory and RPE responses in CHF and healthy controls. However, high volatility exercise induces a significantly greater increase in Lac.

6. High intensity intermittent training is as effective as traditional circuit-based training at improving sub-maximal exercise performance and disease-specific QoL in a short-term twice-weekly exercise programme in a population of elderly CHF of mixed aetiology and co-morbidities.

Table 9.1: Table of responses to hypotheses

Study	Hypothesis	Response
1a	Physiological parameters measured in duplicate standard and steep incremental cycle ergometer tests performed one week apart by CHF and control participants will show acceptable reproducibility in terms of statistical significance, re-test correlation and limits of agreement (LOA), and a difference < 10% between tests.	Peak measures showed poor reproducibility in terms of statistical significance and LOA, but acceptable reproducibility in terms of re-test correlation and < 10% difference between the first and second test. Sub-maximal measures showed good reproducibility in terms of statistical significance, re-test correlation and < 10% difference between the first and second test, but poor reproducibility in terms of LOA.
1b	Intermittent exercise training workloads derived from a steep test will differ to those derived from a standard test in CHF and control participants.	Intermittent exercise training workloads derived from a steep test and a standard test are not different in CHF. Intermittent exercise training workloads derived from a steep test are lower than those derived from a standard test in controls
2	Intermittent exercise will elicit similar cardiovascular and respiratory responses, but higher metabolic and RPE responses than continuous exercise in CHF. In control participants there will be no difference in cardiovascular, respiratory, metabolic or RPE responses to intermittent and continuous exercise.	There is no difference in cardiovascular, respiratory, metabolic or RPE responses between continuous and intermittent exercise in CHF or control participants
3	High volatility intermittent exercise will elicit higher cardiovascular, respiratory, metabolic and RPE responses than low volatility intermittent exercise or continuous exercise of matched total workload in CHF and control participants.	High volatility intermittent exercise elicits higher metabolic responses than low volatility intermittent exercise or continuous exercise of matched total workload in CHF and control participants. There is no difference in cardiovascular, respiratory or RPE responses between high and low volatility intermittent exercise or continuous exercise of matched total workload in CHF and control participants.
4	There will be no difference between the effect of traditional circuit-based training and high intensity intermittent training on functional capacity, ventilatory efficiency, BNP and quality of life in CHF on a 6 week CR programme.	There is no difference between the effect of traditional circuit-based training and high intensity intermittent training on functional capacity, ventilatory efficiency, BNP and quality of life in CHF on a 6 week CR programme.

9.11 Future directions

Given the limited resources for supervised CR, it is important to assess the long-term effects of short-term programmes, and this would be one key research direction to follow on from this thesis. There is concern that short-term CR programmes followed by home-based training are ineffective in older CHF (Haykowsky et al., 2005; Witham et al., 2007), and that adherence to exercise decreases once a supervised programme ends (Willenheimer et al., 2001; McKelvie et al., 2002). It appears that training benefits may continue to accrue as long as an adequate dose of exercise is maintained. For example, functional capacity and QoL remained significantly higher at 12 month follow-up in a group who followed a 4 month high intensity programme compared with a "usual care" control group. The authors speculated that intensity might be the important factor in long-term improvements, and based on patient comments, that patients in the exercise group were motivated by the programme to continue exercising on their own (Nilsson et al., 2008c). Several other studies also demonstrate that improvements in exercise capacity and QoL after short-term supervised training can be maintained long-term (Kavanagh et al., 1996). A retrospective study reported that patients involved in an 8 week training programme with no formalised exercise intervention thereafter, demonstrated fewer cardiac events and days in hospital when compared with their non-trained counterparts 5 years later (Hagerman et al., 2005). Another 5 year follow up study revealed that patients who had attended a CR programme were more likely to take regular exercise and maintain better functional capacity (Austin et al., 2008). A 6 year follow-up on a small sample of CHF after intensive residential rehabilitation reported that exercise capacity was preserved, and ventricular and function size were maintained (Muller et al., 2009). The level of support from health professionals once an exercise programme has ended may be a factor in determining whether prolonged benefits can be gained even if the supervised programme is of a short duration (Austin et al., 2005b; Beer et al., 2008). The next logical study would be to assess the effects of current circuit-based training and high intensity intermittent training after Phase 4 community-based CR, and beyond.

There is limited information about the volume or intensity of exercise achieved in a CR exercise session. Two studies have assessed the exercise dose in terms of energy expenditure, using indirect calorimetry, prediction equations and estimations based on

the HR/VO_2 relationship from a cardiopulmonary exercise test (Schairer et al., 1998; Savage et al., 2000). Both studies reported energy expenditures below the ~300 kcal required from each of the thrice weekly sessions to achieve the minimum 1,000 kcal per week recommended to benefit cardiovascular health (Balady et al., 2000). Savage et al (2000) estimated an average energy expenditure of 270 ± 112 kcal in patients with coronary artery disease during a 48 ± 6 min "aerobic" session spent on a combination of treadmill, rowing, stepping and arm ergometers. Although UK surveys of CR (BACR Survey, Coronary Prevention Group Survey, NACR) provide some information on the frequency and duration of training, there is no information on estimated exercise intensity (Taylor et al., 2007). One small study of 6 CHF has previously reported no differences in VO_2, HR, BP or RPE between circuit training and continuous exercise at 70-80% HR_{max} (Green et al., 2001). Chapter 7 of this thesis suggested that the circuit-based training methods commonly used in UK practice do not necessarily correspond with the concept of moderate intensity exercise, i.e. exercise below VT. The different exercises that comprise the circuit are likely to produce an exercise dose of varying intensity, but this has not been previously evaluated. A comprehensive assessment of the physiological intensity of a CR training session is now required, using measurements of VO_2, HR, Lac and motion analysis.

The optimal dose of exercise is not only the dose that provides the greatest health benefits while minimising the risks to the patient, but must also be achievable and enjoyable in order to encourage adherence. Investigations into the link between exercise intensity, affective responses (e.g. pleasure-displeasure) and adherence conclude that exercise above VT appears to reduce pleasure (Ekkekakis et al., 2008). A psychophysiological investigation into the cognitive and physiological factors that influence affective responses during exercise in CHF patients is warranted. More specifically, following on from Chapter 7 of this thesis, it would be interesting to compare the affective responses during circuit training and high intensity intermittent training in a CR setting.

Recent studies that include a more heterogeneous CHF population tend to report smaller changes in physiological parameters than previous studies, and this may lead to a mistaken conclusion that exercise is of no benefit to many patients. However, it is important to integrate clinical results and prognostic markers with measurement of health status in order to assess the true "value" of the intervention to the patient (Jette

and Downing, 1994). An important goal in the health care of individuals with chronic disease is to improve function and well-being, which is indicated by an individual's perception of his or her QoL. It is clear that improvements in physiological measures are not necessarily a pre-requisite for improvements in QoL. Despite the fact that CHF may have a poor prognosis, small increases in QoL and exercise tolerance could translate into meaningful improvements in a patient's ability to enjoy daily activities. Traditional tools to assess health related QoL in CHF, such as MLHFQ and SF-36, have been criticised for being designed from the "expert" rather than the patient's point of view, and for lacking sensitivity to detect clinically meaningful changes (Green et al., 2000; Dunderdale et al., 2007). Future studies investigating the effect of high intensity intermittent and circuit-based training on improvements in QoL of CHF patients should use the recently developed patient-centred tools in order expand current understanding of the true benefit of these exercise training interventions. Two such measurement tools are The Kansas City Cardiomyopathy Questionnaire (Green et al., 2000) used in the HF-ACTION trial (Flynn et al., 2009) and the patient-centred instrument currently being developed by UK health practitioners for CHF patients (Dunderdale et al., 2007).

To summarise, the directions for future research resulting from this thesis are:-

1. An investigation into the long-term effects of current circuit-based training and high intensity intermittent training in CHF
2. A comprehensive assessment of the physiological intensity of a CR training session, using measurements of VO_2, HR, Lac and motion analysis.
3. An investigation into the affective responses during circuit training and high intensity intermittent training in a CR setting.
4. The assessment of health-related QoL following different CR exercise programmes using recently developed patient-centred tools that are sensitive to the detection of clinically meaningful improvements.

References

Adamopoulos, S., Parissis, J., Karatzas, D., Kroupis, C., Georgiadis, M., et al. (2002) Physical Training Modulates Proinflammatory Cytokines and the Soluble Fas/Soluble Fasligand System in Patients with Chronic Heart Failure. *J Am Coll Cardiol,* 39**:** 653.

Adamopoulos, S., Parissis, J., Kroupis, C., Georgiadis, M., Karatzas, D., et al. (2001) Physical Training Reduces Peripheral Markers of Inflammation in Patients with Chronic Heart Failure. *Eur Heart J,* 22**:** 791-797.

Adamopoulos, S., Parissis, J. T. & Kremastinos, D. T. (2003) New Aspects for the Role of Physical Training in the Management of Patients with Chronic Heart Failure. *Int J Cardiol,* 90**:** 1-14.

Agostoni, P. (2006) Cardiopulmonary Exercise Testing for Heart Failure Patients: A Hodgepodge of Techniques, Parameters and Interpretations. In Other Words, the Need for a Time-Break. *Eur Heart J,* 27**:** 633-634.

Agostoni, P., Bianchi, M., Moraschi, A., Palermo, P., Cattadori, G., et al. (2005) Work-Rate Affects Cardiopulmonary Exercise Test Results in Heart Failure. *Eur J Heart Failure,* 7**:** 498.

Ainsworth, B. E., Haskell, W. L., Whitt, M. C., Irwin, M. L., Swartz, A. M., et al. (2000) Compendium of Physical Activities: An Update of Activity Codes and Met Intensities. *Med Sci Sports Exerc,* 32**:** S498-S516.

American College of Sports Medicine (2006) *Acsm's Guidelines for Exercise Testing and Prescription. 7th Edition.,* Philadelphia, Lippincott Williams & Wilkins.

Anand, I. S., Fisher, L. D., Chiang, Y.-T., Latini, R., Masson, S., et al. (2003) Changes in Brain Natriuretic Peptide and Norepinephrine over Time and Mortality and Morbidity in the Valsartan Heart Failure Trial (Val-Heft). *Circulation,* 107**:** 1278-1283.

Arad, M., Adler, Y., Koren-Morag, N., Natanzon, S., Sela, B.-A., et al. (2008) Exercise Training in Advanced Heart Failure Patients: Discordance between Improved Exercise Tolerance and Unchanged Nt-Probnp Levels. *Int J Cardiol* 126**:** 114-119.

Arena, R., Guazzi, M., Myers, J. & Abella, J. (2007) The Prognostic Value of Ventilatory Efficiency with Beta-Blocker Therapy in Heart Failure. *Med Sci Sports Exerc.* , 39**:** 213-9.

Arena, R., Guazzi, M., Myers, J. & Peberdy, M. A. (2006) Prognostic Value of Heart Rate Recovery in Patients with Heart Failure. *Am Heart J,* 151**:** 851.

Arena, R., Myers, J., Aslam, S. S., Varughese, E. B. & Peberdy, M. A. (2003) Technical Considerations Related to the Minute Ventilation/Carbon Dioxide Output Slope in Patients with Heart Failure. *Chest,* 124**:** 720-727.

Association of Chartered Physiotherapists in Cardiac Rehabilitation (2009) Standards for Physical Activity and Exercise in the Cardiac Population 2009. ACPICR.

Astrand, I., Astrand, P. O. & Christensen, H. (1960a) Circulatory and Respiratory Adaptations to Severe Muscular Work. *Acta Physiologica Scandinavica,* 50**:** 254-8.

Astrand, I., Astrand, P. O., Christensen, H. & Hedman, R. (1960b) Intermittent Muscular Work. *Acta Physiologica Scandinavica,* 48**:** 448-53.

Astrand, P., Rodahl, K., Dahl, H. & Stromme, S. (2003) *Textbook of Work Phsyiology. Physiological Bases of Exercise,* Champaign, IL, Human Kinetics.

Atkinson, G. & Nevill, A. (2007) Method Agreement and Measurement Error. IN Winter, E. M., Jones, A. M., Davison, R. C., Bromley, P. D. & Mercer, T. H. (Eds.) *Sport and Exercise Physiology Testing Guidelines. The British Association of Sport and Exercise Sciences Guide. Volume 2: Exercise and Clinical Testing.* London, Routledge.

Atkinson, G. & Nevill, A. N. (1998) Statistical Methods for Assessing Measurement Error (Reliability) in Variables Relevant to Sports Medicine. *Sports Med,* 26**:** 217-238.

Austin, J., Williams, R., Ross, L., Moseley, L. & Hutchison, S. (2005a) Randomised Controlled Trial of Cardiac Rehabilitation in Elderly Patients with Heart Failure. *Eur J Heart Fail,* 7**:** 411 - 417.

Austin, J., Williams, R., Ross, L., Moseley, L. & Hutchison, S. (2005b) Randomised Controlled Trial of Cardiac Rehabilitation in Elderly Patients with Heart Failure. *Eur J Heart Failure,* 7**:** 411.

Austin, J., Williams, W. R., Ross, L. & Hutchison, S. (2008) Five-Year Follow-up Findings from a Randomized Controlled Trial of Cardiac Rehabilitation for Heart Failure. *Eur J Cardiovasc Prev Rehabil,* 15**:** 162-167.

Balady, G. J., Ades, P. A., Comoss, P., Limacher, M., Pina, I. L., et al. (2000) Core Components of Cardiac Rehabilitation/Secondary Prevention Programs : A Statement for Healthcare Professionals from the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation Writing Group. *Circulation,* 102**:** 1069-1073.

Bard, R. L. (2005) Cardiopulmonary Exercise Testing in Patients with Heart Failure. *J Am Coll Cardiol,* 45**:** 163.

Bassett, D. R. & Howley, E. T. (2000) Limiting Factors for Maximum Oxygen Uptake and Determinants of Endurance Performance. *Med Sci Sports Exerc,* 31**:** 70-84.

Beale, L., Silberbauer, J., Lloyd, G., Carter, H., Doust, J., et al. (2010) Exercise Heart Rate Guidelines Overestimate Recommended Intensity for Chronic Heart Failure Patients. *Brit J Cardiol,* 17**:** 133-7.

Beaver, W. L., Wasserman, K. & Whipp, B. J. (1986) A New Method for Detecting Anaerobic Threshold by Gas Exchange. *J Appl Physiol,* 60**:** 2020-2027.

Beckers, P. J., Denollet, J., Possemiers, N. M., Wuyts, F. L., Vrints, C. J., et al. (2008) Combined Endurance-Resistance Training Vs. Endurance Training in Patients with Chronic Heart Failure: A Prospective Randomized Study. *Eur Heart J,* 29**:** 1858-1866.

Beer, M., Wagner, D., Myers, J., Sandstede, J., Köstler, H., et al. (2008) Effects of Exercise Training on Myocardial Energy Metabolism and Ventricular Function Assessed by Quantitative Phosphorus-31 Magnetic Resonance Spectroscopy and Magnetic Resonance Imaging in Dilated Cardiomyopathy. *J Am Coll Cardiol,* 51**:** 1883.

Belardinelli, R., Georgiou, D., Cianci, G., Berman, N., Ginzton, L., et al. (1995a) Exercise Training Improves Left Ventricular Diastolic Filling in Patients with Dilated Cardiomyopathy : Clinical and Prognostic Implications. *Circulation,* 91**:** 2775-2784.

Belardinelli, R., Georgiou, D., Cianci, G. & Purcaro, A. (1999) Randomized, Controlled Trial of Long-Term Moderate Exercise Training in Chronic Heart Failure: Effects on Functional Capacity, Quality of Life, and Clinical Outcome. *Circulation,* 99**:** 1173-1182.

Belardinelli, R., Georgiou, D., Scocco, V., Barstow, T. & Purcaro, A. (1995b) Low Intensity Exercise Training in Patients with Chronic Heart Failure. *Am J Coll Cardiol,* 26**:** 975 - 982.

Bensimhon, D., R. , Leifer, E., S. , Ellis, S., J. , Fleg, J., L. , Keteyian, S., J. , et al. (2008) Reproducibility of Peak Oxygen Uptake and Other Cardiopulmonary Exercise Testing Parameters in Patients with Heart Failure (from the Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training). *Am J Cardiol,* 102**:** 712-717.

Berent, R., von Duvillard, S., Crouse, S., Auer, J., Green, J., et al. (2009) Short-Term Residential Cardiac Rehabilitation Reduces B-Type Natriuretic Peptide. *Eur J Cardiovasc Prev Rehabil.* .

Bethell, H., Lewin, R. & Dalal, H. (2004) Cardiac Rehabilitation in the United Kingdom. *Heart,* 95**:** 271-275.

Bhatia, V., Nayyar, R. & Dhindsa, S. (2003) Brain Natriuretic Peptide in Diagnosis and Treatment of Heart Failure. *J Postgrad Med,* 49**:** 182-5.

Billat, V., L. (2001) Interval Training for Performance: A Scientific and Empirical Practice. Special Recommendations for Middle- and Long-Distance Running. Part I: Aerobic Interval Training. *Sports Med,* 31**:** 13-31.

Billat, V., L. , Slawinski, J., Bocquet, V., Demarle, A., Lafitte, L., et al. (2000) Intermittent Runs at the Velocity Associated with Maximal Oxygen Uptake Enables Subjects to Remain at Maximal Oxygen Uptake for a Longer Time Than Intense but Submaximal Runs. *Eur J Appl Physiol,* 81**:** 188.

Billat, V. L., Sirvent, P., Py, G., Koralsztein, J.-P. & Mercier, J. (2003) The Concept of Maximal Lactate Steady State: A Bridge between Biochemistry, Physiology and Sport Science. *Sports Med* 33**:** 407-426.

Bland, J. M. & Altman, D. G. (1986) Statistical Methods for Assessing Agreement between Two Methods of Clinical Measurement. *Lancet,* 8.

Borg, G. (1970) Perceived Exertion as an Indicator of Somatic Stress. *Scand J Rehabil Med,* 2**:** 92.

Borg, G. (1998) *Borg's Perceived Exertion and Pain Scales* Champaign, IL, Human Kinetics.

Bouchard, C. & Rankinen, T. (2001) Individual Differences in Response to Regular Physical Activity. *Med. Sci. Sports Exerc.,* 33**:** S446-S451.

Boudreau, M. & Genovese, J. (2007) Cardiac Rehabilitation: A Comprehensive Program for the Management of Heart Failure. *Prog Cardiovasc Nursing,* 22**:** 88-92.

Braith, R. W., Welsch, M. A., Feigenbaum, M. S., Kluess, H. A. & Pepine, C. J. (1999) Neuroendocrine Activation in Heart Failure Is Modified by Endurance Exercise Training. *J Am Coll Cardiol,* 34**:** 1170.

Braunstein, J. B., Anderson, G. F., Gerstenblith, G., Weller, W., Niefeld, M., et al. (2003) Noncardiac Comorbidity Increases Preventable Hospitalizations and Mortality among Medicare Beneficiaries with Chronic Heart Failure. *J Am Coll Cardiol,* 42**:** 1226-1233.

Brawner, C. A., Keteyian, S. J. & Ehrman, J. K. (2002) The Relationship of Heart Rate Reserve to Vo2 Reserve in Patients with Heart Disease. . *Med Sci Sports Exerc. ,* 34**:** 418-22.

Brickley, G., Green, S., Jenkins, D. G., McEinery, M., Wishart, C., et al. (2007) Muscle Metabolism During Constant- and Alternating-Intensity Exercise around Critical Power. *Int J Sports Med.***:** 300.

British Association for Cardiac Rehabilitation (2006) *Bacr Phase Iv Instructor Training Module. 4th Edition.,* Leeds, UK, Human Kinetics Europe.

British Heart Foundation (2009) National Audit of Cardiac Rehabilitation. Annual Statistical Report 2009.

Brodie, D., Bethell, H. & Breen, S. (2006) Cardiac Rehabilitation in England: A Detailed National Survey. *Eur J Cardiovasc Prev Rehabil,* 13**:** 122-128.

Brubaker, P., H. , Moore, J. B., Stewart, K., P. , Wesley, D., J. & Kitzman, D., W. (2009) Endurance Exercise Training in Older Patients with Heart Failure: Results from a Randomized, Controlled, Single-Blind Trial. *Journal of the American Geriatrics Society,* 57**:** 1982-1989.

Buchfuhrer, M. J., Hansen, J. E., Robinson, T. E., Sue, D. Y., Wasserman, K., et al. (1983) Optimizing the Exercise Protocol for Cardiopulmonary Assessment. *J Appl Physiol,* 55**:** 1558-1564.

Buckley, J. (2006) Exercise Physiology and Monitoring of Exercise in Cardiac Rehabilitation. IN Throw, M. (Ed.) *Exercise Leadership in Cardiac Rehabilitation: An Evidence-Based Approach.* Chichester, John Wiley & Sons, Ltd.

Buckley, J. & Eston, R. (2007) Ratings of Perceived Exertion. IN Winter, E. M., Jones, A. M., Davison, R. C., Bromley, P. D. & Mercer, T. H. (Eds.) *Sport and Exercise Physiology Testing Guidelines. The British Associaton of Sport and Exercise Sciences Guide. Volume 2: Exercise and Clinical Testing.* London, Routledge.

Burnley, M., Doust, J. H. & Jones, A. M. (2006) Time Required for the Restoration of Normal Heavy Exercise Vo2 Kinetics Following Prior Heavy Exercise. *J Appl Physiol,* 101**:** 1320-1327.

Butterfield, J., Faddy, S., Davidson, P. & Ridge, B. (2008) Exercise Training in Patients with Stable Chronic Heart Failure: Effects on Thoracic Impedance Cardiography and B-Type Natriuretic Peptide. *J Cardiopulm Rehabil Prev. ,* 28**:** 33-37.

Chang, R.-K. R., Qi, N., Larson, J., Rose-Gottron, C. & Cooper, D. (2005) Comparison of Upright and Semi-Recumbent Postures for Exercise Echocardiography in Healthy Children. *Am J Cardiol,* 95**:** 918-921.

Christensen, H., Hedman, R. & Saltin, B. (1960) Intermittent and Continuous Running. (a Further Contribution to the Physiology of Intermittent Work.). *Acta Physiologica Scandinavica,* 50**:** 269-86.

Chua, B. M. D. M. T. P., Ponikowski, M. D. P., Harrington, M. D. & Anker, M. D. S. D. (1997) Clinical Correlates and Prognostic Significance of the Ventilatory Response to Exercise in Chronic Heart Failure. *J Am Coll Cardiol,* 29**:** 1585.

Chua, T. P., Clark, A. I., Amadi, A. A. & Coats, A. J. S. (1996) Relation between Chemosensitivity and the Ventilatory Response to Exercise in Chronic Heart Failure. *J Am Coll Cardiol,* 27**:** 650-657.

Clark, A. L. (2006) Origin of Symptoms in Chronic Heart Failure. *Heart,* 92**:** 12-16.

Clark, A. L., Poole-Wilson, P. A. & Coats, A. J. S. (1996) Exercise Limitation in Chronic Heart Failure: Central Role of the Periphery. *J Am Coll Cardiol,* 28**:** 1092.

Coats, A., Adamopoulos, S., Meyer, T., Conway, J. & Sleight, P. (1990a) Effects of Physical Training in Chronic Heart Failure. *Lancet,* 335**:** 63 - 66.

Coats, A. J., Adamopoulos, S., Radaelli, A., McCance, A., Meyer, T. E., et al. (1992a) Controlled Trial of Physical Training in Chronic Heart Failure. Exercise Performance, Hemodynamics, Ventilation, and Autonomic Function. *Circulation,* 85**:** 2119-2131.

Coats, A. J., Adamopoulos, S., Radaelli, A., McCance, A., Meyer, T. E., et al. (1992b) Controlled Trial of Physical Training in Chronic Heart Failure. Exercise Performance, Hemodynamics, Ventilation, and Autonomic Function. *Circulation,* 85**:** 2119 - 31.

Coats, A. J. S., Adamopoulos, S., Meyer, T. E., Conway, J. & Sleight, P. (1990b) Effects of Physical Training in Chronic Heart Failure. *The Lancet,* 335**:** 63.

Coats, A. J. S., Clark, A. L., Piepoli, M., Volterrani, M. & Poole-Wilson, P. A. (1994) Symptoms and Quality of Life in Heart Failure: The Muscle Hypothesis. *British Heart Journal,* 72**:** S36.

Cohen-Solal, A., Chabernaud, J. M. & Gourgon, R. (1990) Comparison of Oxygen Uptake During Bicycle Exercise in Patients with Chronic Heart Failure and in Normal Subjects. *J Am Coll Cardiol. ,* 16**:** 80-85.

Cohen-Solal, A., Czitrom, D., Geneves, M. & Gourgon, R. (1997) Delayed Attainment of Peak Oxygen Consumption after the End of Exercise in Patients with Chronic Heart Failure. *Int J Cardiol,* 60**:** 23.

Cohen-Solal, A., Zannad, F., Kayanakis, J. G., Gueret, P., Aupetit, J. F., et al. (1991) Multicentre Study of the Determination of Peak Oxygen Uptake and Ventilatory Threshold During Bicycle Exercise in Chronic Heart Failure: Comparison of Graphical Methods, Interobserver Variability and Influence of the Exercise Protocol. *Eur Heart J,* 12**:** 1055-1063.

Cohen, R. A., Moser, D. J., Clark, M. M., Aloia, M. S., Cargill, B. R., et al. (1999) Neurocognitive Functioning and Improvement in Quality of Life Following Participation in Cardiac Rehabilitation. *Am J Cardiol,* 83**:** 1374-1378.

Commission for Healthcare Audit and Inspection (2007) Pushing the Boundaries: Improving Services for People with Heart Failure. Service Review. Commission for Healthcare Audit and Inspection.

Conn, E. H., Williams, R. S. & Wallace, A. G. (1982) Exercise Responses before and after Physical Conditioning in Patients with Severely Depressed Left Ventricular Function. *Am J Cardiol* 49**:** 296-300.

Conraads, V. M., Beckers, P., Vaes, J., Martin, M., Van Hoof, V., et al. (2004) Combined Endurance/Resistance Training Reduces Nt-Probnp Levels in Patients with Chronic Heart Failure. *Eur Heart J,* 25**:** 1797-1805.

Conraads, V. M. A., Vanderheyden, M., Paelinck, B., Verstreken, S., Blankoff, I., et al. (2007) The Effect of Endurance Training on Exercise Capacity Following Cardiac Resynchronization Therapy in Chronic Heart Failure Patients: A Pilot Trial. *Eur J Cardiovasc Prev Rehabil,* 14**:** 99-106.

Cooke, C. B. (2001) Maximal Oxygen Uptake, Economy and Efficiency. IN Eston, R. & Reilly, T. (Eds.) *Kinanthropometry and Exercise Physiology Laboratory Manual: Tests, Procedures and Data. Volume 2 Exercise Physiology*. 3 ed. London, Routledge.

Cooper, C. B. & Storer, T. W. (2001) *Exercise Testing and Interpretation: A Practical Approach,* Cambridge, Cambridge University Press.

Coplan, N. L., Gleim, G. W. & Nicholas, J. A. (1986) Using Exercise Respiratory Measurements to Compare Methods of Exercise Prescription. *Am J Cardiol,* 58**:** 832.

Corra , U., Giannuzzi, P., Adamopoulos, S., Bjornstad, H., Bjarnason-Weherns, B., et al. (2005) Executive Summary of the Position Paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology (Esc): Core Components of Cardiac Rehabilitation in Chronic Heart Failure. *European Journal of Cardiovascular Prevention & Rehabilitation,* 12**:** 321-325.

Corra, U., Giordano, A., Bosimini, E., Mezzani, A., Piepoli, M., et al. (2002) Oscillatory Ventilation During Exercise in Patients with Chronic Heart Failure: Clinical Correlates and Prognostic Implications. *Chest,* 121**:** 1572-1580.

Cowie, M., Collinson, P. O., Dargie, H., Hobbs, R., McDonagh, T. A., et al. (2010) Recommendations on the Clinical Use of B-Type Natriuretic Peptide Testing (Bnp or Ntprobnp) in the Uk and Ireland. *Brit J Cardiol,* 17**:** 76-80.

Crimi, E., Ignarro, L., Cacciatore, F. & Napoli, C. (2009) Mechanisms by Which Exercise Training Benefits Patients with Heart Failure. *Nat Rev Cardiol.,* 6**:** 292-300.

Dao, Q., Krishnaswamy, P., Kazanegra, R., Harrison, A., Amirnovin, R., et al. (2001) Utility of B-Type Natriuretic Peptide in the Diagnosis of Congestive Heart Failure in an Urgent-Care Setting. *J Am Coll Cardiol,* 37**:** 379-385.

Dassonville, J., Beillot, J., Lessard, Y., Jan, J., Andre, A., et al. (1998) Blood Lactate Concentrations During Exercise: Effect of Sampling Site and Exercise Mode. *J Sports Med Phys Fitness,* 38**:** 39-46.

Daussin, F., Ponsot, E., Dufour, S., Lonsdorfer-Wolf, E., Doutreleau, S., et al. (2007) Improvement of Vo_{2max} by Cardiac Output and Oxygen Extraction Adaptation During Intermittent Versus Continuous Endurance Training. *Eur J Appl Physiol,* 101**:** 377-383.

Daussin, F. N., Zoll, J., Dufour, S. P., Ponsot, E., Lonsdorfer-Wolf, E., et al. (2008) Effect of Interval Versus Continuous Training on Cardiorespiratory and Mitochondrial Functions: Relationship to Aerobic Performance Improvements in Sedentary Subjects. *Am J Physiol Regul Integr Comp Physiol,* 295**:** R264-272.

Davies, E. J., Moxham, T., Rees, K., Singh, S., Coats, A. J. S., et al. (2010) Exercise Based Rehabilitation for Heart Failure (Review). *The Cochrane Library*.

Davis, J. A., Whipp, B. J., Lamarra, N., Huntsman, D. J., Frank, M. H., et al. (1982) Effect of Ramp Slope on Determination of Aerobic Parameters from the Ramp Exercise Test. *Med Sci Sports Exerc,* 14**:** 339-343.

De Backer, I. C., Schep, G., Hoogeveen, A., Vreugdenhil, G., Kester, A. D., et al. (2007) Exercise Testing and Training in a Cancer Rehabilitation Program: The Advantage of the Steep Ramp Test. *Arch Phys Med and Rehabil,* 88**:** 610-616.

de Groote, P., Dagorn, J., Soudan, B., Lamblin, N., McFadden, E., et al. (2004) B-Type Natriuretic Peptide and Peak Exercise Oxygen Consumption Provide Independent Information for Risk Stratification in Patients with Stable Congestive Heart Failure. *J Am Coll Cardiol,* 43**:** 1584-9.

de Mello Franco, F. G., Santos, A. C., Rondon, M. U. P., Trombetta, I. C., Strunz, C., et al. (2006) Effects of Home-Based Exercise Training on Neurovascular Control in Patients with Heart Failure. *Eur J Heart Fail,* 8**:** 851-855.

Dekerle, J., Baron, B., Dupont, L., Vanvelcenaher, J. & Pelayo, P. (2003) Maximal Lactate Steady State, Respiratory Compensation Threshold and Critical Power. *Eur J Appl Physiol,* 89**:** 281-288.

Demopoulos, L., Yeh, M., Gentilucci, M., Testa, M., Bijou, R., et al. (1997a) Nonselective ß-Adrenergic Blockade with Carvedilol Does Not Hinder the Benefits of Exercise Training in Patients with Congestive Heart Failure. *Circulation,* 95**:** 1764-1767.

Demopoulos, M. D. L., Bijou, M. D. R., Fergus, M. D. I., Jones, R. N. M., Strom, M. D. F. J., et al. (1997b) Exercise Training in Patients with Severe Congestive Heart Failure: Enhancing Peak Aerobic Capacity While Minimizing the Increase in Ventricular Wall Stress. *J Am Coll Cardiol,* 29**:** 597.

Dimopoulos, S., Anastasiou-Nana, M., Sakellariou, D., Drakos, S., Kapsimalakou, S., et al. (2006) Effects of Exercise Rehabilitation Program on Heart Rate Recovery in Patients with Chronic Heart Failure. *Eur J Cardiovasc Prev Rehabil.* , 13**:** 67-73.

Drexler, H., Riede, U., Munzel, T., Konig, H., Funke, E., et al. (1992) Alterations of Skeletal Muscle in Chronic Heart Failure. *Circulation,* 85**:** 1751-1759.

Dubach, M. D. P., Myers, P. F. J., Dziekan, M. D. G. & Goebbels, M. D. U. (1997) Effect of High Intensity Exercise Training on Central Hemodynamic Responses to Exercise in Men with Reduced Left Ventricular Function. *J Am Coll Cardiol,* 29**:** 1591.

Dunderdale, K., Furze, G., Thompson, D. R., Beer, S. F. & Miles, J. N. V. (2007) Health-Related Quality of Life from the Perspective of Patients with Chronic Heart Failure. *Br J Cardiol,* 14**:** 207-212.

Dwyer, J. (1994) Metabolic Character of Exercise at Traditional Training Intensities in Cardiac Patients and Healthy Persons. *J Cardiopulmonary Rehabil,* 14**:** 189-96.

Earnest, C. P. (2008) Exercise Interval Training: An Improved Stimulus for Improving the Physiology of Pre-Diabetes. *Medical hypotheses,* 71**:** 752-761.

Ekkekakis, P., Hall, E. & Petruzzello, S. (2008) The Relationship between Exercise Intensity and Affective Responses Demystified: To Crack the 40-Year-Old Nut, Replace the 40-Year-Old Nutcracker! *Annals of Behavioral Medicine,* 35**:** 136-149.

Elborn, J. S., Stanford, C. F. & Nicholls, D. P. (1990) Reproducibility of Cardiopulmonary Parameters During Exercise in Patients with Chronic Cardiac Failure. The Need for a Preliminary Test. *Eur Heart J,* 11**:** 75-81.

Ennezat, P. V., Malendowicz, S. L., Testa, M., Colombo, P. C., Cohen-Solal, A., et al. (2001) Physical Training in Patients with Chronic Heart Failure Enhances the Expression of Genes Encoding Antioxidative Enzymes. *J Am Coll Cardiol,* 38**:** 194-198.

Essen, B., Hagenfeldt, L. & Kaijser, L. (1977) Utilization of Blood-Borne and Intramuscular Substrates During Continuous and Intermittent Exercise in Man. *J Physiol,* 265**:** 489-506.

Essen, B. & Kaijser, L. (1978) Regulation of Glycolysis in Intermittent Exercise in Man. *J Physiol,* 281**:** 499-511.

Eston, R., Williams, J. G. & Faulkner, J. (2009) Control of Exercise Intensity Using Heart Rate, Perceived Exertion and Other Non-Invasive Procedures. IN Eston, R. & Riley, R. L. (Eds.) *Kinanthropometry and Exercise Physiology Laboratory Manual.* 3rd ed. London, Routledge.

European Heart Failure Training Group (1998) Experience from Controlled Trials of Physical Training in Chronic Heart Failure. Protocol and Patient Factors in Effectiveness in the Improvement in Exercise Tolerance. *Eur Heart J,* 19**:** 466-475.

Fan, S., Lyon, C., Savage, P., Ozonoff, A., Ades, P., et al. (2009) Outcomes and Adverse Events among Patients with Cardiac Defibrillators in Cardiac Rehabilitation: A Case-Controlled Study. *J Cardiopolm Rehabil Prev,* 29**:** 40-43.

Faude, O., Kindermann, W. & Meyer, T. (2009) Lactate Threshold Concepts: How Valid Are They? *Sports Med,* 39**:** 469-490.

Feiereisen, P., Delagardelle, C., Vaillant, M., Lasar, Y. & Beissel, J. (2007) Is Strength Training the More Efficient Training Modality in Chronic Heart Failure? *Med Sci Sports Exerc,* 39**:** 1910-7.

Fleg, J. L., Pina, I. L., Balady, G. J., Chaitman, B. R., Fletcher, B., et al. (2000) Assessment of Functional Capacity in Clinical and Research Applications : An Advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association. *Circulation,* 102**:** 1591-1597.

Fletcher, G. F., Balady, G. J., Amsterdam, E. A., Chaitman, B., Eckel, R., et al. (2001) Exercise Standards for Testing and Training: A Statement for Healthcare Professionals from the American Heart Association. *Circulation,* 104**:** 1694-1740.

Flynn, K. E., Pina, I. L., Whellan, D. J., Lin, L., Blumenthal, J. A., et al. (2009) Effects of Exercise Training on Health Status in Patients with Chronic Heart Failure: Hf-Action Randomized Controlled Trial. *JAMA,* 301**:** 1451-1459.

Forissier, J. F., Vernochet, P., Bertrand, P., Charbonnier, B. & Monpere, C. (2001) Influence of Carvedilol on the Benefits of Physical Training in Patients with Moderate Chronic Heart Failure. *Eur J Heart Failure,* 3**:** 335.

Foster, C., Georgakopoulos, N. & Meyer, K. (1998) Physiological and Pathological Aspects of Exercise Left Ventricular Function. *Med Sci Sports Exerc,* 10**:** S379-86.

Foster, C., Meyer, K., Georgakopoulos, N., Ellestad, A., Fitzgerald, D., et al. (1999) Left Ventricular Function During Interval and Steady State Exercise. *Med Sci Sports Exerc.* , 31**:** 1157-62.

Fraga, R., Franco, F. G., Roveda, F., de Matos, L. N. J., Braga, A. M. F. W., et al. (2007) Exercise Training Reduces Sympathetic Nerve Activity in Heart Failure Patients Treated with Carvedilol. *Eur J Heart Fail,* 9**:** 630.

Freimark, D., Shechter, M., Schwamenthal, E., Tanne, D., Elmaleh, E., et al. (2007) Improved Exercise Tolerance and Cardiac Function in Severe Chronic Heart Failure Patients Undergoing a Supervised Exercise Program. *Int J Cardiol,* 116**:** 309.

Gademan, M. G. J., Swenne, C. A., Verwey, H. F., van der Laarse, A., Maan, A. C., et al. (2007) Effect of Exercise Training on Autonomic Derangement and Neurohumoral Activation in Chronic Heart Failure. *Journal of Cardiac Failure,* 13**:** 294.

Georgiou, D., Chen, Y., Appadoo, S., Belardinelli, R., Greene, R., et al. (2001) Cost-Effectiveness Analysis of Long-Term Moderate Exercise Training in Chronic Heart Failure. *Am J Cardiol,* 87**:** 984-988.

Giannuzzi, P., Saner, H., Bjornstad, H., Fioretti, P., Mendes, M., et al. (2003a) Secondary Prevention through Cardiac Rehabilitation: Position Paper of the Working Group on Cardiac Rehabilitation and Exercise Physiology of the European Society of Cardiology. *Eur Heart J,* 24**:** 1273-1278.

Giannuzzi, P., Tavazzi, L., Meyer, K., Perk, J., Drexler, H., et al. (2001) Recommendations for Exercise Training in Chronic Heart Failure Patients. Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. *Eur Heart J,* 22**:** 125-135.

Giannuzzi, P., Temporelli, P. L., Corra, U. & Tavazzi, L. (2003b) Antiremodeling Effect of Long-Term Exercise Training in Patients with Stable Chronic Heart Failure: Results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (Elvd-Chf) Trial. *Circulation,* 108**:** 554-559.

Gibbons, R. J., Balady, G. J., Beasley, J. W., Faafp, J. W., Bricker, J. T., et al. (1997) Acc/Aha Guidelines for Exercise Testing: Executive Summary : A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *Circulation,* 96**:** 345-354.

Gielen, S., Adams, V., Mobius-Winkler, S., Linke, A., Erbs, S., et al. (2003) Anti-Inflammatory Effects of Exercise Training in the Skeletal Muscle of Patients with Chronic Heart Failure. *J Am Coll Cardiol,* 42**:** 861.

Gielen, S., Adams, V., Niebauer, J., Schuler, G. & Hambrecht, R. (2005) Aging and Heart Failure--Similar Syndromes of Exercise Intolerance? Implications for Exercise-Based Interventions. *Heart Fail Monit.,* 4**:** 130-6.

Gordon, A., Tyni-Lenné, R., Persson, H., Kaijser, L., Hultman, E., et al. (1996) Markedly Improved Skeletal Muscle Function with Local Muscle Training in Patients with Chronic Heart Failure. *Clinical Cardiology,* 19**:** 568-74.

Gordon, N. F. & Scott, C. B. (1995) Exercise Intensity Prescription in Cardiovascular Disease. Theoretical Basis for Anaerobic Threshold Determination. *J Cardiopulmonary Rehabil,* 15**:** 193-196.

Gorostiaga, E., Walter, C., Foster, C. & Hickson, R. (1991) Uniqueness of Interval and Continuous Training at the Same Maintained Exercise Intensity. *Eur J Appl Physiol Occup Physiol.,* 63**:** 101-7.

Gottlieb, S. S., Fisher, M. L., Freudenberger, R., Robinson, S., Zietowski, G., et al. (1999) Effects of Exercise Training on Peak Performance and Quality of Life in Congestive Heart Failure Patients. *Journal of Cardiac Failure,* 5**:** 188.

Green, C. P., Porter, C. B., Bresnahan, D. R. & Spertus, J. A. (2000) Development and Evaluation of the Kansas City Cardiomyopathy Questionnaire: A New Health Status Measure for Heart Failure. *J Am Coll Cardiol,* 35**:** 1245-1255.

Green, D., Watts, K., Maiorana, A. & O'Driscoll, J. (2001) A Comparison of Ambulatory Oxygen Consumption During Circuit Training and Aerobic Exercise in Patients with Chronic Heart Failure. *J Cardiopulm Rehabil.,* 21**:** 167-174.

Guyatt, G. H., Feeny, D. H. & Patrick, D. L. (1993) Measuring Health-Related Quality of Life. *Ann Intern Med,* 118**:** 662-9.

Hagberg, L. A. & Lindholm, L. (2006) Review Article: Cost-Effectiveness of Healthcare-Based Interventions Aimed at Improving Physical Activity. *Scand J Public Health,* 34**:** 641-653.

Hagerman, I., Tyni-Lenne, R. & Gordon, A. (2005) Outcome of Exercise Training on the Long-Term Burden of Hospitalisation in Patients with Chronic Heart Failure. A Restrospective Study. *Int J Cardiol,* 98**:** 487.

Hambrecht, M. D. R., Fiehn, M. D. E., Yu, M. D. J., Niebauer, M. D. J., Weigl, M. D. C., et al. (1997) Effects of Endurance Training on Mitochondrial Ultrastructure and Fiber Type Distribution in Skeletal Muscle of Patients with Stable Chronic Heart Failure. *J Am Coll Cardiol,* 29**:** 1067.

Hambrecht, R., Fiehn, E., Weigl, C., Gielen, S., Hamann, C., et al. (1998) Regular Physical Exercise Corrects Endothelial Dysfunction and Improves Exercise Capacity in Patients with Chronic Heart Failure. *Circulation,* 98**:** 2709-2715.

Hambrecht, R., Gielen, S., Linke, A., Fiehn, E., Yu, J., et al. (2000) Effects of Exercise Training on Left Ventricular Function and Peripheral Resistance in Patients with Chronic Heart Failure: A Randomized Trial. *JAMA,* 283**:** 3095-3101.

Hambrecht, R., Niebauer, J., Fiehn, E., Kalberer, B., Offner, B., et al. (1995a) Physical Training in Patients with Stable Chronic Heart Failure: Effects on Cardiorespiratory Fitness and Ultrastructural Abnormalities of Leg Muscles. *J Am Coll Cardiol,* 25**:** 1239-49.

Hambrecht, R., Niebaure, J., Fiehn, E., Kalbere, B., Offner, B., et al. (1995b) Physical Training in Patients with Stable Chronic Heart Failure: Effects on Cardiorespiratory Fitness and Ultra-Structural Abnormalities of Leg Muscles. *Am J Coll Cardiol,* 25**:** 1239 - 1249.

Harris, S., LeMaitre, J. P., Mackenzie, G., Fox, K. A. A. & Denvir, M. A. (2003) A Randomised Study of Home-Based Electrical Stimulation of the Legs and Conventional Bicycle Exercise Training for Patients with Chronic Heart Failure. *Eur Heart J,* 24**:** 871-878.

Haskell, W. L. (2001) What to Look for in Assessing Responsiveness to Exercise in a Health Context. *Med Sci Sports Exerc,* 33**:** S454-S458.

Haskell, W. L., Lee, I.-M., Pate, R. R., Powell, K. E., Blair, S. N., et al. (2007) Physical Activity and Public Health: Updated Recommendation for Adults from the American College of Sports Medicine and the American Heart Association. *Circulation,* 116**:** 1081-1093.

Haykowsky, M., Vonder Muhll, I., Ezekowitz, J. & Armstrong, P. (2005) Supervised Exercise Training Improves Aerobic Capacity and Muscle Strength in Older Women with Heart Failure. *Can J Cardiol.,* 21**:** 1277-80.

Haykowsky, M. J., Liang, Y., Pechter, D., Jones, L. W., McAlister, F. A., et al. (2007) A Meta-Analysis of the Effect of Exercise Training on Left Ventricular Remodeling in Heart Failure Patients: The Benefit Depends on the Type of Training Performed. *J Am Coll Cardiol,* 49**:** 2329 - 2336.

Hepple, R. T., Liu, P. P., Plyley, M. J. & Goodman, J. M. (1999) Oxygen Uptake Kinetics During Exercise in Chronic Heart Failure: Influence of Peripheral Vascular Reserve. *Clin. Sci.,* 97**:** 569-577.

Hobbs, F. D. R., Kenkre, J. E., Roalfe, A. K., Davis, R. C., Hare, R., et al. (2002) Impact of Heart Failure and Left Ventricular Systolic Dysfunction on Quality of Life. A Cross-Sectional Study Comparing Common Chronic Cardiac and Medical Disorders and a Representative Adult Population. *Eur Heart J,* 23**:** 1867-1876.

Hopkins, W., Schabort, E. & Hawley, J. (2001) Reliability of Power in Physical Performance Tests. *Sports Medicine,* 31**:** 211-34.

Hopkins, W. G. (2000a) Measures of Reliability in Sports Medicine and Science. *Sports Med,* 30**:** 1-15.

Hopkins, W. G. (2000b) A New View of Statistics: Calculations of Reliability. *Http://Www.Sportsci.Org/Resource/Stats/Index.Html*.

Hornig, B., Maier, V. & Drexler, H. (1996) Physical Training Improves Endothelial Function in Patients with Chronic Heart Failure. *Circulation,* 25**:** 210 - 214.

Hunt, S. A., Abraham, W. T., Chin, M. H., Feldman, A. M., Francis, G. S., et al. (2005) Acc/Aha 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult--Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society. *Circulation,* 112**:** 1825-1852.

Ingle, L. (2007) Theoretical Rationale and Practical Recommendations for Cardiopulmonary Exercise Testing in Patients with Chronic Heart Failure. *Heart Failure Rev,* 12**:** 12-22.

Ingle, L. (2008) Prognostic Value and Diagnostic Potential of Cardiopulmonary Exercise Testing in Patients with Chronic Heart Failure. *Eur J Heart Fail,* 10**:** 112.

Jette, D. U. & Downing, J. (1994) Health Status of Individuals Entering a Cardiac Rehabilitation Program as Measured by the Medical Outcomes Study 36-Item Short-Form Survey (Sf-36). *Phys Ther,* 74**:** 521-527.

Jette, M., Heller, R., Landry, F. & Blumchen, G. (1991) Randomized 4-Week Exercise Program in Patients with Impaired Left Ventricular Function. *Circulation,* 84**:** 1561-1567.

Johnson, J. S., Carlson, J. J., VanderLaan, R. L. & Langholz, D. E. (1998) Effects of Sampling Interval on Peak Oxygen Consumption in Patients Evaluated for Heart Transplantation. *Chest,* 113**:** 816-819

Jolly, K., Taylor, R. S., Lip, G. Y. H., Davies, M., Davis, R., et al. (2009) A Randomized Trial of the Addition of Home-Based Exercise to Specialist Heart Failure Nurse Care: The Birmingham Rehabilitation Uptake Maximisation Study for Patients with Congestive Heart Failure (Brum-Chf) Study. *Eur J Heart Fail,* 11**:** 205-213.

Jolly, K., Tayor, R., Lip, G., Greenfield, S., Davies, M., et al. (2007) Home-Based Exercise Rehabilitation in Addition to Specialist Heart Failure Nurse Care: Design, Rationale and Recruitment to the Birmingham Rehabilitation Uptake Maximisation Study for Patients with Congestive Heart Failure (Brum-Chf): A Randomised Controlled Trial. *BMC Cardiovascular Disorders,* 7**:** 9.

Jondeau, G., Katz, S. D., Zohman, L., Goldberger, M., McCarthy, M., et al. (1992) Active Skeletal Muscle Mass and Cardiopulmonary Reserve. Failure to Attain Peak Aerobic Capacity During Maximal Bicycle Exercise in Patients with Severe Congestive Heart Failure. *Circulation,* 86**:** 1351-1356.

Jones, A. M. & Poole, D. C. (2005) *Oxygen Uptake Kinetics in Sport, Exercise and Medicine,* London, Routledge.

Jones, A. M., Vanhatalo, A. T. & Doust, J. D. (2007) Aerobic Exercise Performance. IN Eston, R. & Reilly, T. (Eds.) *Kinanthropometry and Exercise Physiology Laboratory Manual: Tests, Procedures and Data. Volume 2 Exercise Physiology.* 3 ed. London, Routledge.

Jonsdottir, S., Andersen, K. K., Sigursson, A. F. & Sigursson, S. B. (2006) The Effect of Physical Training in Chronic Heart Failure. *Eur J Heart Fail,* 8**:** 97.

Katz, S. D., Berkowitz, R. & LeJemtel, T. H. (1992) Anaerobic Threshold Detection in Patients with Congestive Heart Failure. *Am J Cardiol,* 69**:** 1565.

Kavanagh, T., Myers, M. G., Baigrie, R. S., Mertens, D. J., Sawyer, P., et al. (1996) Quality of Life and Cardiorespiratory Function in Chronic Heart Failure: Effects of 12 Months' Aerobic Training. *Heart,* 76**:** 42-49.

Kemps, H., M. , Schep, G., de Vries, W. R., Schmikli, S. L., Zonderland, M. L., et al. (2008) Predicting Effects of Exercise Training in Patients with Heart Failure Secondary to Ischemic or Idiopathic Dilated Cardiomyopathy. *Am J Cardiol,* 102**:** 1073-1078.

Kemps, H., M., Schep, G., Hoogsteen, J., Thijssen, E. J. M., De Vries, W. R., et al. (2009) Oxygen Uptake Kinetics in Chronic Heart Failure: Clinical and Physiological Aspects. *Neth Heart J.* , 17**:** 238-244.

Kervio, G., Carre, F. & Ville, N. S. (2003) Reliability and Intensity of the Six-Minute Walk Test in Healthy Elderly Subjects. *Med Sci Sports Exerc,* 35**:** 169-174.

Keteyian, S. (2010) Exercise in the Management of Patients with Chronic Heart Failure. *Current Heart Failure Reports,* 7**:** 35-41.

Keteyian, S. J., Brawner, C. A., Ehrman, J. K., Ivanhoe, R., Boehmer, J. P., et al. (2010) Reproducibility of Peak Vo2 and Other Cardiopulmonary Exercise Parameters: Implications for Clinical Trials and Clinical Practice *Chest*.

Keteyian, S. J., Brawner, C. A., Schairer, J. R., Levine, T. B., Levine, A. B., et al. (1999) Effects of Exercise Training on Chronotropic Incompetence in Patients with Heart Failure. *Am Heart J,* 138**:** 233.

Keteyian, S. J., Levine, A. B., Brawner, C. A., Kataoka, T., Rogers, F. J., et al. (1996) Exercise Training in Patients with Heart Failure a Randomized, Controlled Trial. *Ann Intern Med,* 124**:** 1051-1057.

Kiilavuori, K., Näveri, H., Ikonen, T., Leinonen, H. & Sovijärvi, A. (1996) Effect of Physical Training on Exercise Capacity and Gas Exchange in Patients with Chronic Heart Failure. *Chest,* 110**:** 985-91.

Kiilavuori, K., Naveri, H., Salmi, T. & Harkonen, M. (2000) The Effect of Physical Training on Skeletal Muscle in Patients with Chronic Heart Failure. *Eur J Heart Fail,* 2**:** 53-63.

Kiilavuori, K., Toivonen, L., Naveri, H. & Leinonen, H. (1995) Reversal of Autonomic Derangements by Physical Training in Chronic Heart Failure Assessed by Heart Rate Variability. *Eur Heart J,* 16**:** 490-495.

Kim, S., Yamabe, H. & Yokoyama, M. (1999) Hemodynamic Characteristics During Treadmill and Bicycle Exercise in Chronic Heart Failure. *Japanese Circulation Journal,* 63**:** 965-70.

Kjaer, A., Appel, J., Hildebrandt, P. & Petersen, C. L. (2004) Basal and Exercise-Induced Neuroendocrine Activation in Patients with Heart Failure and in Normal Subjects. *Eur J Heart Fail,* 6**:** 29.

Klecha, A., Kawecka-Jaszcz, K., Bacior, B., Kubinyi, A., Pasowicz, M., et al. (2007) Physical Training in Patients with Chronic Heart Failure of Ischemic Origin: Effect on Exercise Capacity and Left Ventricular Remodeling. *Eur J Cardiovasc Prev Rehabil,* 14**:** 85-91.

Kobayashi, N., Tsuruya, Y., Iwasawa, T., Ikeda, N., Hashimoto, S., et al. (2003) Exercise Training in Patients with Chronic Heart Failure Improves Endothelial Function Predominantly in the Trained Extremities. *Circ J,* 67**:** 505-510.

Koike, A., Itoh, H., Doi, M., Taniguchi, K., Marumo, F., et al. (1990) Beat-to-Beat Evaluation of Cardiac Function During Recovery from Upright Bicycle Exercise in Patients with Coronary Artery Disease. *Am Heart J,* 120**:** 316-323.

Koike, A., Itoh, H., Taniguchi, K. & Hiroe, M. (1989) Detecting Abnormalities in Left Ventricular Function During Exercise by Respiratory Measurement. *Circulation,* 80**:** 1737-46.

Kruger, S., Graf, J. u., Kunz, D., Stickel, T., Hanrath, P., et al. (2002) Brain Natriuretic Peptide Levels Predict Functional Capacity in Patients with Chronic Heart Failure. *J Am Coll Cardiol,* 40**:** 718-22.

Lamas, G. A., Ellenbogen, K. A., With the Assistance of Charles H. Hennekens, M. D. D. & Alicia Montanez, M. D. (2004) Evidence Base for Pacemaker Mode Selection: From Physiology to Randomized Trials. *Circulation,* 109**:** 443-451.

Larsen, A. I., Aarsland, T., Kristiansen, M., Haugland, A. & Dickstein, K. (2001) Assessing the Effect of Exercise Training in Men with Heart Failure. Comparison of Maximal, Submaximal and Endurance Exercise Protocols. *Eur Heart J,* 22**:** 684-692.

Larsen, A. I., Lindal, S., Aukrust, P., Toft, I., Aarsland, T., et al. (2002) Effect of Exercise Training on Skeletal Muscle Fibre Characteristics in Men with Chronic Heart Failure. Correlation between Skeletal Muscle Alterations, Cytokines and Exercise Capacity. *Int J Cardiol,* 83**:** 25-32.

Lavie, C., J. , Milani, R., V. & Ventura, H., O. (2009) Exercise Training and Heart Failure in Older Adults - Dismal Failure or Not Enough Exercise? *Journal of the American Geriatrics Society,* 57**:** 2148-2150.

Lee, A. P., Ice, R., Blessey, R. & Sanmarco, M. E. (1979) Long-Term Effects of Physical Training on Coronary Patients with Impaired Ventricular Function. *Circulation,* 60**:** 1519-1526.

Lee, S., Stevens, T. L., Sandberg, S. M., Heublein, D. M., Nelson, S. M., et al. (2002) The Potential of Brain Natriuretic Peptide as a Biomarker for New York Heart Association Class During the Outpatient Treatment of Heart Failure. *Journal of Cardiac Failure,* 8**:** 149-154.

Levy, W. C., Maichel, B. A., Steele, N. P., Leclerc, K. M. & Stratton, J. R. (2004) Biomechanical Efficiency Is Decreased in Heart Failure During Low-Level Steady State and Maximal Ramp Exercise. *Eur J Heart Fail,* 6**:** 917.

Linke, A., Schoene, N., Gielen, S., Hofer, J., Erbs, S., et al. (2001) Endothelial Dysfunction in Patients with Chronic Heart Failure: Systemic Effects of Lower-Limb Exercise Training. *J Am Coll Cardiol,* 37**:** 392.

Lloyd-Williams, F., Mair, F. & Leitner, M. (2004) Exercise Training and Heart Failure: A Systematic Review of Current Evidence. *Brit J Gen Prac,* 52**:** 47 - 55.

Lloyd-Williams, F., Mair, F. S. & Leitner, M. (2002) Exercise Training and Heart Failure: A Systematic Review of Current Evidence. *Br J Gen Pract,* 52**:** 47-55.

Lonsdorfer-Wolf, E., Richard, R., Doutreleau, S., Billat, V., Oswald-Mammosser, M., et al. (2003) Pulmonary Hemodynamics During a Strenuous Intermittent Exercise in Healthy Subjects. *Med Sci Sports Exerc.,* 35**:** 1866-74.

Lunde, P. K., Sjaastad, I., Schiotz Thorud, H. M. & Sejersted, O. M. (2001) Skeletal Muscle Disorders in Heart Failure. *Acta Physiologica Scandinavica,* 171**:** 277-294.

Macfarlane, D. J., Lee, C. C. Y., Ho, E. Y. K., Chan, K. L. & Chan, D. (2006) Convergent Validity of Six Methods to Assess Physical Activity in Daily Life. *J Appl Physiol,* 101**:** 1328-1334.

Maiorana, A., O'Driscoll, G., Cheetham, C., Collis, J., Goodman, C., et al. (2000) Combined Aerobic and Resistance Exercise Training Improves Functional Capacity and Strength in Chf. *J Appl Physiol,* 88**:** 1565-1570.

Malfatto, G., Branzi, G., Osculati, G., Valli, P., Cuoccio, P., et al. (2009) Improvement in Left Ventricular Diastolic Stiffness Induced by Physical Training in Patients with Dilated Cardiomyopathy. *Journal of Cardiac Failure,* 15**:** 327-333.

Malfatto, G., Branzi, G., Riva, B., Sala, L., Leonetti, G., et al. (2002) Recovery of Cardiac Autonomic Responsiveness with Low-Intensity Physical Training in Patients with Chronic Heart Failure. *Eur J Heart Fail,* 4**:** 159-166.

Marburger, C. T., Brubaker, P. H., Pollock, W. E., Morgan, T. M. & Kitzman, D. W. (1998) Reproducibility of Cardiopulmonary Exercise Testing in Elderly Patients with Congestive Heart Failure. *Am J Cardiol,* 82**:** 905.

Maresh, C. M. & Noble, B. J. (1984) Utilisation of Perceived Exertion Ratings During Exercise Testing and Training. IN Hall, L., Meyer, G. & Hellerstein, H. (Eds.) *Cardiac Rehabilitation: Exercise Testing and Prescription.* New York, Spectrum.

McConnell, T. R. (2005) A Review to Develop an Effective Exercise Training for Heart Failure Patients. *Europa Medicophysica,* 41**:** 49-56.

McConnell, T. R., Clark, B. A., III, Conlin, N. C. & Haas, J. H. (1993) Gas Exchange Anaerobic Threshold: Implications for Prescribing Exercise in Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev,* 13**:** 31-36.

McKelvie, R. S., Teo, K. K., Roberts, R., McCartney, N., Humen, D., et al. (2002) Effects of Exercise Training in Patients with Heart Failure: The Exercise Rehabilitation Trial (Exert). *Am Heart J,* 144**:** 23.

McLellan, T. & Skinner, J. (1982) Blood Lactate Removal During Active Recovery Related to the Aerobic Threshold. *Int J Sports Med.,* 03**:** 224-229.

McMurray, J. J. V. & Pfeffer, M. A. (2005) Heart Failure. *The Lancet,* 365**:** 1877.

McNairy, M., Gardetto, N., Clopton, P., Garcia, A., Krishnaswamy, P., et al. (2002) Stability of B-Type Natriuretic Peptide Levels During Exercise in Patients with Congestive Heart Failure: Implications for Outpatient Monitoring with B-Type Natriuretic Peptide. *Am Heart J,* 143**:** 406-111.

Metra, M., Ponikowski, P., Dickstein, K., McMurray, J. J. V., Gavazzi, A., et al. (2007) Advanced Chronic Heart Failure: A Position Statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail,* 9**:** 684.

Meyer, K. (2001) Exercise Training in Heart Failure: Recommendations Based on Current Research. *Med Sci Sports Exerc,* 33**:** 525-531.

Meyer, K., Foster, C., Georgakopoulos, N., Hajric, R., Westbrook, S., et al. (1998a) Comparison of Left Ventricular Function During Interval Versus Steady-State Exercise Training in Patients with Chronic Congestive Heart Failure. *Am J Cardiol,* 82**:** 1382.

Meyer, K., Gornandt, L., Schwaibold, M., Westbrook, S., Hajric, R., et al. (1997a) Predictors of Response to Exercise Training in Severe Chronic Congestive Heart Failure. *Am J Cardiol,* 80**:** 56.

Meyer, K., Hajric, R., Westbrook, S., Samek, L., Lehmann, M., et al. (1996a) Ventilatory and Lactate Threshold Determinations in Healthy Normals and Cardiac Patients: Methodological Problems. *Eur J Appl Physiol Occup Physiol. 387-93.,* 72**:** 387-93.

Meyer, K. & Laederach-Hofmann, K. (2003) Effects of a Comprehensive Rehabilitation Program on Quality of Life in Patients with Chronic Heart Failure *Medscape http://www.medscape.com/viewarticle/464678*.

Meyer, K., Lehmann, M., Sunder, G., Keul, J. & Weidemann, H. (1990) Interval Versus Continuous Exercise Training after Coronary Bypass Surgery: A Comparison of Training-Induced Acute Reactions with Respect to the Effectiveness of the Exercise Methods. *Clin Cardiol,* 13**:** 851-61.

Meyer, K., Samek, L., Schwaibold, M., Westbrook, K., Hajric, R., et al. (1996b) Physical Responses to Different Modes of Interval Exercise in Patients with Chronic Heart Failure - Application to Exercise Training. *Eur Heart J,* 17**:** 1040-1047.

Meyer, K., Samek, L., Schwaibold, M., Westbrook, S., Hajric, R., et al. (1997b) Interval Training in Patients with Severe Chronic Heart Failure: Analysis and Recommendations for Exercise Procedures. *Med Sci Sports Exerc. ,* 29**:** 306-12.

Meyer, K., Schwaibold, M., Hajric, R., Westbrook, S., Ebfeld, D., et al. (1998b) Delayed Vo2 Kinetics During Ramp Exercise: A Criterion for Cardiopulmonary Exercise Capacity in Chronic Heart Failure. . *Med Sci Sports Exerc,* 30**:** 643-648.

Meyer, K., Schwaibold, M., Westbrook, S., Beneke, R., Hajric, R., et al. (1996c) Effects of Short-Term Exercise Training and Activity Restriction on Functional Capacity in Patients with Severe Chronic Congestive Heart Failure. *Am J Cardiol,* 78**:** 1017-1022.

Meyer, K., Westbrook, S., Schwaibold, M., Hajric, R., Peters, K., et al. (1997c) Short-Term Reproducibility of Cardiopulmonary Measurements During Exercise Testing in Patients with Severe Chronic Heart Failure. *Am Heart J,* 134**:** 20.

Meyer, T., Gorge, G., Schwaab, B., Hildebrandt, K., Walldorf, J., et al. (2005a) An Alternative Approach for Exercise Prescription and Efficacy Testing in Patients with Chronic Heart Failure: A Randomized Controlled Training Study. *Am Heart J,* 149**:** 926.

Meyer, T., Kindermann, M. & Kindermann, W. (2004a) Exercise Programmes for Patients with Chronic Heart Failure. *Sports Med,* 34**:** 939-954.

Meyer, T., Lucia, A., Earnest, C. P. & Kindermann, W. (2005b) A Conceptual Framework for Performance Diagnosis and Training Prescription from Submaximal Gas Exchange Parameters - Theory and Application. *Int J Sports Med.,* 26**:** S38-S48.

Meyer, T., Schwaab, B., Garge, G., Scharhag, J., Herrmann, M., et al. (2004b) Can Serum Nt-Probnp Detect Changes of Functional Capacity in Patients with Chronic Heart Failure? *Zeitschrift fur Kardiologie,* 93**:** 540.

Meyer, T. I. M., Gabriel, H. H. W. & Kindermann, W. (1999) Is Determination of Exercise Intensities as Percentages of O2max or Hrmax Adequate? *Med Sci Sports Exerc,* 31**:** 1342-45.

Mezzani, A., Corrà, U., Bosimini, E., Giordanob, A. & Giannuzzi, P. (2003) Contribution of Peak Respiratory Exchange Ratio to Peak Vo2 Prognostic Reliability in Patients with Chronic Heart Failure and Severely Reduced Exercise Capacity *Am Heart J,* 145 1102-7.

Mezzani, A., Corra, U., Giordano, A., Cafagna, M., Adriano, E. P., et al. (2007) Unreliability of the %Vo2 Reserve Versus %Heart Rate Reserve Relationship for Aerobic Effort Relative Intensity Assessment in Chronic Heart Failure Patients on or Off Beta-Blocking Therapy. *Eur J Cardiovasc Prev Rehabil,* 14**:** 92-98.

Miche, E., Roelleke, E., Zoller, B., Wirtz, U., Schneider, M., et al. (2009) A Longitudinal Study of Quality of Life in Patients with Chronic Heart Failure Following an Exercise Training Program. *Eur J Cardiovasc Nurs.,* 8**:** 281-7.

Midgley, A. W., Bentley, D. J., Luttikholt, H., McNaughton, L. R. & Millet, G. P. (2008) Challenging a Dogma of Exercise Physiology: Does an Incremental Exercise Test for Valid V-Doto2max Determination Really Need to Last between 8 and 12 Minutes? *Sports Med,* 38**:** 441-447.

Milani, R., V. & Lavie, C., J. (2007) Impact of Cardiac Rehabilitation on Depression and Its Associated Mortality. *The American Journal of Medicine,* 120**:** 799-806.

Mitchell, S. H., Steele, N. P., Leclerc, K. M., Sullivan, M. & Levy, W. C. (2003) Oxygen Cost of Exercise Is Increased in Heart Failure after Accounting for Recovery Costs. *Chest,* 124**:** 572-579.

Muller, L., Myers, J., Kottman, W., Luchinger, R. & Dubach, P. (2009) Long-Term Myocardial Adaptations after Cardiac Rehabilitation in Heart Failure: A Randomized Six-Year Evaluation Using Magnetic Resonance Imaging. *Clinical Rehabilitation,* 23**:** 986-994.

Munkvik, M., Rehn, T. A., SlettalÃ¸kken, G., Hasic, A., Hallen, J., et al. (2010) Training Effects on Skeletal Muscle Calcium Handling in Human Chronic Heart Failure. *Med Sci Sports Exerc,* 42**:** 847-855.

Myers, J. (2001) On the Uniformity of Cardiopulmonary Exercise Testing in Chronic Heart Failure. *Am Heart J,* 142**:** 384-387.

Myers, J., Goldsmith, R. L., Keteyian, S. J., Brawner, C. A., Brazil, D. A., et al. (2010) The Ventilatory Anaerobic Threshold in Heart Failure: A Multicenter Evaluation of Reliability. *J Cardiac Failure,* 16**:** 76-83.

Myers, J., Gullestad, L., Vagelos, R., Do, D., Bellin, D., et al. (1998) Clinical, Hemodynamic, and Cardiopulmonary Exercise Test Determinants of Survival in Patients Referred for Evaluation of Heart Failure. *Ann Intern Med,* 129**:** 286-293.

Myers, J., Hadley, D., Oswald, U., Bruner, K., Kottman, W., et al. (2007) Effects of Exercise Training on Heart Rate Recovery in Patients with Chronic Heart Failure. *Am Heart J,* 153**:** 1056-1063.

National Collaborating Centre for Chronic Conditions (2003) Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care. *NICE guideline.*

Nechwatal, R., Duck, C. & Gruber, G. (2002) Physical Training as Interval or Continuous Training in Chronic Heart Failure for Improving Functional Capacity, Hemodynamics and Quality of Life--a Controlled Study. *Z Kardiol,* 91**:** 328-37.

Nelson, M. E., Rejeski, W. J., Blair, S. N., Duncan, P. W., Judge, J. O., et al. (2007) Physical Activity and Public Health in Older Adults: Recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation,* 116**:** 1094-1105.

Neubauer, S. (2007) The Failing Heart. An Engine out of Fuel. *N Engl J Med,* 356**:** 1140-1151.

Nilsson, B. B., Hellesnes, B., Westheim, A. & Risberg, M. A. (2008a) Group-Based Aerobic Interval Training in Patients with Chronic Heart Failure: Norwegian Ullevaal Model. *Phys Ther,* 88**:** 523-535.

Nilsson, B. B., Westheim, A. & Risberg, M. A. (2008b) Effects of Group-Based High-Intensity Aerobic Interval Training in Patients with Chronic Heart Failure. *Am J Cardiol,* 102**:** 1361-1365.

Nilsson, B. B., Westheim, A. & Risberg, M. A. (2008c) Long-Term Effects of a Group-Based High-Intensity Aerobic Interval-Training Program in Patients with Chronic Heart Failure. *Am J Cardiol,* 102**:** 1220-1224.

Noble, B. J. & Robertson, R. J. (1996) *Perceived Exertion,* Champaign, IL, Human Kinetics.

O'Connor, C. M., Whellan, D. J., Lee, K. L., Keteyian, S. J., Cooper, L. S., et al. (2009) Efficacy and Safety of Exercise Training in Patients with Chronic Heart Failure: Hf-Action Randomized Controlled Trial. *JAMA,* 301**:** 1439-1450.

O'Donovan, G., Blazevich, A. J., Boreham, C., Cooper, A. R., Crank, H., et al. (2010) The Abc of Physical Activity for Health: A Consensus Statement from the British Association of Sport and Exercise Sciences. *Journal of Sports Sciences,* 28**:** 573 - 591.

Oja, P. (2001) Dose Response between Total Volume of Physical Activity and Health and Fitness. *Med Sci Sports Exerc,* 33**:** S428-S437.

Owen, A. & Croucher, L. (2000) Effect of an Exercise Programme for Elderly Patients with Heart Failure. *Eur J Heart Fail,* 2**:** 65-70.

Packer, M. (1992) The Neurohormonal Hypothesis: A Theory to Explain the Mechanism of Disease Progression in Heart Failure. *J Am Coll Cardiol,* 20**:** 248.

Packer, M. (2003) Should B-Type Natriuretic Peptide Be Measured Routinely to Guide the Diagnosis and Management of Chronic Heart Failure? *Circulation,* 108**:** 2950-2953.

Page, E., Cohen-Solal, A., Jondeau, G., Douard, H., Roul, G., et al. (1994) Comparison of Treadmill and Bicycle Exercise in Patients with Chronic Heart Failure. *Chest,* 106**:** 1002-1006.

Palmer, G. S., Borghouts, L. B., Noakes, T. D. & Hawley, J. A. (1999) Metabolic and Performance Responses to Constant-Load Vs. Variable-Intensity Exercise in Trained Cyclists. *J Appl Physiol,* 87**:** 1186-1196.

Panton, L., Graves, J., Pollock, M., Garzarella, L., Carroll, J., et al. (1996) Relative Heart Rate, Heart Rate Reserve, and Vo2 During Submaximal Exercise in the Elderly. *J Gerontol A Biol Sci Med Sci.,* 51**:** M165-71.

Parnell, M. M., Holst, D. P. & Kaye, D. (2005) Augmentation of Endothelial Function Following Exercise Training Is Associated with Increased L-Arginine Transport in Human Heart Failure. *Clin Sci,* 109**:** 523-30.

Parnell, M. M., Holst, D. P. & Kaye, D. M. (2002) Exercise Training Increases Arterial Compliance in Patients with Congestive Heart Failure. *Clin. Sci.,* 102**:** 1-7.

Pascual-Figal, D., Peñafiel, P., Nicolas, F., de la Morena, G., Ansaldo, P., et al. (2008) Prognostic Value of Bnp and Cardiopulmonary Exercise Testing in Patients with Systolic Heart Failure on Beta-Blocker Therapy *Rev Esp Cardiol,* 61**:** 260-268.

Passino, C., Poletti, R., Bramanti, F., Prontera, C., Clerico, A., et al. (2006a) Neuro-Hormonal Activation Predicts Ventilatory Response to Exercise and Functional Capacity in Patients with Heart Failure. *Eur J Heart Fail,* 8**:** 46.

Passino, C., Severino, S., Poletti, R., Piepoli, M. F., Mammini, C., et al. (2006b) Aerobic Training Decreases B-Type Natriuretic Peptide Expression and Adrenergic Activation in Patients with Heart Failure. *J Am Coll Cardiol,* 47**:** 1835-39.

Patwala, A. Y., Woods, P. R., Sharp, L., Goldspink, D. F., Tan, L. B., et al. (2009) Maximizing Patient Benefit from Cardiac Resynchronization Therapy with the Addition of Structured Exercise Training: A Randomized Controlled Study. *J Am Coll Cardiol,* 53**:** 2332-2339.

Philp, A., Macdonald, A. L. & Watt, P. W. (2005) Lactate - a Signal Coordinating Cell and Systemic Function. *J Exp Biol,* 208**:** 4561-4575.

Picozzi, N. M., Clark, A. L., Lindsay, K. A., McCann, G. P. & Hillis, W. S. (1999) Responses to Constant Work Exercise in Patients with Chronic Heart Failure. *Heart,* 82**:** 482-485.

Piepoli, M., Clark, A. L., Volterrani, M., Adamopoulos, S., Sleight, P., et al. (1996) Contribution of Muscle Afferents to the Hemodynamic, Autonomic, and Ventilatory Responses to Exercise in Patients with Chronic Heart Failure : Effects of Physical Training. *Circulation,* 93**:** 940-952.

Piepoli, M. F., Davos, C., Francis, D. P. & Coats, A. J. (2004) Exercise Training Meta-Analysis of Trials in Patients with Chronic Heart Failure (Extramatch Collaborative). *BMJ,* 328**:** 189-192.

Piepoli, M. F., Scott, A. C., Capucci, A. & Coats, A. J. S. (2001) Skeletal Muscle Training in Chronic Heart Failure. *Acta Physiologica Scandinavica,* 171**:** 295-303.

Pina, I. L., Apstein, C. S., Balady, G. J., Belardinelli, R., Chaitman, B. R., et al. (2003) Exercise and Heart Failure: A Statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention. *Circulation,* 107**:** 1210-1225.

Poole, D. C. & Gaesser, G. A. (1985) Response of Ventilatory and Lactate Thresholds to Continuous and Interval Training. *J Appl Physiol,* 58**:** 1115-1121.

Prescott, E., Hjardem-Hansen, R., Dela, F., Teisner, A. S. & Nielsen, H. (2009) Exercise Training in Older Patients with Systolic Heart Failure: Adherence, Exercise Capacity, Inflammation and Glycemic Control *Scand Cardiovasc J,* 43**:** 249-255.

Puhan, M., Busching, G., Schunemann, H., vanOort, E., Zaugg, C., et al. (2006) Interval Versus Continuous High-Intensity Exercise in Chronic Obstructive Pulmonary Disease: A Randomized Trial *Ann Intern Med,* 145**:** 816-825.

Puhan, M., Busching, G., vanOort, E., Zaugg, C., Schunemann, H., et al. (2004) Interval Exercise Versus Continuous Exercise in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease. Study Protocol for a Randomised Controlled Trial. *BMC Pulmonary Medicine,* 4**:** 5.

Quittan, M., Sturm, B., Wiesinger, G. F., Pacher, R. & Fialka-Moser, V. (1999) Quality of Life in Patients with Chronic Heart Failure: A Randomised Controlled Trial of Changes Induced by a Regular Exercise Program *J Rehabil. Med,* 31**:** 223 - 228.

Rajappan, K., Bellenger, N. G., Anderson, L. & Pennell, D. J. (2000) The Role of Cardiovascular Magnetic Resonance in Heart Failure. *Eur J Heart Fail,* 2**:** 241-252.

Rector, T. & Cohn, J. (2004) Minnesota Living with Heart Failure Questionnaire. Instructions for Data Collection and Scoring. Www.Mlfhq.Org/.

Rector, T. S. (2005) The Minnesota Living with Heart Failure Questionnaire.

Rector, T. S. & Cohn, J. N. (1992) Assessment of Patient Outcome with the Minnesota Living with Heart Failure Questionnaire: Reliability and Validity During a Randomized, Double-Blind, Placebo-Controlled Trial of Pimobendan. *American Heart Journal,* 124**:** 1017-1025.

Rector, T. S., Francis, G. S. & Cohn, J. N. (1987a) Patients' Self-Assessment of Their Congestive Heart Failure. Part 1 Patient Preceived Dysfunction and Its Poor Correlation with Maximal Exercise Tests. *Heart Failure,* Oct/Nov**:** 192-6.

Rector, T. S., Kubo, S. H. & Cohn, J. N. (1987b) Patients' Self-Assessment of Their Congestive Heart Failure. Part 2 Content Reliability and Validity of the New Measure, the Minnesota Living with Heart Failure Quesionnaire. *Heart Failure,* Oct/Nov**:** 198-209.

Rees, K., Taylor, R., Singh, S., Coats, A. & Ebrahim, S. (2004) Exercise Based Rehabilitation for Heart Failure. *Cochrane Database Syst Rev. 2004;(3),* 2004**:** CD003331.

Reilly, T. (2007) Circadian Rhythms. IN Winter, E. M., Jones, A. M., Davison, R. C., Bromley, P. D. & Mercer, T. H. (Eds.) *Sport and Exercise Physiology Testing Guidelines. The British Associaton of Sport and Exercise Sciences Guide. Volume 2: Exercise and Clinical Testing.* London, Routledge.

Roditis, P., Dimopoulos, S., Sakellariou, D., Sarafoglou, S., Kaldara, E., et al. (2007) The Effects of Exercise Training on the Kinetics of Oxygen Uptake in Patients with Chronic Heart Failure. *Eur J Cardiovasc Prev Rehabil,* 14**:** 304-311.

Roveda, F., Middlekauff, H. R., Rondon, M. U. P. B., Reis, S. F., Souza, M., et al. (2003) The Effects of Exercise Training on Sympathetic Neural Activation in Advanced Heart Failure: A Randomized Controlled Trial. *J Am Coll Cardiol,* 42**:** 854.

Rozanski, A., Qureshi, E. A. & Bornstein, A. (2001) Postexercise Left Ventricular Function: A Comparative Assessment by Different Noninvasive Imaging Modalities. *Prog Cardiovasc Dis.,* 43**:** 335-350.

Sabelis, L. W. E., Senden, P. J., Te Boekhorst, B. C. M., Hulzebos, H. J., Van De Wiel, A., et al. (2004) Does Physical Training Increase Insulin Sensitivity in Chronic Heart Failure Patients? *Clin. Sci.,* 106**:** 459-466.

Savage, P. D., Brochu, M., Scott, P. & Ades, P. A. (2000) Low Caloric Expenditure in Cardiac Rehabilitation. *Am Heart J,* 140**:** 527-533.

Schairer, J. R., Kostelnik, T., Proffitt, S. M., Faitel, K. I., Windeler, S., et al. (1998) Caloric Expenditure During Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev.,* 18**:** 290-294.

Scott, A., Antonishen, K., Johnston, C., Pearce, T., Ryan, M., et al. (2006) Effect of Semirecumbent and Upright Body Position on Maximal and Submaximal Exercise Testing. *Measurement in Physical Education and Exercise Science,* 10**:** 41 - 50.

Scott, A. C., Francis, D., Davies, L. C., Ponikowski, P., Coats, A., et al. (2000) Contribution of Skeletal Muscle 'Ergoreceptors' in the Human Leg to Respiratory Control in Chronic Heart Failure *J. Physiol.,* 529**:** 863-870.

Senden, P. J., Sabelis, L. W., Zonderland, M. L., van de Kolk, R., Meiss, L., et al. (2004) Determinants of Maximal Exercise Performance in Chronic Heart Failure. *Eur J Cardiovasc Prev Rehabil,* 11**:** 41-7.

Seta, Y., Shan, K., Bozkurt, B., Oral, H. & Mann, D. L. (1996) Basic Mechanisms in Heart Failure: The Cytokine Hypothesis. *Journal of Cardiac Failure,* 2**:** 243.

Sietsema, K. E., Ben-Dov, I., Zhang, Y. Y., Sullivan, C. & Wasserman, K. (1994) Dynamics of Oxygen Uptake for Submaximal Exercise and Recovery in Patients with Chronic Heart Failure. *Chest,* 105**:** 1693-1700.

Simonton, C. A., Higginbotham, M. B. & Cobb, F. R. (1988) The Ventilatory Threshold: Quantitative Analysis of Reproducibility and Relation to Arterial Lactate Concentration in Normal Subjects and in Patients with Chronic Congestive Heart Failure. *Am J Cardiol,* 62**:** 100.

Smart, N., Haluska, B., Jeffriess, L., Case, C. & Marwick, T. H. (2006) Cardiac Contributions to Exercise Training Responses in Patients with Chronic Heart Failure: A Strain Imaging Study. *Echocardiography,* 23**:** 376-382.

Smart, N. & Steele, M. (2009) Systematic Review of the Effect of Aerobic and Resistance Exercise Training on Systemic Brain Natriuretic Peptide (Bnp) and N-Terminal Bnp Expression in Heart Failure Patients *Int J Cardiol,* 140**:** 260-65.

Spertus, J. A., Peterson, E. v., Breda, Conard, M., W., Heidenreich, P., A., Krumholz, H., M., et al. (2005) Monitoring Clinical Changes in Patients with Heart Failure: A Comparison of Methods. *American Heart Journal,* 150**:** 707-715.

Stolen, K. Q., Kemppainen, J., Ukkonen, H., Kalliokoski, K. K., Luotolahti, M., et al. (2003) Exercise Training Improves Biventricular Oxidative Metabolism and Left Ventricular Efficiency in Patients with Dilated Cardiomyopathy. *J Am Coll Cardiol,* 41**:** 460-467.

Strzelczyk, T. A., Quigg, R. J., Pfeifer, P. B., Parker, M. A. & Greenland, P. (2001) Accuracy of Estimating Exercise Prescription Intensity in Patients with Left Ventricular Systolic Dysfunction. *J Cardiopulmonary Rehabil,* 21**:** 158-163

Sullivan, M. J., Higginbotham, M. B. & Cobb, F. R. (1988) Exercise Training in Patients with Severe Left Ventricular Dysfunction. Hemodynamic and Metabolic Effects. *Circulation,* 78**:** 506-515.

Swedberg, K., Cleland, J., Dargie, H., Drexler, H., Follath, F., et al. (2005) Guidelines for the Diagnosis and Treatment of Chronic Heart Failure: Executive Summary (Update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J,* 26**:** 1115-1140.

Tabata, I., Nishimura, K., Kouzaki, M., Hirai, Y., Ogita, F., et al. (1996) Effects of Moderate-Intensity Endurance and High-Intensity Intermittent Training on Anaerobic Capacity and Vo_{2max}. *Med Sci Sports Exerc,* 28**:** 1327-30.

Tabet, J.-Y., Meurin, P., Beauvais, F., Weber, H., Renaud, N., et al. (2008) Absence of Exercise Capacity Improvement after Exercise Training Program: A Strong Prognostic Factor in Patients with Chronic Heart Failure. *Circ Heart Fail,* 1**:** 220-226.

Tabet, J.-Y. B., Florence; Thabut, Gabriel; Tartiere, Jean-Michel; Logeart, Damien; Cohen-Solal, Alain (2003) A Critical Appraisal of the Prognostic Value of the Ve/Vco2 Slope in Chronic Heart Failure. *Eur J Cardiovasc Prev Rehabil,* 10**:** 267-272.

Tanehata, M., Adachi, H., Oshima, S., Taniguchi, K., Itoh, H., et al. (1999) The Time from Anaerobic Threshold (at) to Respiratory Compensation Point Reflects the Rate of Aerobic and Anaerobic Metabolism after the at in Chronic Heart Failure Patients. *Jpn Circ J,* 63**:** Vol. 63. 274-277.

Tavazzi, L., Giannuzzi, P., Dubach, P., Opasich, C., Myers, J., et al. (2001) Recommendations for Exercise Testing in Chronic Heart Failure Patients. Working Group on Cardiac Rehabilitation & Excercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. *Eur Heart J,* 22**:** 37-45.

Taylor, A. (1999) Physiological Response to a Short Period of Exercise Training in Patients with Chronic Heart Failure. *Physiotherapy Research International,* 4**:** 237-249.

Taylor, R. S., Bethell, H. J. & Brodie, D. A. (2007) Clinical Trials Versus the Real World: The Example of Cardiac Rehabilitation *Brit J Cardiol,* 14**:** 175-178.

Thompson, P. D., Franklin, B. A., Balady, G. J., Blair, S. N., Corrado, D., et al. (2007) Exercise and Acute Cardiovascular Events: Placing the Risks into Perspective: A Scientific Statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology (in Collaboration with the American College of Sports, Medicine). *Circulation,* 115**:** 2358-2368.

Trohman, R. G., Kim, M. H. & Pinski, S. L. (2004) Cardiac Pacing: The State of the Art. *The Lancet,* 364**:** 1701-1719.

Tyni-Lenné, R., Gordon, A., Jansson, E., Bermann, G. & Sylvén, C. (1997) Skeletal Muscle Endurance Training Improves Peripheral Oxidative Capacity, Exercise Tolerance, and Health-Related Quality of Life in Women with Chronic Congestive Heart Failure Secondary to Either Ischemic Cardiomyopathy or Idiopathic Dilated Cardiomyopathy. *Am J Cardiol,* 80**:** 1025-1029.

Tyni-Lenné, R., Gordon, A. & Sylvén, C. (1996) Improved Quality of Life Inchronic Heart Failure Patients Following Local Endurance Training with Leg Muscles. *Journal of Cardiac Failure,* 2**:** 111-117.

Vallebona, A., Gigli, G., Orlandi, S. & Reggiardo, G. (2005) Heart Rate Response to Graded Exercise Correlates with Aerobic and Ventilatory Capacity in Patients with Heart Failure. *Clin Cardiol.,* 28**:** 25-9.

van den Berg-Emons, R., Balk, A., Bussmann, H. & Stam, H. (2004) Does Aerobic Training Lead to a More Active Lifestyle and Improved Quality of Life in Patients with Chronic Heart Failure? *Eur J Heart Fail,* 6**:** 95-100.

Van Laethem, C., Van De Veire, N., Backer, G. D., Bihija, S., Seghers, T., et al. (2007) Response of the Oxygen Uptake Efficiency Slope to Exercise Training in Patients with Chronic Heart Failure. *Eur J Heart Fail,* 9**:** 625.

van Tol, B. A. F., Huijsmans, R. J., Kroon, D. W., Schothorst, M. & Kwakkel, G. (2006) Effects of Exercise Training on Cardiac Performance, Exercise Capacity and Quality of Life in Patients with Heart Failure: A Meta-Analysis. *Eur J Heart Fail,* 8**:** 841-850.

Vanhees, L., Kornaat, M., Defoor, J., Aufdemkampe, G., Schepers, D., et al. (2004) Effect of Exercise Training in Patients with an Implantable Cardioverter Defibrillator. *Eur Heart J,* 25**:** 1120-1126.

Ventura-Clapier, R. (2009) Exercise Training, Energy Metabolism, and Heart Failure. *Appl Physiol Nutr Metab.,* 34**:** 336-9.

Ventura-Clapier, R., Mettauer, B. & Bigard, X. (2007) Beneficial Effects of Endurance Training on Cardiac and Skeletal Muscle Energy Metabolism in Heart Failure. *Cardiovascular Research,* 73**:** 10.

Vogeser, M. & Jacob, K. (2001) B-Type Natriuretic Peptide (Bnp): Validation of an Immediate Response Assay. *Clin Lab.,* 47**:** 29-33.

Vogiatzis, I., Nanas, S. & Roussos, C. (2002) Interval Training as an Alternative Modality to Continuous Exercise in Patients with Copd. *Eur Respir J,* 20**:** 12-19.

Walsh-Riddle, M. & Blumenthal, J. A. (1989) Cardiovascular Responses During Upright and Semi-Recumbent Cycle Ergometry Testing. *Med Sci Sports Exerc,* 21**:** 581-585.

Walther, C., Gielen, S. & Hambrecht, R. (2004) The Effect of Exercise Training on Endothelial Function in Cardiovascular Disease in Humans. *Exerc Sport Sci Rev.,* 32**:** 129-134.

Warburton, D., Taylor, A., Bredin, S., Esch, B., Scott, J., et al. (2007) Central Haemodynamics and Peripheral Muscle Function During Exercise in Patients with Chronic Heart Failure. *Appl. Physiol. Nutr. Metab. ,* 32**:** 318–331.

Ware, J., Snow, K., Kosisnki, M. & Gandek, B. (1993) Sf-36 Health Survey. Manaul and Interpretation Guide.

Ware, J. E. & Sherbourne, C. D. (1992) The Mos 36-Item Short-Form Health Survey (Sf-36): I. Conceptual Framework and Item Selection *Medical Care,* 30**:** 473-483.

Wasserman, K., Hansen, J. E., Sue, D. Y., Stringer, W. W. & Whipp, B. J. (2005) *Principles of Exercise Testing and Interpretation Including Pathophysiology and Clinical Applications,* Philadelphia, Lippincott Williams and Wilkins.

Weber, K. T., Kinasewitz, G. T., Janicki, J. S. & Fishman, A. P. (1982) Oxygen Utilization and Ventilation During Exercise in Patients with Chronic Cardiac Failure. *Circulation,* 65**:** 1213-1223.

Whaley, M. H., Brubaker, P. H., Kaminsky, L. A. & Miller, C. R. (1997) Validity of Rating of Perceived Exertion During Graded Exercise Testing in Apparently Healthy Adults and Cardiac Patients. *J Cardiopulm Rehabil Prev,* 17**:** 261-267.

Whellan, D. J., O'Connor, C. M., Lee, K. L., Keteyian, S. J., Cooper, L. S., et al. (2007) Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (Hf-Action): Design and Rationale. *Am Heart J,* 153**:** 201.

Whipp, B. J., Davis, J. A., Torres, F. & Wasserman, K. (1981) A Test to Determine Parameters of Aerobic Function During Exercise. *J Appl Physiol,* 50**:** 217-221.

Wielenga, R. P., Huisveld, I. A., Bol, E., Dunselman, P. H. J. M., Erdman, R. A. M., et al. (1998) Exercise Training in Elderly Patients with Chronic Heart Failure. *Coronary Artery Disease,* 9**:** 765-770.

Wielenga, R. P., Huisveld, I. A., Bol, E., Dunselman, P. H. J. M., Erdman, R. A. M., et al. (1999) Safety and Effects of Physical Training in Chronic Heart Failure. Results of the Chronic Heart Failure and Graded Exercise Study (Change). *Eur Heart J,* 20**:** 872-879.

Willenheimer, R., Erhardt, L., Cline, C., Rydberg, E. & Israelsson, B. (1998) Exercise Training in Heart Failure Improves Quality of Life and Exercise Capacity. *Eur Heart J,* 19**:** 774-781.

Willenheimer, R., Rydberg, E., Cline, C., Broms, K., Hillberger, B., et al. (2001) Effects on Quality of Life, Symptoms and Daily Activity 6 Months after Termination of an Exercise Training Programme in Heart Failure Patients. *Int J Cardiol,* 77**:** 25-31.

Williams, A. D., Selig, S., Hare, D. L., Hayes, A., Krum, H., et al. (2004) Reduced Exercise Tolerance in Chf May Be Related to Factors Other Than Impaired Skeletal Muscle Oxidative Capacity. *Journal of Cardiac Failure,* 10**:** 141.

Wilson, J. R., Groves, J. & Rayos, G. (1996) Circulatory Status and Response to Cardiac Rehabilitation in Patients with Heart Failure. *Circulation,* 94**:** 1567-1572.

Wisloff, U., Stoylen, A., Loennechen, J. P., Bruvold, M., Rognmo, O., et al. (2007) Superior Cardiovascular Effect of Aerobic Interval Training Versus Moderate Continuous Training in Heart Failure Patients: A Randomized Study. *Circulation,* 115**:** 3086-3094.

Witham, M. D., Argo, I. S., Johnston, D. W., Struthers, A. D. & McMurdo, M. E. T. (2007) Long-Term Follow-up of Very Old Heart Failure Patients Enrolled in a Trial of Exercise Training. *The American Journal of Geriatric Cardiology,* 16**:** 243-248.

Witham, M. D., Gray, J. M., Argo, I. S., Johnston, D. W., Struthers, A. D., et al. (2005) Effect of a Seated Exercise Program to Improve Physical Function and Health Status in Frail Patients > 70 Years of Age with Heart Failure. *Am J Cardiol,* 95**:** 1120-1124.

Witte, K. K. & Clark, A. L. (2007) Why Does Chronic Heart Failure Cause Breathlessness and Fatigue? *Progress in Cardiovascular Diseases,* 49**:** 366-384.

Witte, K. K. A. & Clark, A. L. (2005) Cycle Exercise Causes a Lower Ventilatory Response to Exercise in Chronic Heart Failure. *Heart,* 91**:** 225-226.

Witte, K. K. A., Cleland, J. G. F. & Clark, A. L. (2006) Chronic Heart Failure, Chronotropic Incompetence, and the Effects of {Beta} Blockade. *Heart,* 92**:** 481-486.

Witte, K. K. A., Thackray, S., Nikitin, N. P., Cleland, J. G. F. & Clark, A. L. (2005) The Effects of Long-Term [Beta]-Blockade on the Ventilatory Responses to Exercise in Chronic Heart Failure. *Eur J Heart Failure,* 7**:** 612.

Wolk, R., Johnson, B. D., Somers, V. K., Allison, T. G., Squires, R. W., et al. (2005) Effects of [Beta]-Blocker Therapy on Ventilatory Responses to Exercise in Patients with Heart Failure. *Journal of Cardiac Failure,* 11**:** 333.

Wu, A. H. B. & Smith, A. (2004) Biological Variation of the Natriuretic Peptides and Their Role in Monitoring Patients with Heart Failure. *Eur J Heart Fail,* 6**:** 355.

Yoshida, T., Takeuchi, N. & Suda, Y. (1982) Arterial Versus Venous Blood Lactate Increase in the Forearm During Incremental Bicycle Exercise *Eur J Appl Physiol Occup Physiol.,* 50**:** 87-93.

Zwisler, A.-D. O., Soja, A. M. B., Rasmussen, S., Frederiksen, M., Abadini, S., et al. (2008) Hospital-Based Comprehensive Cardiac Rehabilitation Versus Usual Care among Patients with Congestive Heart Failure, Ischemic Heart Disease, or High Risk of Ischemic Heart Disease: 12-Month Results of a Randomized Clinical Trial. *Am Heart J,* 155**:** 1106.

APPENDICES

List of Appendices

APPENDIX 1: TABLE OF EXERCISE TRAINING STUDIES IN CHRONIC HEART FAILURE

Table A1: Summary of aerobic exercise training studies in CHF

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Adamopoulos et al (2001)	Home-based setting, Athens, Greece	Randomised cross-over study of CHF after 12 weeks' home-based training /detraining	n=12 CHF and 10 healthy controls. CHF: Age 60 ± 2 yrs; NYHA II-III; LVEF 24 ± 2%; ischaemic aetiology n=6, DCM n=6	5 x 30 min per week home-based cycling @ 70-80% HR_{max} for 12 weeks	CPET on cycle ergometer, peripheral inflammatory markers	Significant increase in VO_{2peak} (15%) and correlated reduction in inflammatory markers after training.
Adamopoulos et al (2002)			n=24 CHF and 20 healthy controls. CHF: Age 55 ± 2 yrs; NYHA II-III; LVEF 23 ± 1%; ischaemic aetiology 46%, DCM 54%		proinflammatory cytokines (TNF-alpha, IL-6, sTNF-RI, sTNF-RII, sIL-6R and sFas)	Significant reduction in plasma pro-inflammatory cytokines and soluble aptosis mediators (correlated with increase in VO_{2peak}) in CHF after training vs no training, but not in controls
Arad et al (2008)	Hospital outpatient setting, Israel	Prospective study following consecutive patients enrolled in a cardiac rehabilitation programme (E)	n=30 NYHA III CHF, M/F 24/6, Age 61 ± 13 yrs; LVEF 27 ± 4%; ischaemic aetiology 77%, medication: ACE inhibitors/ARB 97%, diuretics 100%, digoxin 67%, β-blockers 77%	2 x 60 min sessions (45 min treadmill, stair climbing, cycle @ 60-70% HRR) per week for 18 weeks	CPET on treadmill (modified Bruce), 6-min walk distance, tissue doppler echocardiography, impedance cardiography, MLHFQ, serum NT-proBNP	Significant improvement in VO_{2max} (13%), 6-min walk distance (39%), cardiac index (15%), peripheral vascular resistance (11%), LVEF (11%), pulmonary artery pressure (12%), but no change in NT-proBNP in C.
Freimark et al (2007)		Patients unable to attend acting as control group (C)	n=66 NYHA III CHF (E/C) n=44/12, M/F (EvsC) 35/9 vs 8/4, Age 62±13/61±12 yrs; LVEF (E/C) 25±5/22 ± 4%; ischaemic aetiology 43/17%, medication: ACE inhibitors 44/12%, diuretics 100/100%, digoxin 61/67%, β-blockers 64/91%			Significant improvement in functional and hemodynamic parameters in E vs C.
Tenenbaum et al (2006)		Follow-up of long-term (E1) vs intermediate term (E2) attendees	n=42 CHF (E1/E2) n=22/20	2 x 60 min sessions per week for 3 years (E1) or 1.6 years (E2)	Survival, modified Bruce protocol, 6 min walk distance	Significant improvement at 3 year follow-up in survival, and exercise tolerance (13%) in E1 vs E2

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Austin et al (2005) Austin et al (2008)	Hospital outpatient then community setting, Abergavenny, UK	RCT comparing cardiac rehabilitation with usual care. Follow-up at 5 years	Randomised, n=200 CHF LVEF < 40% (E/C) 100/100; Age (E/C) 72 ± 6/ 72 ± 7yrs; M/F (E vs C) 44/56 vs 42/58; NYHA II/III 56/44 vs 47/53 ; aetiology: ischaemic cardiomyopathy 75/79, DCM 6/5, hypertension 17/14, unknown 2/2; atrial fibrillation 23/35; medication ACE inhibitors 84/79, diuretics 88/87, β-blockers 34/26, angiotensin II antagonists 13/8	8 week cardiac rehabilitation programme: 2 x exercise sessions per week for 8 weeks, then 1 x per week community-based for 16 weeks according to BACR guidelines, plus guidelines for 3 x per week home-based sessions	6-min walk distance, QoL via MLHFQ and EuroQoL, number and length of stay of hospital admissions	Significant improvement in 6-min walk distance (16%), MLFHQ and EuroQoL plus fewer admissions and days in hospital in exercise vs control At 5 yrs walk distance deteriorated significantly more in controls vs than exercise (-11% vs -5%). Improved MLFHQ score was sustained in both groups. No significant difference in survival or hospital admission
Beer et al (2008)	Hospital outpatient setting, Germany	RCT comparing exercise training with usual care	Randomised, n=24 CHF (E/C) 12/12; Age (E/C) 53 ± 12/58 ± 6 yrs; LVEF (E/C) 29 ± 10/25 ± 10%; aetiology: 100% DCM; medication (E/C) ACE inhibitors 12/11, digoxin 5/6, diuretics 10/10, β-blockers 9/9	5 x 45 min sessions per week for 2 months: cycle ergometer plus dynamic exercises @ 60-80% VO_{2peak}, RPE 13-15. Counselling to maintain activity in 6 month follow-up	CPET on cycle ergometer, magnetic resonance imaging (MRI), phosphorous-31 magnetic resonance spectroscopy (P-MRS)	Significant increase in VO_{2peak} (17%), VO_2 at VT (46%) at 8 months. LVESV and LVEF unchanged at 2 but improved at 8 months vs C. No change in RV parameters or LV energy metabolism
Braith et al (1999)	USA	RCT comparing exercise training with usual care	Randomised, n=69 CHF (E/C) 30/39; Age (E/C) 70 ± 5/70 ± 6 yrs; LVEF (E/C) 32 ± 9/30 ± 9 %; NYHA II/III/IV (E vs C) 15/15/0 vs 16/12/1; medication (E/C) ACE inhibitors 80/86 %, digoxin 70/72 %, diuretics 87/86 %, β-blockers 20/13 %, calcium channel blockers 30/21 %	3 x 60 min supervised sessions per week for 16 weeks. Walking & cycling 20-30 min @ 40-50% HRR, progressing to 30-40 min @ 60-70% HRR	Resting and peak exercise neurohormones (angiotensin II, aldosterone, vasopressin, atrial natriuretic peptide)	No change in resting or peak hormone levels in controls. No change in peak hormone levels in exercise group, but significant reduction in resting levels of angiotensin (-26%), aldosterone (-32%), vasopressin (-30%) and atrial natriuretic peptide (-27%)

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Bellardinelli et al (1995) Bellardinelli et al (1999)	Hopsital outpatient setting, Italy	RCT comparing exercise training with usual care	Randomised, n=55 CHF (E/C) 36/19; Age 55 ± 7 yrs; M/F 47/8; NYHA II/III 38/17, LVEF 27 ± 7%; aetiology: ischaemic 67%, DCM 33% ; medication ACE inhibitors 52, digitalis 18, diuretics 46, aspirin 18, warfarin 31 Randomised, n=99 CHF, completed n=94 (E/C) 48/46, Age (E/C) 56 ± 7/ 53 ± 9 yrs; M/F (E/C) 45/5 vs 43/6; NYHA II/III/IV (E/C) 22/18/10 vs 25/16/9, LVEF (E/C) 29 ± 6/ 28 ± 5 %; aetiology (E/C) ischaemic 43/41, DCM 7/8, hypertension 5/3, diabetes 2/3; medication (E/C) ACE inhibitors 90/88 %, digitalis 35/30 %, diuretics 92/90 %, warfarin 68/65 %	3 x 40 min sessions per week for 8 weeks on cycle ergometer @ 60% VO_{2peak} (preceded by 15-20 min warm up) Maintenance programme of 2 x 60 min sessions per week for 12 months	CPET on cycle ergometer (5W every 20 sec), echocardio-grpahy and radio-nuclide angiography Echocardiography (LV diameter, fractional shortening, EF), thallium activity score, QoL via MLHFQ	Significant improvements in functional capacity only in DCM patients with abnormal left ventricular relaxation. Improvement in VO_{2peak} significantly correlated with increase in peak early filling rate, peak filling rate and decrease in atrial filling rate. Improvements in VO_{2peak} (18%), VT (30%) thallium activity score (24%) and QoL in E vs C at 8 weeks and maintained at 12 months. Training associated with lower mortality and hospital admissions.
Brubaker et al (2009)	USA	Retrospective RCT comparing exercise training with usual care	Randomised, n=59 CHF (E/C) 30/29; Age (E/C) 61 ± 6/62 ± 7 yrs; LVEF (E/C) 30 ± 7/30 ± 7%; aetiology: 100% ischaemic; medication (E/C) ACE inhibitors 7/6, digitalis 8/8, diuretics 8/8, β-blockers 2/2	3 x 30-40 min sessions per week for 16 weeks (walking and cycling)	CPET (25W every 3 min), 6 min walk distance, echocardio-graphy (LV volumes, EF, diastolic filling), neurohormones, QoL via SF-36 and MLHFQ	Improvements in peak workload (12%), exercise duration (13%) and aldosterone in E vs C, but not VO_{2peak}, VT or VE/VCO_2 slope, QoL, echocardiographic measures or other neurohormones (inc BNP).

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Coats et al (1990) Coats et al (1992)	Home-based, UK	Cross over RCT comparing exercise training with exercise restriction	Randomised, n=11 male CHF ischaemic aetiology, age 63 ± 7 yrs; LVEF 19 ± 8 % Randomised, n=19 (completed n=17) male CHF ischaemic aetiology, NYHA II-III, age 62±2 yrs; LVEF 19±2%	5 x 20 min sessions per week for 8 weeks on cycle ergometer @ 60-80% HR_{max}	CPET on cycle ergometer (25W increments every 4 min). Haemodynamic measurements (2nd exercise test after 1 hour's rest), heart rate variability, nor-epinephrine spillover.	Improvement in VO_{2peak} and exercise duration (18%), V_E/VCO_2 slope, haemodynamics, autonomic function and symptomatic status
Conraads et al (2007)	Hospital Outpatient setting, Antwerp, Belgium	RCT comparing exercise training with usual care	Randomised, n=17 CRT CHF, (E/C) 8/9 (plus age-matched non-CRT CHF random-ised to E or C), male /female 8/9, age 59 ± 9 yrs		CPET on cycle ergometer, and circulatory power	Increase in VO_{2peak} and circulatory power significantly higher in E than C (40% vs 16% and 74% vs 32% respectively)
Demopoulos et al (1997)	New York, USA	Observational study of CHF pre and post exercise training	n=16 CHF, age 61 ± 2 yrs; M/F 9/7; NYHA II/III/IV 6/7/3, LVEF 21 ± 2%; aetiology (C/I) ischaemic/ DCM 7 /9, medication: ACE inhibitors 100%, diuretics 100%, digoxin=12	4 x 15-60 min sessions per week for 12 weeks (cycle @ 50% VO_{2peak}).	CPET on cycle ergometer ($10W.min^{-1}$) peak reactive hyperaemic calf/ forearm blood flow, LVEDV via echocardiography	Improvement in VO_{2peak} (22% after 6 weeks, further 7% at 12 weeks) and calf, but not forearm, reactive hyperaemia after training. No change in LVEDV
Dimopoulos et al (2006) Roditis et al (2006)	Athens, Greece	RCT parallel two-group study comparing continuous (C) to interval (I) training	Randomised, n=29 CHF, completed n=24 (C/I) 14/11, Age (C/I) 61 ± 10/62 ± 7 yrs; M/F (C vs I)14/0 vs 9/1; NYHA I/II/III 4/9/1 vs 3/6/1, LVEF (C/I) 31 ± 10/ 35 ± 11 %; aetiology (C/I) ischaemic 5/14, DCM 8/6, valvular 1/1; medication (C/I): ACE inhibitors 13/10, diuretics 11/10, digitalis 6/4, β-blockers 12/8	3 x 40 min sessions per week for 12 weeks. C: 50% peak work rate, increased by 5% every 4 weeks; I:30s @ 100% peak work rate, increased by 10% every 4 weeks, alternated with 30s rest	CPET on cycle ergometer, chronotropic response, heart rate recovery at 1 min VO_2 kinetics	Improvement in VO_{2peak} (C 6% ,I: 8%) and VT (C 10% ,I: 6%). Only C showed significant improvements in chronotropic response (26%) and heart rate recovery (61%) at 1 min. Significant increase in VO_{2peak} (C 9% I: 9%), phase I VO_2 kinetics in both C and I. Improvements in phase II kinetics in C only

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Dubach et al (1997)	Residential rehabilitation in the Alps, Switzerland	RCT comparing intensive exercise training with usual care 6 year follow-up	Randomised, n=25 male CHF NYHA II/III (E/C) 12/13; Age (E/C) 56 ± 5/ 55 ± 7 yrs; LVEF (E/C) 32 ± 7/33 ± 8 %; ischaemic aetiology 100%; medication (E/C) : ACE inhibitors 12/13, digoxin 8/7, diuretics 6/7 (E/C) 8/8	2 x 60 min supervised walking sessions per day plus 4 x 45 min sessions per week on cycle ergometer @ 70-80% HR_{max} for 8 weeks	VO_{2peak}, VT, haemodynamic measurements (measured during a 2nd exercise test on a seperate day), LV volume and mass via MRI	Improvement in VO_{2peak} (23%), exercise duration, peak workload and VT at 1 month. Further increase (VO_{2peak} 6%) at 2 months, increase in maximal cardiac output (14%) and a-vO_2 difference (13%) in E vs C. VO_{2peak} was 12% higher than pre-training at 6 year follow up in E vs no change in C. LV mass and volumes tended to decrease in E, but tended to increase in C after 6 years
Ennezat et al (2001)	New York	Parallel design with control group	n=14 CHF NYHA III (E/C) 10/4; age (E/C) 62 ± 6/66 ± 6 aetiology (E/C): ischaemic 6/4; DCM 4/2; LVEF 34 ± 9/27 ± 5 %; medication (E/C) : ACE inhibitors 100%, digoxin 35%, diuretics 100 %, β-blocker 57%	4 x 45 min cycle ergometer sessions per week for 12 weeks @ 50% VO_{2peak}	CPET on treadmill (modified Naughton protocol), muscle biopsies for analysis of endothelial nitric oxide synthase gene and shear stress regulated genes	No significant change in endothelial nitric oxide synthase gene expression. Significant increase in genes encoding antioxidant enzymes
Giannuzzi et al (2003) (ELVD-CHF)	Multicentre oupatient setting, Italy	Multicentre RCT comparing exercise training with usual care	n=90 CHF (E/C) 45/45, Age (E/C) 60 ± 7/ 61 ± 7 yrs; NYHA II/III (E/C) 28/17 vs 33/12, LVEF (E/C) 25 ± 4/ 25 ± 5%; aetiology (E/C) ischaemic 30/30, DCM 12/13, valvular heart disease 3/2, hypertension 30/27; medication (E/C): ACE inhibitors 41/42, diuretics 41/41, digitalis 30/31, β-blockers 10/9	3-5 x supervised cycle ergometer sessions @ 60% VO_{2peak}, plus home-based brisk daily walk > 30 min and intermittent 30 min calisthenics sessions for 6 months	CPET (10$W.min^{-1}$ increments), 6 min walk distance, 2D resting echocardiography, QoL	Significant decrease in EDV (5%) and ESV (9%) in E compared with increases of 6% and 7% respectively in C. Significant improvement in LVEF (16%), VT (17%) and VO_{2peak} (19%), 6 min walk distance (20%) and QoL in E, vs no change in C.

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Gottlieb et al (1999)	Medical Centre, Baltimore, USA	RCT comparing exercise training with usual care	Randomised, n=33 CHF, completed n=25 (E/C) 14/11 (plus 5 C who crossed over to exercise group), Age (E/C) 67 ± 7/64 ± 10 yrs; M/F (E/C) 11/0 vs 3/11; NYHA II/III (E/C) 5/6 vs 4/10, LVEF (E/C) 22 ± 8/ 25 ± 10 %; aetiology (E/C) ischaemic 7/11; medication: ACE inhibitors, diuretics, digoxin, β-blockers	3 sessions per week for 6 months on cycle ergometer and treadmill @ RPE 12-13	VO_{2peak}, 6 min walk distance, QoL via MLHFQ, Medical Outcomes Study and Functional Status Assessment	Improvement in VO_{2peak} (17%) and 6 min walk distance (15%) in exercise vs control. No change in QoL. 6 patients did not tolerate exercise training.
Hagerman et al (2005)	University outpatient setting, Stockholm, Sweden	Retrospecive long-term follow-up comparing exercise training with usual care	n=97 CHF (E/C) 48/49, M/F (E vs C) 28/20 vs 29/20; Age (E/C) 61 ± 9/ 61 ± 5 yrs NYHA II/III (E/C) 26/22 vs 28/21, LVEF (E/C) 28±9/30 ± 17%; aetiology ischaemic 20/28, DCM 27/14, valvular 1/5, hypertension 0/2; medic-ation (E/C): ACE inhibitors 39/29, diuretics 44/45, digitalis 17/14, β-blockers 19/30	3 sessions per week for 8 weeks. 6 & 3 min walk to warm up and cool down, plus 2 leg: 15 min simulataneous knee extensor exercise @ 70% peak; 1 leg: 1 leg at a time for 15 min each @ 35% 2 leg peak.	Mortality, hospitalisation events and days	Significantly fewer hospitalisation events and days due to cardiac events in training vs control at 5 year follow-up. No difference between groups in mortality.
Harris et al (2003)	Home-based, UK	RCT comparing cycle training with functional electrical stimulation	Randomised E1 (cycle) E2 (stimulation), n=49 CHF NYHA II-III (E1/E2) n=24/22; M/F (E1 vs E2) 21/3 vs 17/5, Age 62 ± 11/63 ± 10 yrs; LVEF (E1/E2) 32 ± 9/28 ± 6%; aetiology: ischaemic/DCM (E1 vs E2) 67/33 vs 59/41%; medication (E1/E2): ACE inhibitors 92/100%, diuretics 71/91%, digoxin 38/45%, β-blocker 38/41%	E1: home-based 5 x 30 min cycle ergometer sessions @ 70% HR_{max} for 6 weeks; E2: home-based 5 x 30 min functional electrical stimulation for 6 weeks	CPET on treadmill (modified Bruce), 6-min walk distance, maximum leg strength and quadriceps fatigue index, LVEF via echocardiography, QoL via MLHFQ,	Significant improvements in E1 and E2 (no difference between groups) in 6-min walk distance, treadmill exercise time, maximum leg strength, quadriceps fatigue index and QoL, but not VO_{2peak}.

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Hambrecht et al (1995)	University Cardiology inpatient setting followed by home-based training for 6 months, Germany	RCT comparing exercise training with usual care	Randomised, n=22 M CHF, completed n=18 (E/C) 12/10, Age (E/C) 50 ± 12/ 52 ± 8 yrs; NYHA II/III (E/C) 6/6 vs 6/4, LVEF (E/C) 26 ± 9/ 27 ± 10 %; aetiology (E/C) ischaemic 1/2, DCM 11/8; medication (E/C): ACE inhibitors 12/10, diuretics 10/9, digoxin 10/8, anti-arrhythmic 1/0, nitrates 2/3, calcium channel blockers 1/1	4-6 x 10 min sessions per day @ 70% VO_{2max} (cycle ergometer) for 2 weeks, then 20 min per day (home-based, cycle ergometer @ 70% VO_{2max}) plus 1 x 60 min supervised group sessions per week for 6 months	CPET on cycle ergometer (50W initially, then 25W every 3 min), haemodynamic measurement via thermodilution, muscle biopsy (vastus lateralis), 2-D echocardiography (LV volumes), Minnesota Leisure Time Physical Activity Questionnaire	Increase in VO_{2peak} (31%), VT (23%), oxidative capacity (19 & 41%), maximal cardiac output (19%), peak leg oxygen consumption (45%) and leisure time energy expenditure in E vs C. Compliance = 70% (~ 3 hrs training per week)
Hambrecht et al (1997)			"		Ultrastructural morphometry	Significant improvements in surface density of cytochrome c oxidase-positive mitochondria, mitochondrial cristae (41%) and inner border membrane (92%), and increase in type 1 fibres (8%) in E vs C
Hambrecht et al (1998)			Randomised, n=20 M CHF, completed n=18 (E/C) 10/10, Age (E/C) 54 ± 4/ 56 ± 3 yrs; NYHA II/III (E/C) 7/6 vs 3/4, LVEF (E/C) 24 ± 4/ 23 ± 3 %; aetiology (E/C) ischaemic 3/4, DCM 7/6; medication (E/C): ACE inhibitors 100/100%, diuretics 82/70 %, digoxin 73/70%		Peripheral blood flow (endothelium-dependent and independent arteriolar vasodilation, basal nitric oxide formation)	Increase in VO_{2peak} (26%) and endothelium dependent peripheral blood flow (187%) (with significant correlation between the two) in E vs C

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

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Hambrecht et al (2000)	University Cardiology inpatient setting followed by home-based training for 6 months, Germany	RCT comparing exercise training with usual care	Randomised, n=73 M CHF, completed n=64 (E/C) 36/37, Age (E/C) 54 ± 9/ 55 ± 8 yrs; NYHA I-II/III (E/C) 26/10 vs 28/9, LVEF (E/C) 27 ± 9/ 27 ± 9 %; aetiology (E/C) ischaemic 5/7, DCM 31/30; medication (E/C): ACE inhibitors 94/95%, diuretics 78/78 %, digoxin 76/62%, β-blocker 8/13%, calcium channel blocker 17/14%, anti-arrhythmic 6/8%	4-6 x 10 min sessions per day @ 70% VO_{2max} (cycle ergometer) for 2 weeks, then 20 min per day (home-based, cycle ergometer @ 70% VO_{2max}) plus 1 x 60 min supervised group sessions per week for 6 months	CPET on cycle ergometer (25W increments every 3 min), total peripheral resistance at rest and LV diameter (via thermodilution) and stroke volume during exercise	Increase in VO_{2peak} (26%), VT (33%), decrease in resting heart rate, increase in maximal heart rate, stroke volume (15%) and cardiac output (19%), small but significant decrease in LV diameters and volumes, decrease in total peripheral resistance at rest and peak exercise in E vs C
Gielen et al (2003)			Randomised, n=20 M CHF (E/C) 10/10, plus 10 age-matched healthy controls; Age (E/C) 55 ± 2/ 53 ± 3 yrs; NYHA II/III (E/C) 9/1 vs 9/1, LVEF (E/C) 26 ± 3/ 25 ± 2 %; aetiology (E/C) ischaemic and DCM; medication (E/C): ACE inhibitors 100/90%, diuretics 40/90 %, digitalis 50/50%, β-blockers 40%/40%		Serum markers of inflammation (TNF-α, IL-6, IL-1-β), local markers of inflammation via muscle biopsy (TNF-α, IL-6, IL-1-β and inducible nitric oxide synthase (iNOS).	Increase in VO_{2peak} (29%) & decrease in local TNF-α, IL-1-β and IL-6 (while no change in serum values), and iNOS in E vs C.
Linke et al (2001)			Randomised, n=22 M CHF (E/C) 11/11, NYHA II/III (E vs C) 8/3 vs 8/3; Age (E/C) 58 ± 2/ 59 ± 3 yrs; LVEF (E/C) 26 ± 3/24 ± 2 %; medication (E/C): ACE inhibitors 11/11, diuretics 9/7, digoxin 7/5, β-blockers 5/8	6 x 10 min sessions per day @ 70% VO_{2max} (cycle ergometer) for 4 weeks	Endothelial function (arterial diameter, flow-dependent vasodilation, endothelium-independent vasodilation)	Significant increase in endothelium-dependent vasodilation correlated with improvements in functional capacity in E vs C. No change in endothelium-independent vasodilation

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HF-ACTION: O'Connor et al (2009) Flynn et al (2009) Whellan (2007)	Multicentre outpatient setting (USA, Canada, France)	RCT comparing exercise training with usual care with intention-to-treat analysis	Randomised n=2331 CHF (E/C) n=1172/1159. Median age: 59 yrs; M/F 72/28%; ischaemic aetiology 51%; mean LVEF 25%	~ 3 supervised sessions per week (36 sessions total) within 6 months. Home-based training starting from session 18, and after session 36 comprising the primary setting 5 x per week. Walking or cycling @ 60% HRR for 15-30 min, increasing to 40 min @ 70% HRR, RPE 12-14	Primary endpoints: all-cause mortality and all-cause hospitalisation. Exercise tolerance (VO_{2peak} (treadmill: modified Naughton protocol, or cycle ergometer), heart rate at sub-maximal workload, 6-min walk distance), LVEF via echocardiography, QoL, cost-effective-ness, biomarkers (BNP, TNF, C-reactive protein)	At 30 months: non-significant reductions in all-cause mortality, hospitalisation & key secondary endpoints in E vs C. After adjustment for highly prognostic predictors of the primary end point (e.g. LVEF), training was associated with modest significant reductions for mortality & hospitalisation. Modest but significant improvements in self-reported health status in E vs C
Jetté et al (1991)	Hospital inpatient setting, Germany	RCT comparing exercise training with minimal activity	Randomised, n=39 male post anterior MI (< 10 weeks) CHF (NYHA I-III). E1 or C1: LVEF < 30% (10/8), E2 or C2: LVEF 31-50% (11/10), Age (E1/C1) 54 ± 6/ 51 ± 7 yrs (E2/C2) 46 ± 11/ 52 ± 7 yrs; medication (E1/C1/E2/C2) ACE inhibitors 2/2/0/1, diuretics 6/7/8/4, digitalis 7/6/5/4, β-blocker 3/3/8/5, calcium channel blocker 2/4/2/4, anti-arrhythmic 2/3/1/2	2 x 5 min jog 3 x per week, 30 min calisthenics, 20 min relaxation, 15 min cycle ergometry, walking 30-60 min @ 70-80% HR_{max} 5 days per week for 4 weeks	Supine cycle ergometer maximal exercise test (40W followed by 40W every 4 min), radionuclide ventriculography,	Increase in VO_{2peak} (22%) in LVEF < 30% in E vs C, but no difference in LVEF > 30% group. Associated increase in pulmonary wedge pressure in < 30% E group. Improvements in both < 30% groups in resting LVEF, not associated with exercise capacity.

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Jonsdottir et al (2006)	Hospital outpatient setting, Reykjavik, Iceland	RCT comparing exercise training with usual care	Randomised, n=43 NYHA II-III CHF (E/C) 15/14, M/F (E vs C) 18/4 vs 16/5, Age (E/C) 69 ± 5/ 68 ± 7 yrs; LVEF (E/C) 41 ± 14/ 42 ± 14 %; aetiology (E/C) ischaemic 16/18, AF 4/1, valvular 2/1, hypertension 0/1; medication (E/C): ACE inhibitors 5/8, diuretics 19/17, anti-arrhythmics 14/10, β-blockers 14/11, angiotensin II receptor blockers 10/13	2 x 50 min sessions per week for 5 months. 15 min cycling @ 50% peak work rate plus 20 min circuit resistance exercises @ 20-25% 1RM, increasing in intensity as appropriate.	CPET on cycle ergometer, muscle strength (1RM), plasma ANP & BNP, LVEF via echo-cardiography, QoL (country-specific questionnaire), hospitalisation @ 12 & 28 months' follow-up	Significant improvement in exercise duration and peak work rate (but not VO_{2peak}), and in 6-min walk distance and muscle strength in E vs C. No change or difference between groups in ANP, BNP, LVEF or QoL.
Karapolat et al (2009)	Turkey	RCT comparing hospital-based exercise training with home-based exercise training	Randomised n=74 CHF	E1: hospital-based exercise; E2 home-based exercise for 8 weeks	CPET, 6-min walk distance, QoL via Medical Outcomes Study and SF-36, haemodynamic parameters via echocardiography	Significant improvement in VO_{2peak}, 6-min walk distance, SF-36 subscale scores and LVEF, but no difference between groups
Kavanagh et al (1996)	Toronto, Canada	Non-randomised controlled trial with 12 month follow up	30 CHF (E/C) 21/9, completed (E) n=15, Age (E/C) 62 ± 6/ 65 ± 6 yrs, M/F (E vs C) 17/4 vs 8/1; NYHA II/III (E) 2/19; LVEF (E) 21 ± 2 %; aetiology (E) ischaemic 15, idiopathic cardiomyopathy 2, valvular 3, ethanol-related 1	5 x weekly supervised sessions (50-60% VO_{2peak}) for 16 weeks; then twice weekly for 20 weeks, once monthly for 16 weeks plus home based exercise to complete required 5 weekly sessions	CPET on cycle ergometer (17 $W.min^{-1}$ increments), 6-min walk distance, resting LVEF via radionuclide ventriculography, QoL at 4, 8, 12 , 16, 26 and 52 weeks.	No changes in C. Significant increase in E in LVEF (28%), 6 min walk distance (18% at 16 weeks and 52 weeks), VO_{2peak} (17% at 16 weeks, and at 52 weeks), VT (14% at 52 weeks), and improved QoL at 4 weeks, and further improvement up to 26 wks

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Keteyian et al (1996)	Outpatient clinic, Detroit, USA	RCT comparing exercise training with usual care	Randomised, n=40 M CHF, completed n=29 (E/C) 15/14, Age (E/C) 56 ± 12/ 52 ± 11 yrs; NYHA II/III (E/C) 9/5 vs 12/3, LVEF (E/C) 22 ± 6/ 23 ± 10 %; aetiology (E/C) ischaemic 3/6, DCM 11/9; medication (E/C): ACE inhibitors 14/14, diuretics 12/14, digoxin 13/14, β-blockers 2/0	3 x 33 min sessions per week for 24 weeks. 5 min warm-up and cool-down, 3 x 11 min treadmill, cycle/arm ergometer, rower @ 60-80% HRR, RPE 12-14.	CPET on cycle ergometer (25W every 3 min).	Improvement in VO_{2peak} (16%), exercise duration and peak power output and peak HR in exercise vs control. No change in VT or V_E/VCO_2 slope.
Keteyian et al (1999)			Randomised, n=51 male CHF, completed n=43 (E/C) 22/21, Age (E/C) 57 ± 12/ 55 ± 11 yrs; NYHA II/III (E/C) 16/6 vs 18/3, LVEF (E/C) 22 ± 7/ 22 ± 8 %; aetiology (E/C) ischaemic n=9/7, cardiomyopathy n=13/14; medication (E/C): ACE inhibitors n=21/20, diuretics n=18/19, digoxin n=20/19, β-blockers n=2/1		Chronotropic incompetence, plasma noradrenaline, QoL via MLHFQ	Improvement in VO_{2peak} (14%), exercise duration (24%), peak power output (21%) and peak HR (7%) inE vs C. No change in plasma norepinephrine at rest, submaximal or peak exercise, or in QoL
Klecha et al (2007)	Outpatient rehabilitation setting, Krakow, Poland	RCT comparing exercise training with usual care	Randomised, n=50 CHF (38 M/18 F) NYHA I/II/III, LVEF < 35% (E/C) 25/25; Age (E/C) 60 ± 10/ 61 ± 10 yrs; ischaemic aetiology (E/C) 96/92%; medication (E/C) : ACE inhibitors 100/100%, digitalis 36/32%, anti-arrhythmic 16/20%, diuretics 64%/68%, β-blocker 100/100%	3 x 60 min sessions per week for 6 months (20 min warm up, 25 min cycle ergometer @ 80% HR_{max}, including 4 x 3-min intervals, 15 min relaxation)	CPET on treadmill (modified Bruce protocol), MRI of left ventricle	Significant increase in VO_{2peak} (32%) and VT (24%) VE/VCO_2 slope in E vs C. No significant changes in LV parameters over time, but a tendency towards improved LVEF, EDV and wall motion score index in E whereas opposite trend in C

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Killavuori et al (1995)	Helsinki, Finland	RCT comparing exercise training with usual care	Randomised, n=20 CHF NYHA II-III (E/C) 8/12, M/F (E vs C) 8/0 vs 11/1, Age (E/C) 52 ± 8/ 52 ± 10 yrs; LVEF (E/C) 24 ± 6/24 ± 76%; aetiology (E/C) ischaemic 3/4, DCM 5/8; medication (E/C): ACE inhibitors 8/12, diuretics 7/10, digitalis 8/9, β-blockers 1/2	3 x 30 min per week supervised cycle ergometer sessions @ 50-60% VO_{2peak} for 3 months.	CPET on cycle ergometer (20W every 3 min) and constant load endurance test @ 85% VO_{2peak} , heart rate variability via 20 hr ambulatory ECG and frequency domain analysis	Significant increase in para-sympathetically mediated component of heart rate variability and in exercise endurance at 3 (88%) and 6 months (84%) in E vs C. Non-significant increase in VO_{2peak} (12%), significant increase in VT (21% and 17%), ventilatory response to exercise and maximum workload (18% and 16%) at 3 and 6 months. No change in central haemodynamic parameters. Increase in anaerobic glycolysis enzymes (PFK) (55%) in E vs C, but no change in citric acid cycle, fatty acid oxidation enzymes. or muscle fibre type distribution or size.
Killavuori et al (1996) and (2000)			Randomised, n=27 CHF NYHA II-III (E/C) 12/15, M/F (E vs C) 12/0 vs 14/1, Age (E/C) 52 ± 7/ 52 ± 9 yrs; LVEF (E/C) 24 ± 5/25 ± 7 %; aetiology (E/C) ischaemic 4/5, DCM 8/10; medication (E/C): ACE inhibitors 11/14, diuretics 11/11, digoxin 12/12, β-blockers 4/2	As above, plus supervised, plus home based exercise for a further 3 months	Haemodynamic measurements, muscle biopsy (muscle fibre distribution, glycolysis & fatty acid oxidation enzymes)	
Klecha et al (2007)	Outpatient rehabilitation setting, Krakow, Poland	RCT comparing exercise training with usual care	Randomised, n=50 CHF (38 M/18 F) NYHA I/II/III, LVEF < 35% (E/C) 25/25; Age (E/C) 60 ± 10/ 61 ± 10 yrs; ischaemic aetiology (E/C) 96/92%; medication (E/C) : ACE inhibitors 100/100%, digitalis 36/32%, anti-arrhythmic 16/20%, diuretics 64%/68%, β-blocker 100/100%	3 x 60 min sessions per week for 6 months (20 min warm up, 25 min cycle ergometer @ 80% HR_{max}, including 4 x 3-min intervals, 15 min relaxation)	CPET on treadmill (modified Bruce protocol), MRI of left ventricle	Significant increase in VO_{2peak} (32%) and VT (24%) VE/VCO_2 slope in E vs C. No significant changes in LV parameters over time, but a tendency towards improved LVEF, EDV and wall motion score index in E whereas opposite trend in C

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Kobayashi et al (2003)	Saitama, Japan	RCT comparing exercise training with usual care	Randomised, n=28 CHF NYHA II-III (E/C) 14/14, M/F (E vs C) 12/2 vs 8/6, Age (E/C) 55 ± 2/ 62 ± 2 yrs; LVEF (E/C) 29 ± 2/33 ± 2%; aetiology (E/C) ischaemic 8/5, DCM 9/6; medication (E/C): ACE inhibitor 13/10, β-blocker 10/7	2 x 15 min cycle ergometer sessions per day 2-3 x per week for 3 months @ VT HR	6-min walk distance, humoral factors (noradrenaline, endothelin-1, interleukin-6), endothelial function via flow-mediated vasodilation in upper and lower extremities	Significant increase in 6 min walk distance (14%) and lower limb (but not upper limb) flow-mediated vasodilation in E vs C. No change in humoral factors.
Larsen et al (2002)	Rehabilitation Centre, Norway	Prospective study to evaluate the effects of exercise training	n=15 CHF NYHA II-III; Age 69 ± 8 yrs; LVEF 33 ± 5 %; medication (E/C): ACE inhibitors 13, diuretics 13, digitalis 11	3 x 45 min sessions per week for 3 months, including 25 min aerobic exercise @ 80% max	CPET on cycle ergometer, 6-min walk distance, muscle biopsy, plasma cytokines (TNF-α, IL-8, IL-1)	Significant improvements in VO_{2peak} (11%) and 6 min walk distance (7%) from pre to post exercise, no change in LVEF, IL-6 or IL-8, and small non-significant decrease in TNF-α
Maiorana et al (2000)	Hospital outpatient setting, Perth, Australia	Crossover RCT comparing combined aerobic and resistance training with no formal exercise	Randomised, n=13 male CHF NYHA I-III, Age (mean ± SEM) 60 ± 2 yrs; LVEF 26 ± 3 %; aetiology: ischaemic 7, DCM 6; medication: ACE inhibitors 12, diuretics 6, digoxin 3, β-blockers 2, anti-arrhythmic 2	3 x 60 min sessions per week for 8 weeks. Circuit training (45s work): 7 resistance (55-65% MVC) and 8 aerobic cycle/tread- mill stations (70-85% HR_{peak})	CPET on cycle ergometer (20W every 32 min) and muscular strength (maximum voluntary contraction)	Significant improvements in maximum voluntary contraction, VO_{2peak} (13%), VT after exercise training compared to activity restriction
Malfatto et al (2002)	Hospital outpatient setting, Milan, Italy	Non-randomised controlled trial with 9 month follow up of sub-group	n=45 CHF (E/C 30/15) NYHA II/III. (11E completed further 6 months). M/F (E vs C) 26/4 vs 12/3 %, Age (E/C) 62 ± 7/ 60 ± 16 yrs; LVEF (E/C) 29 ± 7/31 ± 8 %; aetiology (E/C) ischaemic 16/8, idiopathic 14/7; medication ACE inhibitors 100/100%, digitalis 0/0 %, β-blockers 8/51%	5 x 60 min sessions per week for 3 months (calisthenics, treadmill, bike @ 40-50% VO_{2peak}). 6 months further home-based training 2-3 x per week	HR variability at rest (autoregressive power spectral density of RR intervals variability), CPET	Significant improvement in autonomic tone and reactivity to vagal and sympathetic stimuli after 3 months, with a further improvement at 9 months, accompanied by significant improvement in NYHA class and improved VO_{2peak} (20%)

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Malfatto et al (2009)	Hospital outpatient setting, Milan, Italy	RCT comparing exercise and usual care	n=54 CHF (E/C 27/27), NYHA II/III (E vs C) 18/9 vs 20/7; M/F 39/15; Age 65 ± 10 yrs; LVEF 32 ± 5 %; medication (E/C): ACE inhibitors 88/82%, β-blockers 81/79%, diuretics 67/71%	3 x 40 min sessions per week for 12 weeks (cycling/walking @ 60% VO_{2peak}).	LV diastolic stiffness assessed by Doppler echocardiography, CPET, BNP	Significant improvement in LV compliance (27%), reduction in BNP and improvement in exercise performance in E vs C
McKelvie et al (2002) EXERT Trial	Hospital and home-based training, Hamilton & Edmonton, Canada	RCT comparing exercise training with usual care	Randomised, n=181 CHF (E/C 90/91), completed 3 months n= 83, 12 months n=75, NYHA 1/II/III (EvsC) 2/67/31 vs 1/66/33, M/F (E vs C) 82/18 % vs 80/20 %, Age (E/C) 65 ± 1/ 66 ± 1 yrs; LVEF (E/C) 28 ± 1/28 ± 1 %; aetiology (E/C) ischaemic 79/73, hypertensive 7/6, valvular 5/4, idiopathic 6/13, other 6/4; medication (E/C): ACE inhibitors 91/92, diuretics 81/86, digoxin 62/66, β-blockers 23/20, calcium channel blocker 13/9	2 x 60 min supervised sessions per week (30 min cycle, treadmill, arm ergometry @ 60-70% HR_{max} and 30 min resistance @ 40-60% 1RM) plus 1 x 30 min home-based walk for 3 months; followed by 9 months' home-based training on cycle ergometer & free weights	6-min walk distance, CPET on cycle ergometer (17W every 2 min), dynamic muscle strength, cardiac funtion via radionuclide ventriculography, QoL via MLHFQ	Significant increase in 6-min walk distance in E and C at 3 and 12 months, but no between-group differences. Significant increase in VO_{2peak} at 3 months (10%) and 12 months (14%), and in strength (14-16% at 3 months, no further improvement at 12 months) in E vs C. No significant change in cardiac function or QoL.
Meyer et al (1996)	Hospital inpatient setting, Germany	Crossover RCT comparing combined aerobic and resistance training with usual care	Randomised, n=18 male CHF NYHA II/III (8/10), Age (mean ± SEM) 52 ± 2 yrs; LVEF 21 ± 2 %; aetiology: ischaemic 9, DCM; medication (E/C): ACE inhibitors 16, diuretics 16, digoxin/digitalis 14, β-blockers 7	5 x 15 min cycle ergometer (30s work @ 50% MSEC:60s @ 15W) 3 x 10 min treadmill (60s work: 60s low speed) 3 x 20 min flexibility/strength/ inspiratory exercises per week for 3 weeks	CPET on cycle ergometer (12.5 $W.min^{-1}$)	Significant improvement in VO_{2peak} (20%) & VT (24%) after exercise compared with activity restriction

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Meyer et al (2003) (a)	Hospital outpatient setting, Germany	RCT comparing exercise training with usual care	Randomised, n=54 CHF (E/C 26/28), NYHA II/III (E vs C) 19/7 vs 21/7, M/F (E vs C) 21/5 vs 23/5, Age (E/C) 59 ± 10/ 55 ± 9 yrs; LVEF (E/C) 30 ± 13/32 ± 15 %; aetiology (E/C) ischaemic 16/10, DCM 14/14; medication (E/C): ACE inhibitors 24/26, diuretics 24/24, digitalis 20/20, β-blockers 24/24	4 x 45 min cycle ergometer sessions per week for 12 weeks @ VT work rate	CPET on cycle ergometer (5-15 $W.min^{-1}$)	Significant improvement in VT (11.6%) and rightward shift in HR curve at same exercise workload in E vs C
Meyer et al (2003) (b)		Observational study of cardiac rehabilitation	n=51 CHF, NYHA I/II/III 3/26/22, M/F 43/8, Age 59 ± 11 yrs; LVEF (E/C) 30 ± 13/32 ± 15 %; aetiology: ischaemic 28, DCM 19, valvular heart disease 4; medication: ACE inhibitors, diuretics, β-blockers, angiotensin II inhibitors	3 sessions per week (30 min cycle ergometer interval training, 30-45 min calishenics/resitance plus respiratory training and 1 hour per week multidisciplinary education for 12 weeks	CPET on cycle ergometer (12.5 $W.min^{-1}$), 6 min walk distance, and QoL via SF-36 and MLHFQ	Significant improvement in VT (12%), VO_{2peak} (11%), SF-36 physical functioning, role physical and mental health and MLHFQ sum (29%) and physical scores (37%)
Myers et al (2007)	Residential rehabilitation in Switzerland	RCT comparing exercise training with usual care	Randomised, n=24 male post-MI CHF. Age (E/C) 56 ± 5/ 55 ± 7 yrs; LVEF (E/C) 32 ± 7/35 ± 4%; medication (E/C): ACE inhibitors 12/11, diuretics 6/6, digoxin 8/6	2 x 60 min supervised walking sessions per day plus 4 x 45 min on cycle ergometer per week @ 60-80% HRR for 8 weeks	CPET on cycle ergometer, lactate threshold, heart rate recovery	Improvement in VO_{2peak} (29%), lactate threshold (39%) and heart rate recovery in E vs C

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Nechwatal et al (2002)	Germany	RCT comparing interval and continuous training	Randomised E1 (continuous: n=20) E2 (interval n=20) E3 (control: n=10) CHF NYHA I-III ; LVEF (E1/E2/C) 27/29/27 %; aetiology: ischaemic/DCM, 9 evaluated for heart transplant	E1: 6 x 15 min cycle ergometer sessions @ 75% HR_{max} for 3 weeks; E2: 6 x 15 min cycle ergometer sessions with intervals @ 50% steep ramp workload for 3 weeks	CPET on cycle ergometer, haemodynamic measurements and QoL via SF-36	Significant increase in VO_{2peak} (E1: 14%; E2: 14%) and VT (E1: 9%; E2: 8%), but no difference between groups. No change in central haemodynamics in E1, but significant improvement in cardiac index, stroke volume index, and peripheral resistance. QoL improved significantly in both groups, but psychological sum factor improved more in E1.
Nilsson et al (2008) (a) Nilsson et al (2008) (b)	Hospital outpatient setting, Ullevaal, Norway	RCT comparing high intensity aerobic interval training with usual care Long-term follow-up	Randomised, n=80 CHF, completed n=76 (E/C) 38/38, Age (E/C) 69 ± 8/ 72 ± 8 yrs; M/F (E/C) 31/9 vs 32/8; NYHA II/III (E/C) 21/19 vs 26/16, LVEF (E/C) 31 ± 8/ 31 ± 9 %; aetiology (E/C) ischaemic 68/70%, cardiomyopathy 20/18%, hypertension 13/13% n=72 completed follow-up	2 x 50 min per week (32 sessions) for 24 weeks. Upper/lower body endurance and strength exercises including 3 x 5-10 min high intensity intervals @ RPE 15-18. After supervised programme, encouragement to follow local exercise classes and brisk walking	6-min walk distance, peak work rate on incremental cycle ergometer test (10 $W.min^{-1}$), QoL via MLHFQ	Significant improvements in E vs C for 6-min walk distance (+ 58 vs -15 m), peak work rate (+10 vs -1 W), exercise duration (+57 vs -8 s) and MLHFQ improvement (-11 vs +1 points). Significant inverse correlation between QoL and functional capacity. Significant improvements persisted in E vs C for 6-min walk distance, peak work rate exercise duration and MLHFQ
Owen and Croucher (2000)	Hospital outpatient setting, Canterbury, UK	Crossover RCT comparing exercise with usual care	Randomised, n=22 CHF, completed (E/C) n=15/9, Age 81 ± 4 yrs; M/F 75/25 %; LVEF < 40%; aetiology ischaemic 67%, DCM 33%, atrial fibrillation	1 x 60 min exercise class (circuit training alternating aerobic and resistance work @ ≤ 75% HR_{max}) per week for 12 weeks.	6-min walk distance, QoL via MLHFQ	Significant improvement in 6 min walk distance (20%), no change in MLHFQ following training

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Oka et al (2000)	Home-based setting, USA	RCT comparing home-based combined aerobic and resistance training with usual care	Randomised, n=40 CHF (E/C 20/20), aged 30-76 years, NYHA II/III (EvsC) 9/11 vs 16/4, M/F (E vs C) 17/3 vs 14/6, LVEF (E/C) 25 ± 9/22 ± 6 %; aetiology (E/C) ischaemic 8/6, DCM 6/7, hypertension 2/1, other 4/6; medication: ACE inhibitors 14/12, diuretics 19/19 digoxin 18/15, β-blockers 1/4, anti-arrhythmic 13/8	3 x 40-60 min walking at ≤ 70% peak HR plus 2 sessions total body unilateral resistance exercises @ 75% 1RM per week for 3 months	CPET on treadmill (modified Naughton protocol), QoL via Chronic Heart Failure Questionnaire	No change in exercise capacity. Significant improvement in fatigue, emotional functioning and sense of mastery in E vs C. Adherence to aerobic exercise was higher than to resistance, but adherence decreased to 75% at 3 months
Parnell et al (2002) Parnell et al (2005)	Melbourne, Australia	RCT comparing exercise training with usual care	Randomised, 21 CHF (E/C) 11/10, NYHA II/III (EvsC) 7/4 vs 7/3, M/F (E vs C) 10/1 vs 9/1, Age (E/C) 57 ± 15/ 53± 11 yrs; LVEF (E/C) 25 ± 2/24 ± 3 %; aetiology (E/C) ischaemic 2/4, DCM 9/6; medication (E/C): ACE inhibitors & diuretics 100/100 %, digoxin 45/90% β-blockers 72/80%	3 x 30 min sessions (walking, cycling, strength exercises) per week @ 50-60% HR_{max}, progressing to 5-7 x 60 min sessions for 8 weeks	6-min walk distance, QoL via MLHFQ, systemic arterial compliance (non-invasive applanation tonometry), LV function (2-D echocardiography) Forearm blood flow, endothelial function, L-arginine transport	Significant improvement in 6 min walk distance (15%), systemic arterial compliance (35%) and MLHFQ (-22 points) in E vs C. No change in LV dimensions/function. Significant increase in forearm blood flow, endothelial function, L-arginine transport
Passino et al (2006)	Hospital outpatient setting, Pisa, Italy, followed by home-based exercise	RCT comparing exercise with usual care	n=95 CHF (E/C) 47/48 completed 44/41. NYHA I/II/III (E vs C) 6/28/10 vs 8/23/10, M/F 39/5 vs 35/6, Age 60 ± 2/61± 2 yrs; LVEF (E/C) 35 ± 2/32 ± 2 %; aetiology (E/C): ischaemic 27/23, idiopathic DCM 27/23, atrial fibrillation 3/2; medication (E/C): ACE inhibitors 78/79 %, diuretics 82/85 %, β-blockers 72/73 %, angiotensin receptor blockers 7/5%	30 min cycling @ 60% HR_{peak} at least 3 days per week for 9 months	CPET on cycle ergometer ($10.W.min^{-1}$) QoL via MLHFQ, BNP, NT-pro BNP, catecholamines, plasma renin activity, aldosterone	Significant improvement in VO_{2peak} (13%), peak work rate (14%), LVEF (9%), QoL (-22 points), BNP (-34%), NT-pro BNP (-32%), noradrenaline (-26%) inE vs C. No change in plasma renin activity, aldosterone or V_E/VCO_2 slope.

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Patwala et al (2009)	University exercise setting, Liverpool, UK	RCT comparing exercise with usual care in CRT CHF	n=50 CHF (E/C) 25/25, NYHA III-IV, male/female 92/8%, Age 64.4 yrs, LVEF 24 %, atrial fibrillation 34%; medication (E/C): ACE inhibitors or angiotensin receptor blockers 98%, diuretics 96 %, β-blockers 60%	Exercise training commenced 3 months post CRT. 3 x 30 min sessions per week. 10 min treadmill, 10 min cycle, 10 min treadmill @ 80%-90% HR_{peak}	Measurements taken at pre-CRT, 3 and 6 months post CRT. CPET (modified Bruce treadmill protocol), resting/peak cardiac output via rebreathing, resting echochardiography, isokinetic dynamometry QoL via MLHFQ	Significantly greater further improvements in VO_{2peak} (7%), MLHFQ (-9 points), peak skeletal muscle torque, peak cardiac power output and reserve, and ejection fraction (14%) in E vs C
Prescott et al (2009)	Copenhagen, Denmark	Observational study measuring effect of exercise training in older CHF	n=52 CHF, 41 M, 11 F, mean age 68 ± 11 yrs, LVEF 31 ± 9% , NYHA II/III, medication: ACE inhibitor or angiotensin receptor blocker 98%, β-blocker 88%	2 x 60-90 min sessions (15-20 min warm up, 4 x 6 min walking, cycling, stepping @ 70-80% VO_{2peak}, 3 x 20 arm/leg resistance exercises) per week for 8 weeks	6-min walk distance, incremental shuttle walk test, glycemic control, inflammatory/ endothelial function, NT-proBNP, QoL via MLHFQ	Significant improvement in measures of physical fitness (5-7%), but no change in any other measures.
Quittan et al (1999)	Austria	RCT comparing exercise with usual care	Randomised, n=25 CHF, mean age 55 yrs; M/F 23/2 vs 32/8; NYHA II/III, LVEF 18.1 ±8.0% %; aetiology: 100% DCM	2-3 x 60 min sessions (cycling, stepping @ 50% VO_{2max}) per week for 12 weeks	CPET & QoL via SF-36	Significant improvement in QoL (physical and social functioning, role-physical, vitality) and VO_{2peak}. Improvements not correlated
Roveda et al (2003)	Hospital Outpatient Setting, Sao Paulo, Brazil	RCT comparing exercise with usual care	n=16 CHF NYHA II-III (53 ± 9 yrs) (E/C) 7/9 plus 8 healthy controls (46 ± 5 yrs). M/F (E vs C) 5/2 vs 6/3; LVEF (E/C) 35 ± 3/35 ± 3 %; aetiology (E/C): ischaemic 1/0, idiopathic DCM 5/5, chagas disease 1/4; medication (E/C): ACE inhibitors 7/9, diuretics 5/5, digoxin 7/9	3 x 60 min sessions per week for 4 months, including 25-40 cycling @ 10% below respiratory compensation point plus 10 min strength exercises.	CPET on cycle ergometer, forearm blood flow via venous plethys-mography, muscle sympathetic nerve activity, LVEF via 2-D echocardiography	Significant increase in VO_{2peak} (39%) and forearm blood flow (76%), but not LVEF in E vs C. Significant decrease (35%) in muscle sympathetic nerve activity, to levels comparable to healthy controls.

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Roveda group de Mello Franco et al (2006) *(follow-up to Roveda et al, 2003)* Fraga et al (2007)	Hospital Outpatient Setting, Sao Paulo, Brazil	RCT comparing home-based exercise (following supervised exercise training) with usual care sub-study on CHF taking β-blockers	n=29 NYHA II - III CHF (E/C) 17/12 (E only followed up at 8 months n=12); Age 56 ± 3/52 ± 2 yrs; M/F 13/4 vs 9/3; LVEF 29 ± 2/37 ± 3 %; aetiology: ischaemic 5/1, idiopathic DCM 3/5, chagas disease 4/2, hypertensive 5/4; medication (E/C): ACE inhibitors/angiotensin receptor blockers 17/12, diuretics 14/1, digoxin 8/9, β-blockers 15/11 n=27 (carvedilol 15/12)	3 x 60 min supervised sessions per week for 4 months, including 25-40 min cycling @ 10% below respiratory compensation point plus 10 min strength exercises, followed by 4 months' home-based training of equal frequency and intensity (HR) Supervised training for 4 months only	CPET on cycle ergometer, forearm blood flow via venous plethysmo-graphy, muscle sympathetic nerve activity (MSNA), LVEF via 2-D echocardiography, QoL via MLFHQ	After home-based training reduction in forearm vascular resistance and QoL were maintained. Improvements in VO_{2peak} and muscle sympathetic nerve activity were not Significant improvement in VO_{2peak} (21%), forearm blood flow and MSNA in E vs C
Smart et al (2006)	Brisbane, Australia	Prospective study following a single group pre and post training	n=37 CHF; M/F 35/2; age 63 ± 9 yrs; NYHA II/III 8/29; LVEF 29 ± 9%; ischaemic 25, DCM 8, viral/alcoholic DCM 4; medication: ACE inhibitors 36, diuretics 31, digoxin 13, β-blocker 34	3 x sessions per week (cycle ergometer @ 60-70% VO_{2peak}, plus strength exercises from weeks 8-16) for 16 weeks	CPET on cycle ergometer ($10.W.min^{-1}$) resting/peak LVEF via tissue doppler echocardiography	VO_{2peak} increased at 8 (8%) and 16 weeks (21%), and this improvement was related to myocardial function at baseline.
Stolen et al (2003)	Finland	Non RCT comparing exercise with usual care	n=20 CHF (E/C) 9/11 NYHA (E/C) 1.6/1.2, M/F (E vs C) 7/2 vs 7/0, Age 55 ± 8/ 55 ± 8 yrs; LVEF (E/C) 33 ± 8/35 ± 7 %; aetiology: idiopathic DCM; medication: ACE inhibitors 78/86 %, diuretics 33/14 %, digoxin 33/29% , β-blockers 78/100 %	3 x 45 min sessions per week for 5 months @ 50-70% VO_{2peak}, plus twice weekly resistance training starting after 4 weeks.	CPET (cycle), LV function via 2-D echocardiography, myocardial perfusion and oxidative metabolism via positron emission tomography	Significant increase in VO_{2peak} (27%), and stroke volume (11%), LVEF (16%), LVESD and myocardial work efficiency, plus reduction in basal myocardial perfusion, RV and LV oxidative metabolism (10%) in E vs C

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Sullivan et al (1988 & 1989)	Outpatient rehabilitation clinic, The Netherlands	Prospective study following a single group pre and post training	n=16 CHF, completed n=12, age 57 ± 10 yrs; NYHA I-III (mean 2.4 ± 0.6), LVEF 24 ± 10%; medication: ACE inhibitors 4, diuretics 12, digoxin 11	3-5 hr per week supervised training @ 75% VO_{2peak} (cycling, stair climbing, walking/jogging) for 16-24 weeks	CPET on cycle ergometer, constant load test @ ~ 80% peak workload, haemodynamic measurements	Significant increase in VO_{2peak} (23%), VT (20%), peak leg blood flow (20%), peak central aterio-venous oxygen difference (11%), and submaximal exercise performance, but not central haemodynamic measures
Taylor et al (1999)	Hospital outpatient setting, London	Randomised crossover study comparing exercise with a control period	n=8 M CHF, NYHA II-III, ischaemic aetiology n=6	3 sessions per week for 8 weeks. Warm up, ≤ 30 min cycling @ 45-70% VO_{2peak})	Treadmill exercise tolerance test, blood flow via venous occlusion plethysmography	Significant increase in exercise capacity from 3.4 to 4 METS, non-significant improvements in blood flow, but benefits lost after 2 months' cessation of exercise
Tyni-Lenné et al (1996) and Gordon et al (1996)	Hospital outpatient setting, Huddinge, Sweden	RCT comparing one and two legged exercise with usual care	Randomised, n=21 M CHF, NYHA II/III, mean age 60 yrs (range 43-73), LVEF 28 ± 11 %, aetiology: ischaemic 12, DCM 9, medication: ACE inhibitors 19, diuretics 21, digoxin 9, β-blockers 10	3 sessions per week for 8 weeks. 6 & 3 min walk to warm up and cool down, plus 2 leg: 15 min simultaneous knee extensor exercise @ 70% peak; 1 leg: 1 leg at a time for 15 min each @ 35% 2 leg peak.	CPET on cycle ergometer (10 $W.min^{-1}$), 6-min walk distance, QoL via Sickness Impact Profile and Sense of Coherence Scale, muscle strength and muscle biopsy for citrate synthase	Significant increase in 6-min walk distance in 2 and 1 legged (12% and 5%) compared with C, and in QoL (improvements in 2 legged > 1 legged), but not in VO_{2peak} (+3-4%). Significant increase in strength (16%) in 2 legged, and in citrate synthase activity (35%) in 1/2 leg vs C.
Tyni-Lenné et al (1997)		Crossover RCT comparing exercise with usual care	Randomised, n=16 female CHF, NYHA II/III, mean age 63 ± 10 yrs , LVEF 28-30 %, aetiology: ischaemic 11, DCM 5, medication: ACE inhibitors 12, diuretics 13, digoxin 4, β-blockers 8, calcium antagonists 2	3 x 15 min knee extensor exercise (@ 65-75% peak) sessions per week for 8 weeks. 6 & 3 min walk to warm up and cool down		Significant increase in citrate synthase (44%), lactate dehydrogenase (23%), oxidative vs glycolytic capacity (23%), and in VO_{2peak} (14%), 6-min walk distance and QoL

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Van den Berg-Emons et al (2004)	Rotterdam, The Netherlands	RCT comparing exercise training with usual care	Randomised, n=34 CHF (E/C) 18/16; Age 59±12/59± 11 yrs; M/F (E/C) 12/6 vs 13/3; NYHA II/III (E/C) 10/8 vs 10/6; LVEF 24 ± 9/28 ± 6 %; aetiology (E/C) ischaemic 6/8, idiopathic DCM 11/6, hypertension 0/1, valvular disease 1/1	2 x 1 hour exercise classes per week for 3 months (cycling, walking and games @ 60% HRR)	CPET on cycle ergo-meter (10 $W.min^{-1}$), 6-min walk distance, muscle strength, daily activity (accelerometry) QoL via MLHFQ, Medical Psychological Questionnaire for heart patients, Hospital Anxiety and Depression Scale.	No significant difference in changes between E and C for daily activity or QoL. Mean improvements in peak power, 6-min walk distance, extension and flexion peak torque and depression > in E vs C. Significant correlation between VO_{2peak} and daily activity.
Van Laetham (2007)	Belgium	Observational study measuring changes after cardiac rehabilitation	n=35 CHF, NYHA II-III, M/F 26/9, Age 54 ± 9 yrs; LVEF 31 ± 10%; aetiology: ischaemic 23, DCM 12; medication: ACE inhibitor 33, diuretics 15, digoxin 7, β-blocker 32; ICD 3, atrial fibrillation/flutter 2	2 x 1 hour circuit training sessions (including 25 min total time on aerobic exercises @ 70-85% HR_{peak}, alternated with muscles strengthening exercises) per week for 6 months (40 sessions)	CPET on cycle ergometer (25 W initial load, 10 $W.min^{-1}$ increments), oxygen uptake efficiency slope (OUES), 6 min walk distance	Significant increase in VO_{2peak} (18%), peak work rate (24%), VT (20%), OUES (14%), 6 min walk distance and decrease in V_E/VCO_2 slope (6%) after 3 months. Improvements in OUES best correlated with improvements in VO_{2peak}. At 6 months further improvement in VT, peak work rate & 6 min walk.
Wielenga et al (1998) Wielenga et al (1999)	Outpatient rehabilitation clinic, The Netherlands	RCT comparing exercise training with usual care	n=67 M ischaemic and DCM CHF NYHA II-III, mean age 64 yrs, LVEF < 40% Randomised, n=80 CHF, completed n= 67 (E/C) 35/32; Age 63±2/65±1 yrs; NYHA II/III (E/C) 26/9 vs 19/13; LVEF 30±2/25±2 %; aetiology ischaemic 14/13, DCM 21/19; ACE inhibitors 26/25, diuretics 30/27, digoxin 27/23, β-blockers 2/1	3 x 45 min sessions per week for 12 weeks (10 min walking, cycling, ball games @ 60% HRR, separated by 5 min rest)	CPET (modified Naughton protocol) QoL via Heart Patients Psychological Questionnaire/Self-awareness of general well-being test	Significant improvements in exercise capacity and QoL in both older (> 65 yrs) and younger (< 65 yrs) CHF No significant improvement in VO_{2peak} in E (10%) vs C (5%), despite increase in exercise duration (24% vs 1%), VT (15% vs 5%), submaximal V_E/VCO_2 & QoL

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Willenheimer et al (1998)	Malmo, Sweden	RCT comparing exercise training with usual care	Randomised, n=54 CHF, completed n= 49 (E/C) 26/23 ; Age (E/C) 64 ± 9/ 64 ± 5 yrs; NYHA I/ II/III (E/C) 3/8/16 vs 3/11/8; LVEF (E/C) 36 ±11/35 ±11 %; ischaemic aetiology 78/73; medication: ACE inhibitors 100/100 %, diuretics 93/95 %, digitalis 30/50%	3 x 15-45 min sessions per week interval training (90s @ 80% VO_{2peak} HR ± 5 beats.min$^{-1,}$ or RPE 15, for as long as possible, 30s rest) for 16 weeks	CPET on cycle ergometer (30W start, 10 W.min^{-1} increments), LV function via echocardiography, dyspnea-fatigue index, QoL and habitual physical activity	No significant improvement in VO_{2peak} or VT in E (5%) vs C, despite significant increase in exercise duration (7W, 6%) and global QoL. Greater improvement in M (n=11) with ischaemic vs non-ischaemic aetiology and F.
Wisloff et al (2007)	Hospital outpatient setting, Trondheim, Norway	RCT comparing aerobic interval training (E1) with moderate continuous training (E2) and usual care (C)	Randomised, n=27 post-infarction CHF LVEF < 40%, (E1/E2/C) n=9/9/9; Age (E1/E2/C) 76 ± 13/ 74 ± 12/77 ± 9 yrs; M/F (E1/E2/C) 6/3 vs 7/2 vs 7/2; BMI (E1/E2/C) 26 ± 2/25 ± 3/25 ± 3 kg/m^2; medication: ACE inhibitors 100% patients, diuretics n=5/4/5, β-blockers 100%	2 x supervised treadmill sessions plus 1 home-based session per week for 12 weeks. E1: 4 x 4 min intervals @ 90-95% HR_{max} interspersed with 3 min recovery @ 50-70% HR_{max}: total 38 min. E2: 47 min @ 70-75% HR_{max}. Isocaloric.	CPET on treadmill, endothelial function via ultrasound, LV function via echocardiography, skeletal muscle function via muscle biopsy, QoL via MacNew Questionnaire	Significantly greater improvement in endothelial function and VO_{2peak} in E1 interval (46%) vs E2 continuous group (14%). Decreased LVESV (18%) and EDV (25%), increased LVEF (35%), decreased BNP (40%) and improved mitochondrial function in E1 only. QoL improved in E1 and E2. No changes in C
Witham et al (2005) and (2007)	Hospital outpatient setting, Dundee, Scotland	RCT comparing seated exercise with usual care (plus long-term follow-up)	Randomised, n=82 CHF, completed n=68 (E/C) 36/32. Age (E/C) 80 ± 6 /81 ± 4 yrs; M (E/C) 63%/46%; NYHA II/III (E/C) 25 vs 16/ 21 vs 20; ischaemic aetiology (E/C) 76%/56%; BMI (E/C) 26±4/26±5 kg/m^2; sinus rhythm/atrial fibrillation (E/C) 36 vs 5/33 vs 8	0-3 months: twice weekly supervised sessions. Warm-up, 20 min upper/lower limb exercise, whole body aerobic movements RPE 11-13, cool-down. Wrist/ankle weights for progression. 3-6 month home-based: same exercises 2-3 x per week	6-min walk distance, physical activity via accelerometry, Guyatt CHF questionnaire, Hospital Anxiety and Depression score, Philadelphia Geriatric Morale Scale at 3 & 6 months and follow-up (mean 19 months)	No improvement in 6-min walk distance (or difference between E and C). Significant increase in physical activity in E vs C at 6 months only. No significant differences in health-related QoL or psychological status. No significant differences between E and C at long-term follow-up.

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Table A2: Summary of combined aerobic and resistance exercise training studies in CHF

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Beckers et al (2008)	Hospital outpatient setting, Antwerp, Belgium	RCT comparing combined aerobic (CT) and resistance training with endurance training (ET)	Randomised, n=58 CHF (CT/ET) 28/30. Age 58±11 /59±11 yrs; M/F (CT vs ET) 18/10 vs 24/6; NYHA II/III (CT/ET) 9/19 vs 12/18; LVEF 26±7%/23±9% ischaemic aetiology (CT/ET) 16/18, idiopathic DCM 18/12; medication (CT/ET): ACE inhibitors 96/100%, diuretics 85/70%, digoxin 39/30%, β-blockers 57/90%	3 x 1 hour sessions per week for 6 months. CT: month 0-2: 10 min endurance (90% HR @ respiratory compensation point) plus 40 min resistance work @ 50-60% 1RM; month 2-4: 2 x 8 min endurance, 30 min resistance. month 4-6: 3 x 15 min endurance/10 min resistance. ET: 5 x 8 min treadmill, cycle, stair, step, arm ergometer, increasing to 3 x 15 min, with 2 min recovery 3 x 1 hour sessions per week (10 min endurance plus 40 min resistance for 2 months, then 25 min endurance plus 25 min resistance for 2 months)	CPET on cycle ergo-meter (10-20 $W.min^{-1}$), LV dimensions via 2-D echocardiography, LVEF via radionuclide ventriculography, muscular strength and endurance via1RM and linear isokinetic measurements, QoL via Health Complaints Scale CPET on treadmill, NT-pro BNP, resting echocardiography (M mode and tissue doppler)	CT more effective than ET at improving strength, submaximal exercise performance and QoL, whereas maximal exercise capacity improved to the same extent in CT and ET (5-11%), as did LVEF (10-25%). No change in LV volumes or BNP. Significant improvement (-23%) in NT-proBNP, LV end systolic diameter (-9%), A wave and E/A ratio (reflecting LVED pressure and filling pressures), and VO_{2peak} (11%), VT (13%) and $Watt_{max}/VO_{2peak}$ (27%) in E vs C
Conraads et al (2004)		Non-randomised combined endurance & resistance training with untrained control group	n=49 CHF (controls unable to attend exercise) (E/C) 27/22. Age (E/C) 59 ± 2 /59 ± 2 yrs; male/female (E vs C) 21/6 vs 15/7; NYHA II/III (E/C) 6/21 vs 10/12; LVEF (E/C) 26 ± 1%/ 26 ± 1%; aetiology (E/C) ischaemic 19/6, idiopathic 8/6; medication: ACE inhibitors 26/21, diuretics 20/17, digoxin 10/9, β-blockers 16/14			

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Feiereisen et al (2007)		RCT comparing exclusive strength training (ST) with traditional endurance training (ET) and combined endurance and resistance training (CT)	Randomised, n=45 CHF NYHA II-III, (ST/ET/CT) n=15/15/15, plus control group (con) n=15; Age (ST/ET/CT/con) 59 ± 7/ 61 ± 6/58 ± 6/56 ± 8 yrs; M/F (ST/ET/CT/con) 11/4 vs 13/2 vs 14/1 vs 13/2; ischaemic/non-ischaemic aetiology (ST/ET/CT/con) 7/8 vs 7/8 vs 8/7 vs 9/6	3 sessions per week for 3 months. ST: 10 resistance machine exercises @ 60-70% 1RM, 2 min recovery phases; ET: 20 cycle and 20 min treadmill 60% - 75% VO_{2peak}; CT 20 min cycle (60-75% VO_{2peak}) , 5 resistance machine exercises (60-70% 1RM)	CPET on cycle ergometer, isokinetic strength test, thigh muscle volume via CT scan, LV function via radionuclide ventriculography, QoL via MLHFQ	Significant improvement in VO_{2peak}, peak workload, thigh muscle volume and knee extensor endurance in the ST, EC and CT compared to control. No differences between training modalities. Knee extensor strength, LVEF and cardiac function improved in ST, EC and CT more than control, but not statistical ly significant
Haykowsky et al (2005)	Edmonton, Canada	RCT comparing aerobic training (E1) with combined aerobic and strength training (E2) for 3 months supervised and 3 months unsupervised	Randomised, n=20 female CHF (E/C) 10/10. Age 72 ± 8 yrs	E1: 2 aerobic sessions (@ 60-70%) HRR per week for 3 months, then 3 months unsupervised sessions @ RPE 12-14. E2: Same as E1 plus additional 1-2 sets low-moderate strength training 2 x per week.	CPET, muscle strength, QoL	Significant increase in VO_{2peak} (12%) and leg strength (13%) in E1 and E2 after supervised training, but this returned to baseline after unsupervised training period. Upper body strength increased (23%) after supervised training in E2 only. No change in QoL
Mandic et al (2009)	Cardiac rehabilitation centre, Alberta, Canada	RCT comparing combined aerobic and resistance training (E1) with aerobic training (E2) and usual care (C)	Randomised, n=42 CHF, (E1/E2/C) n=14/15/13; Age 63±1/59 ±11/62±13 yrs; M/F (E1/E2/C) 11/3 vs 11/4 vs 10/3; LVEF (E1/E2/C) 30 ± 11/34 ± 14/29 ± 11 %; ischaemic/non-ischaemic aetiology (E1/E2/C) 7/7 vs 8/7 vs 4/9	E1: 15 min treadmill + 15 min arm/leg ergometer @ 50-70% HRR plus 1-2 sets 10-15 reps of 6 upper and lower body resistance exercises @50-70% 1RM E2: 15 min treadmill + 15 min cycle ergometer @ 50-70% HRR	CPET on cycle ergometer (increments 15W every 2 min), LV systolic function via 2-D echocardiography, muscular strength/ endurance using 1RM, QoL via MLHFQ and MacNew Heart Disease Questionnisaire	Intention-to-treat analysis: no change in VO_{2peak}, systolic function or QoL in E1 or E2 vs C. Combined training (E1) improved upper extremity muscular strength and endurance vs aerobic training (E2) or C. In compliant participants (> 80% sessions) VO_{2peak} & QoL increased in E2 vs E1 and C.

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

Study	Setting	Design	Sample	Exercise Intervention	Outcome Variables	Results
Miche et al (2009)	Hospital inpatient setting, Germany	Longitudinal study measuring improvements in quality of life after cardiac rehabilitation	n=116 CHF, NYHA I-III, Group 1 > 70 yrs; Group 2 < 70 yrs; Age (1/2) 74 ± 3/ 61 ± 6 yrs; LVEF (1/2) 34 ± 6/33 ± 8%; aetiology (1/2): ischaemic 76/77 %, DCM 11/20%, valvular 13/3%; medication (1/2): ACE inhibitors 65/73%, diuretics 67/54%, digoxin 13/31%, β-blockers 72/70%	3 x 15-20 min supervised cycle ergometer sessions (60-80% VO_{2peak}) 2-3 strength training sessions per week for 4 weeks	CPET on cycle ergometer (25W, then 10W every 1-2 min), 6 min walk test, QoL via SF-36, Hospital Anxiety & Depression Scale (HADS) @ 4 weeks and 6 months' follow-up	Improvement in VO_{2peak} in both groups at 4 weeks (> 70 yrs: 10%, < 70 yrs: 17%), further improvement at 6 months in > 70 yrs only (13%). Improved LVEF, LVESV and LVEDV, 6-min walk distance and QoL. In > 70 yrs QoL improvements not maintained at 6 months.
Sabelis et al (2004)	Hospital outpatient setting, The Netherlands	RCT comparing exercise with usual care	Randomised n=77 CHF NYHA II-III LVEF < 35% age 40-70 years, completed n=61 (E/C) 36/25; male/female (E vs C) 25/11 vs 20/5 ; aetiology (E/C): ischaemic 53/52 %, dilated 47/48%; medication (E/C): ACE inhibitors 75/84%, diuretics 53/60%, digoxin 13/31%, β-blockers 50/52%	2 x 60 min supervised sessions per week (warm-up, interval training 30s work @ 50% steep test max/60s recovery plus strength and endurance exercises @ 70% steep test HR_{max}) and 2 x 11 min home-based strength and endurance sessions for 6 months	CPET on cycle ergometer (20W every 3 min), insulin sensitivity (euglycaemic hyperinsulinaemic clamp)	Significant increase in VO_{2peak} (6%) in E vs C. No significant effect of training on insulin sensitivity, although change in insulin sensitivity correlated positively with change in VO_{2peak}

Abbreviations: ACE angiotensin converting enzyme; BMI body mass index; BNP B-type natriuretic peptide; CPET cardiopulmonary exercise test; C control group; E exercise group; DCM dilated cardiomyopathy; EDV end diastolic volume; ESV end systolic volume; HR heart rate; LVEF left ventricular ejection fraction; M/F male/female MLHFQ Minnesota Living with Heart Failure Questionnaire; NT-BNP N terminal b-type natriuretic peptide; NYHA New York Heart Association; QoL quality of life; RCT randomised controlled trial; RV right ventricular; SF-36 Short-Form 36 Questionnaire; VO_{2peak} peak oxygen uptake; VT ventilatory threshold, 1RM 1 repetition maximum

APPENDIX 2: OUTCOME MEASURES NOT USED IN THIS THESIS

6 minute walk test (6MWT)

The 6MWT is widely used as a measure of functional capacity in elderly patients with CHF, and is useful for prognosis, when the "gold standard" cardiopulmonary exercise test is not feasible (Ingle et al., 2007). Although it is simple to administer and does not require expensive equipment, it does take 6 minutes to administer. It is not appropriate for patients with orthopaedic limitation, and is influenced by patient motivation. Furthermore, the validity of this test to determine functional capacity in older CHF has been questioned (Maldonado-Martin et al., 2006). In the experiments in this thesis, cardiopulmonary exercise testing was the main outcome measure. It was not considered appropriate to burden the experimenter or participants with this extra test.

Oxygen uptake efficiency slope

The oxygen uptake efficiency slope (OUES) is a non-linear description of the ventilatory response to incremental exercise. It describes the relationship between VO_2 and V_E via a logarithmic transformation of V_E, thus representing the absolute rate of increase in VO_2 per 10-fold increase in V_E. It is reduced in CHF due to a combination of gas exchange, metabolic and ergoreflex abnormalities. Lower values are associated with worsening symptoms, and it is a good prognostic indicator (Davies et al., 2006). The authors speculate that its prognostic value is improved as its calculation separates the exercise-induced changes in ventilation from any hyperventilation at rest. The OUES from the first 50% or maximal cardiopulmonary exercise test data does not vary (< 1%) from data from whole test. This measurement is therefore considered most useful for risk assessment in patients who are unable to perform maximal cardiopulmonary exercise testing. In the experiments in this thesis, maximal cardiopulmonary exercise data collection was achieved for the majority of patients, and VE/VCO_2 slope was used as a measure of ventilatory efficiency.

APPENDIX 3: LOCAL RESEARCH ETHICS COMMITTEE APPROVAL

Brighton and Mid Sussex Research Ethics Committee
East Sussex Research Ethics Committee

Brighton and Hove City Teaching PCT
6th Floor
Vantage Point
New England Road
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08 April 2005

Ms Louisa M A Beale
PhD Student/Lecturer
University of Brighton
Chelsea School
Hillbrow, Denton Road
Eastbourne
BN20 7SP

Dear Ms Beale

Full title of study: ***Intermittent Exercise Training in Heart Failure Rehabilitation: INTEXT Heart Failure Study***

REC reference number: ***05/Q1905/7***

Thank you for your letter of 18 March 2005, responding to the Committee's request for further information on the above research and submitting revised documentation. The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type:	Version:	Dated:	Date Received:
Application	3	06/01/2005	07/01/2005
Investigator CV		01/12/2004	07/01/2005
Protocol	1	01/12/2004	07/01/2005
Covering Letter		06/01/2005	07/01/2005
Covering Letter		11/02/2005	14/02/2005
Summary/Synopsis	1	05/01/2005	07/01/2005
Peer Review		12/11/2005	07/01/2005
Copy of Questionnaire			07/01/2005
Copies of Advertisements	2. Phase 1	10/02/2005	14/02/2005
Letters of Invitation to Participants	1	05/01/2005	07/01/2005

GP/Consultant Information Sheets	1	31/12/2005	07/01/2005
Participant Information Sheet	Phase 2 - version 4	17/03/2005	23/03/2005
Participant Information Sheet	Phase 1 - version 4	17/03/2005	23/03/2005
Participant Consent Form	1. Phase 2	04/01/2005	07/01/2005
Participant Consent Form	2. Phase 1	10/02/2005	14/02/2005
Response to Request for Further Information	2	18/03/2005	23/03/2005
Response to Request for Further Information			14/02/2005
Other		05/01/2005	07/01/2005
Copy letter from Head of Dept.		05/01/2005	07/01/2005
Summary CV for Supervisor		01/12/2005	07/01/2005

Management approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final management approval from the R&D Department for the relevant NHS care organisation.

Notification of other bodies

The Committee Administrator will notify the research sponsor and the R& D Department for the NHS care organisation that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/Q1905/7	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project,

Yours sincerely,

Michelle Roman
Research Ethics Committee Coordinator
East Sussex Local Research Ethics Committee

On behalf of the Chairman

Tel. 01273 0296437
email:michelle.roman@bhcpct.nhs.uk

Enclosures
Standard approval conditions
Site approval form (SF1)

APPENDIX 4: PARTICIPANT INFORMATION SHEETS

January 2006

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Investigators:
Louisa Beale & Dr Gary Brickley

Dr John Silberbauer & Dr Guy Lloyd

Participant Information Sheet

Study Title

Intermittent Exercise Training in Heart Failure Rehabilitation: INTEXT Heart Failure Study: Phase 1

Invitation paragraph

Before you decide if you would like to participate in this research study, it is important that you understand why the research is being done, and what it will involve. Please take time to read the following information carefully. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to participate.

What is the purpose of the study?

Heart failure is now recognised as a major public health problem in the UK. There are currently about 900,000 individuals with this condition, many of whom suffer disabling symptoms which severely reduce their quality of life. Heart failure patients require continual care and support, drawing upon the limited resources of the National Health Service. Previous studies show that exercise training for heart failure patients improves their ability to perform daily activities, enables a better quality of life, reduces time spent in hospital and may prolong their lives. Supervised medical exercise training is safe, and is recommended as part of the standard treatment of heart failure.

It is not yet clear what the best amount and type of physical activity is for this population, but intermittent exercise (i.e. short intervals of harder exercise with regular rest periods in between) may be a better way of training than continuous exercise (i.e. a longer bout of moderate exercise).

This study aims to compare the short-term effects of different bouts of intermittent exercise with a continuous exercise bout. The study duration is 4-6 weeks.

Why have I been chosen?

12 heart failure patients, and 12 healthy participants will be studied. Heart failure patients will be identified by the Cardiology Department at Eastbourne DGH or by the Community Heart Failure Nurse, and invited to participate in the study. Healthy participants will be invited to participate in the study via advertisements in local clubs, libraries, newspapers etc.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, the cardiologist will study your medical notes to ensure that you are suitable to participate in the study. You will be given this information sheet to keep, and be asked to sign a consent form. We will then send your GP a letter advising him/her that you are participating in the study. If you decide to take part, you are still free to withdraw at any time, and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

The tests will be carried out at the Coronary Care Unit (CCU) at Eastbourne District General Hospital, Kings Drive, Eastbourne, BN21 2UD. The testing area is on a ward, and is curtained off to allow full privacy. All the sessions will be conducted under the direct supervision of a cardiologist and an exercise physiologist.

Number of hospital visits: There are a total of 6 hospital visits, one a week. The first 2 visits will last about 3 hours, and the next 4 will last about one hour.

Exercise Tests

On the first visit, you will perform 2 exercise tests (described below) on an exercise bike.

Peak oxygen uptake test: this will involve you pedalling for about 10 minutes, starting off easy and becoming progressively harder until you cannot continue.

You will then have 1 hour's rest before the next test, which is:

Short-term exercise capacity test: this will involve you pedalling for about 60-90 seconds, also starting off easy then becoming progressively harder.

Your second visit will take place one week later, when these two tests will be repeated.

Continuous and Intermittent Exercise Bouts: the next 4 weeks will involve 1 visit each week to the hospital. During each visit you will perform a different exercise protocol, lasting approximately 15-20 minutes, on the exercise bike. For example, one protocol requires you to pedal at a constant moderate work rate for 15-20 minutes; another requires you to pedal at a harder work rate for 30 seconds and then pedal at an easy work rate for 60 seconds before repeating the 30 seconds harder pedalling, and repeating this sequence about 10 times.

It is possible that it will only be necessary for you to complete 2 of these 4 protocols, meaning that you will only need to make 4 visits, rather than 6, to complete the study.

Measurements involved:

On the initial visit, your height and weight will be recorded.

During all of the visits we will measure your heart rate and take an electrical recording of you heart's activity with an electrocardiogram (ECG). We will also measure your blood pressure, oxygen saturation and the air you breathe out, both at rest and during exercise. You will therefore be fitted with electrodes on your chest, a blood pressure cuff on your arm, an oxygen pulse monitor on your finger, and a face mask around your mouth and nose. None of these should cause you any discomfort. The face mask will not restrict your breathing, but your voice will be muffled when you have this on so, before the testing starts, we will discuss hand signals with you so that you can communicate with us during the test. We will also ask you to tell us how hard you feel you are working, by pointing to a chart (called a rating of perceived exertion (RPE) scale) at regular intervals during the test.

We will also take a sound wave picture of your heart with an echocardiogram, at rest and immediately after exercise. For this the cardiologist will require you to remove clothing on the top part of your body.

A small tube will be inserted into a vein in your arm before the testing. Blood samples will be taken from this before, during and after exercise in order to measure hormones, by-products of energy release and heart failure markers in the blood.

What do I have to do?

During the period between the testing sessions you may continue your normal lifestyle. However, we ask that you do not do any exhausting exercise for 48 hours before the visit, and you should not drink any alcohol for 24 hours before each testing session.

You should have a light meal 2-3 hours before testing. It is best to avoid eating for at least an hour before exercising, and avoid caffeinated drinks for 3-4 hours beforehand.

You should wear light clothes and shoes that are comfortable for cycling.

What are the possible disadvantages and risks of taking part?

Exercise can provide many cardiovascular benefits, but it also carries risks. The incidence of sudden death during exercise for healthy individuals is estimated to be 1 death per 18,000. Exercise complications and death are more frequent in older populations and those with cardiac disease, but are still rare. It is estimated that there are approximately 6 major complications for every 10,000 exercise tests. Previous research in heart failure patients reports no increase in adverse events or death due to exercise testing or training.

You may experience some discomfort during the testing. The exercise tests will require you to keep pedalling for as long as you can, and you are likely to feel your heart rate and breathing increase (you may feel breathless), and to feel fatigued, particularly in the legs. Although we will encourage you to keep going for as long as you can, **you are free to stop the tests at any time.** During the 4 continuous and intermittent exercise bouts the exercise will range from easy to hard, and you should not experience any discomfort other than the increase in heart rate, breathing, body temperature and muscle fatigue which is normal during physical activity.

The insertion of the tube into a vein in your arm involves a moment of slight discomfort, and may cause minor bruising, but drawing the blood samples should not cause further discomfort. Standard hygiene procedures will be put in place at all times.

What are the possible benefits of taking part?

Exercise training is recommended for heart failure patients. It improves fitness and the ability to perform daily activities, thus enabling a better quality of life, and a reduction in time spent in hospital. This study will give you the opportunity to exercise in a supervised medical setting, and will help us to set up a new exercise rehabilitation programme which may benefit you and other heart failure patients in the community.

What if new information becomes available?

If new information relevant to the research becomes available during the study, you will be informed.

What happens when the research study stops?

You will be informed whether or not there is a suitable exercise rehabilitation programme for you to join (on a voluntary basis) at Eastbourne DGH.

What if something goes wrong?

It is extremely unlikely that you will be harmed as a result of this research. In the unlikely event that you are harmed by taking part in this research, the Trust compensation procedure will be followed. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of the study, the National Health Service complaints mechanism will be available to you.

Will my taking part in this study be kept confidential?

If you consent to take part in the study, your medical records will be inspected by the Cardiologist, and your GP will be notified of your participation in the trial. All information which is collected about you during the study will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

The results of the study will be published in journals, presented at conferences, and reported to local and national organisations. This is likely to occur from 1 to 5 years after the study completion. You will be provided with a copy of the published results on request.

The blood samples will be analysed for the purposes of this study only. In the unlikely event that any abnormality is found in the blood tests, full information will be provided to you (unless you choose not to receive this information), and you will be directed to the cardiologist and/or your GP, as appropriate, to discuss these.

Who is organising and funding the research?

The study is being organised by researchers at University of Brighton and Eastbourne District General Hospital. East Sussex Hospitals NHS Trust and the Peel Medical Research Trust have provided funding to cover expenses for the testing.

Who has reviewed the study?

The study has been reviewed by the East Sussex Local Research Ethics Committee.

Contact for further information

If you would like any further information, please contact

Louisa Beale
Chelsea School (Eastbourne campus)
University of Brighton
Hillbrow
Denton Road
Eastbourne BN20 7SP
01435 813759 or 07780 601005
lb33@bton.ac.uk

who will be happy to address any questions or concerns that you may have.

If you decide to voluntarily participate in this study, you will be given a copy of this information sheet and a signed consent form to keep.

Thank you for your participation in the study.

University of Brighton

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University of Brighton
Telephone: 01273 643759 or 07780 601005
e-mail: lb33@brighton.ac.uk

Investigators:
Louisa Beale & Dr Gary Brickley

East Sussex Hospitals NHS
NHS Trust

East Sussex Health Authority
Eastbourne District General Hospital
Telephone: 01323 417 400, Bleep 0437
e-mail: Robert.McIntosh@esht.nhs.uk

Dr Robert McIntosh & Dr Guy Lloyd

Participant Information Sheet

Study title

Intermittent Exercise Training in Heart Failure Rehabilitation: INTEXT Heart Failure Study: Phase 2

Invitation paragraph

Before you decide if you would like to participate in this research study, it is important that you understand why the research is being done, and what it will involve. Please take time to read the following information carefully. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to participate.

What is the purpose of the study?

Heart failure is now recognised as a major public health problem in the UK. There are currently about 900,000 individuals with this condition, many of whom suffer disabling symptoms which severely reduce their quality of life. Heart failure patients require continual care and support, drawing upon the limited resources of the National Health Service. Previous studies show that exercise training for heart failure patients improves their ability to perform daily activities, enables a better quality of life, reduces time spent in hospital and may prolong their lives. Supervised medical exercise training is safe, and is recommended as part of the standard treatment of heart failure.

It is not yet clear what the best amount and type of physical activity is for this population, but intermittent exercise (i.e. short intervals of harder exercise with regular rest periods in between) may be a better way of training than continuous exercise (i.e. a longer bout of moderate exercise).

This study aims to compare the effects of an intermittent exercise training programme and a continuous exercise training programme on cardio-respiratory fitness and quality of life in heart failure patients. The study duration is 8 weeks.

Why have I been chosen?

40 heart failure patients will be identified by the Heart Failure Nurse at Eastbourne DGH and invited to participate in the study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, the cardiologist will study your medical notes to ensure that you are suitable to participate in the study. You will be given this information sheet to keep, and be asked to sign a consent form. We will then send your GP a letter advising him/her that you are participating in the study. If you decide to take part, you are still free to withdraw at any time, and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

The tests will be carried out in an exercise testing room at the Cardiology Department at Eastbourne District General Hospital, Kings Drive, Eastbourne, BN21 2UD. All the sessions will be conducted under the direct supervision of a cardiologist and an exercise physiologist.

The exercise training will be carried out in the Physiotherapy Department at Eastbourne District General Hospital for 6 weeks. During the training sessions you will be exercising with other participants and patients on the cardiac rehabilitation programme and will be supervised by trained cardiac nurses and exercise physiologists, with at least one member of staff for every three participants.

Number of hospital visits: There will be 2 testing sessions, and 12 training sessions over a period of 8 weeks. You will need to attend at least 10 out of the 12 training sessions in order to complete the study. Each testing and training session will last approximately one hour. The timetable below shows which sessions will take place in each week.

Week	Visits
1	Testing session
2	*Exercise training programme starts*
	2 x training sessions per week at Eastbourne DGH for 6 weeks
8	Testing session

Exercise Tests

During the testing sessions, you will perform a “peak oxygen uptake test” on an exercise bike. This will involve you pedalling for about 10 minutes, starting off easy and becoming progressively harder until you cannot continue.

Measurements involved:

On the initial visit, your height and weight will be recorded.

During the testing sessions in weeks 1 and 8 we will measure your heart rate and take an electrical recording of you heart's activity with an electrocardiogram (ECG). We will also measure your blood pressure and the air you breathe out, both at rest and during exercise. You will therefore be fitted with electrodes on your chest, a blood pressure cuff on your arm, and a face mask around your mouth and nose. The face mask will not restrict your breathing, but your voice will be muffled when you have this on so, before the testing starts, we will discuss hand signals with you so that you can communicate with us during the test. We will also ask you to tell us how hard you feel you are working, by pointing to a chart (called a rating of perceived exertion (RPE) scale) at regular intervals during the test. We will also take a sound wave picture of your heart with an echocardiogram, at rest and immediately after exercise. For this the cardiologist will require you to remove clothing on the top part of your body. None of these procedures should cause you any discomfort.

A small blood sample will be taken from a vein in your arm before the testing in order to measure heart failure markers in the blood.

Exercise training programme

After your first exercise testing session, you will begin your twice weekly exercise training programme. At each session you will first warm up gradually by walking and performing arm and leg movements and stretches for 15 minutes. For the next 20 minutes you will either do a combination of aerobic exercises (walking, stepping up and down, cycling) and strength exercises (lifting small weights) or do interval training on an exercise bike (pedalling for short periods at a harder work rate with recovery periods of easier pedalling in between). As you get fitter, this 20 minutes of exercise may be increased gradually to 30 minutes if appropriate. We will be comparing the two different types of exercise training, so at the beginning of the study you will be randomly assigned to one of these two different training groups. This means that the groups are selected by a computer, which has no information about the individual, i.e. by chance. The exercise session will then finish with a 10 minute cool down of gentle movements and stretching.

You will repeat the exercise testing sessions at the end of the training programme.

<u>What do I have to do?</u>

During the period between the testing and training sessions you may continue your normal lifestyle. However, we ask that you do not do any exhausting exercise for 48 hours before or drink any alcohol for 24 hours before the testing sessions.

<u>What are the possible disadvantages and risks of taking part?</u>

Exercise can provide many cardiovascular benefits, but it also carries risks. The incidence of sudden death during exercise for healthy individuals is estimated to be 1 death per 18,000. Exercise complications and death are more frequent in older populations and those with cardiac disease, but are still rare. It is estimated that there are approximately 6 major complications for every 10,000 exercise tests. Previous research in heart failure patients reports no increase in adverse events or death due to exercise testing or training.

You may experience some discomfort during the exercise tests. These tests will require you to keep pedalling for as long as you can, and you are likely to feel your heart rate and breathing increase (you may feel breathless), and to feel fatigued, particularly in the legs. Although we will encourage you to keep going for as long as you can, **you are free to stop the tests at any time.** During the exercise training sessions you should not experience any discomfort other than the increase in heart rate, breathing, body temperature and muscle fatigue which is normal during physical activity.

The blood sampling from the vein in your arm involves a moment of slight discomfort, and may cause minor bruising. Standard hygiene procedures will be put in place at all times.

What are the possible benefits of taking part?

Exercise training is recommended for heart failure patients. It improves fitness and the ability to perform daily activities, thus enabling a better quality of life, and a reduction in the time spend in hospital. This study will give you the opportunity to participate in a medically supervised, structured exercise training programme, and will help us to set up a new exercise rehabilitation programme which may benefit you and other heart failure patients in the community.

What if new information becomes available?

If new information relevant to the research becomes available during the study, you will be informed.

What happens when the research study stops?

You will be informed whether or not there is a suitable exercise rehabilitation programme for you to join (on a voluntary basis).

What if something goes wrong?

It is extremely unlikely that you will be harmed as a result of this research. In the unlikely event that you are harmed by taking part in this research, the Trust compensation procedure will be followed. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of the study, the National Health Service complaints mechanism will be available to you.

Will my taking part in this study be kept confidential?

If you consent to take part in the study, your medical records will be inspected by the Cardiologist, and your GP will be notified of your participation in the trial. All information which is collected about you during the study will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

The results of the study will be published in journals, presented at conferences, and reported to local and national organisations. This is likely to occur from 1 to 5 years after the study completion. You will be provided with a copy of the published results on request.

The blood samples will be analysed for the purposes of this study only. In the unlikely event that any abnormality is found in the blood tests, full information will be provided to you (unless you choose not to receive this information), and you will be directed to the cardiologist and/or your GP, as appropriate, to discuss these.

Who is organising and funding the research?

The study is being organised by researchers at University of Brighton and Eastbourne District General Hospital. Funding to cover expenses for the testing is currently being sought from grant-making organisations.

Who has reviewed the study?

The study has been reviewed by the East Sussex Local Research Ethics Committee.

Contact for further information

If you would like any further information, please contact

Louisa Beale
Welkin Laboratories, Chelsea School (Eastbourne campus)
University of Brighton, Carlisle Road, Eastbourne BN20 7SP
Tel: 01273 643759 or 07780 601005 email: lb33@bton.ac.uk

who will be happy to address any questions or concerns that you may have.

If you decide to voluntarily participate in this study, you will be given a copy of this information sheet and a signed consent form to keep.

Thank you for your participation in the study.

APPENDIX 5: STATISTICAL RESULTS

Statistical Results: Study 2 (Chapter 5)

2-way mixed design ANOVA (difference between CON and MED and Controls and CHF)

Dependent variable		degrees of freedom (df)	F value	significance (*P* value)	effect size (partial $\eta^{2)}$	observed power
Resting VO_2 ($ml.min^{-1}$)	exercise protocol	1	0.006	0.937	0.000	0.051
	protocol*group	1	0.238	0.632	0.016	0.074
	group	1	2.927	0.108	0.163	0.360
Unloaded VO_2 ($ml.min^{-1}$)	exercise protocol	1	0.724	0.408	0.046	0.125
	protocol*group	1	0.264	0.615	0.017	0.077
	group	1	8.245	0.012*	0.355	0.765
Total exercise VO_2 (work-rest) (ml)	exercise protocol	1	0.299	0.533	0.020	0.081
	protocol*group	1	0.036	0.852	0.002	0.054
	group	1	5.656	0.031*	0.274	0.604
Average 15-20 min net work VO_2 ($ml\ min^{-1}$)	exercise protocol	1	0.002	0.096	0.000	0.050
	protocol*group	1	0.134	0.719	0.009	0.064
	group	1	4.198	0.050*	0.219	0.483
Work economy (VO_2/W)	exercise protocol	1	0.005	0.944	0.000	0.051
	protocol*group	1	0.680	0.422	0.043	0.121
	group	1	5.108	0.039*	0.254	0.561
Recovery VO_2 (3 min) (ml)	exercise protocol	1	0.991	0.335	0.062	0.154
	protocol*group	1	3.977	0.065	0.210	0.463
	group	1	0.080	0.781	0.005	0.058
Ventilation ($L.min^{-1}$)	exercise protocol	1	5.422	0.034*	0.266	0.586
	protocol*group	1	0.251	0.624	0.016	0.076
	group	1	1.964	0.181	0.116	0.259
RER	exercise protocol	1	1.956	0.182	0.115	0.258
	protocol*group	1	0.122	0.731	0.008	0.062
	group	1	0.000	1.000	0.000	0.050
Heart Rate ($beats.min^{-1}$)	exercise protocol	1	0.092	0.765	0.006	0.059
	protocol*group	1	1.011	0.331	0.063	0.156
	group	1	24.981	0.000*	0.625	0.997
Blood Pressure (systolic) ($mm.Hg^{-1}$)	exercise protocol	1	0.099	0.757	0.007	0.060
	protocol*group	1	0.241	0.630	0.016	0.075
	group	1	12.78	0.003*	0.460	0.916
Blood Lactate ($mmol.L^{-1}$)	exercise protocol	1	3.534	0.080	0.191	0.421
	protocol*group	1	0.204	0.658	0.013	0.071
	group	1	0.411	0.531	0.027	0.092

* $P \leq 0.05$.

Non-parametric tests

Wilcoxon Signed Ranks (difference between CON & MED)

Dependent variable		df	Z score	*P* value
Rating of Perceived Exertion	exercise protocol	1	-0.818	0.414

Mann Whitney U Test (difference between Controls and CHF in CON & MED)

Dependent variable			df	Z score	*P* value
Rating of Perceived Exertion	CON	group	1	-2.001	0.045*
	MED	group	1	-3.424	0.001*

* $P \leq 0.05$.

3-way mixed design ANOVA (difference between CON and MED and Controls and CHF over time)

Dependent variable		df	F value	significance (*P* value)	partial η^2	observed power
Average VO_2 ($ml.min^{-1}$)	exercise protocol	1	0.673	0.425	0.043	0.120
	protocol*group	1	0.400	0.537	0.026	0.091
	time	1.836‡	65.437	0.000*	0.814	1.000
	time*group	1.836‡	2.406	0.113	0.138	0.416
	time*protocol	1.836‡	8.465	0.002*§	0.361	0.930
	time*protocol*group	1.836‡	5.381	0.013*	0.264	0.772
	group	1	3.258	0.091	0.178	0.394
Blood lactate concentration ($mmol.L^{-1}$)	exercise protocol	1	0.807	0.383	0.051	0.134
	protocol*group	1	0.115	0.739	0.008	0.062
	time	1.836‡	19.076	0.000*	0.560	0.991
	time*group	1.836‡	2.079	0.143	0.122	0.393
	time*protocol	1.836‡	4.085	0.030*§	0.214	0.660
	time*protocol*group	1.836‡	0.171	0.832	0.011	0.073
	group	1	0.031	0.863	0.002	0.053
Heart rate ($beats.min^{-1}$)	exercise protocol	1	0.013	0.913	0.001	0.051
	protocol*group	1	0.462	0.510	0.037	0.096
	time	1.589‡	29.797	0.000*	0.713	1.000
	time*group	1.589‡	12.164	0.001*	0.503	0.972
	time*protocol	1.824‡	0.347	0.692	0.028	0.097
	time*protocol*group	3	0.368	0.776	0.030	0.100
	group	1	17.109	0.001*	0.588	0.966

* $P \leq 0.05$. ‡Greenhouse Gaesser correction applied for non-spherical data. § Follow-up t-tests with Bonferroni adjustment were not significant

Statistical Results: Study 3 (Chapter 6)

2-way mixed design ANOVA (difference between CON, LOW and HIGH and Controls and CHF)

Dependent variable		degrees of freedom (df)	F value	significance (*P* value)	effect size (partial $\eta^{2)}$	observed power
Resting VO_2 ($ml.min^{-1}$)	exercise protocol	2	0.482	0.624	0.042	0.119
	protocol*group	2	2.392	0.115	0.179	0.431
	group	1	1.513	0.244	0.121	0.203
Unloaded VO_2 ($ml.min^{-1}$)	exercise protocol	2	0.413	0.666	0.036	0.108
	protocol*group	2	0.165	0.849	0.015	0.072
	group	1	3.188	0.102	0.225	0.371
Total exercise VO_2 (work-rest) (ml)	exercise protocol	2	0.068	0.934	0.006	0.059
	protocol*group	2	0.264	0.770	0.023	0.086
	group	1	6.510	0.027*	0.372	0.642
Average 15-20 min net work VO_2 ($ml\ min^{-1}$)	exercise protocol	2	0.463	0.636	0.044	0.115
	protocol*group	2	0.818	0.456	0.076	0.170
	group	1	5.456	0.042*	0.353	0.559
Work economy (VO_2/W)	exercise protocol	2	0.420	0.662	0.037	0.109
	protocol*group	2	0.290	0.751	0.026	0.090
	group	1	0.319	0.548	0.028	0.081
Recovery VO_2 (3 min) (ml)	exercise protocol	2	0.656	0.529	0.056	0.146
	protocol*group	2	0.743	0.487	0.063	0.160
	group	1	0.003	0.959	0.000	0.050
Ventilation ($L.min^{-1}$)	exercise protocol	2	3.887	0.034*§	0.245	0.645
	protocol*group	2	2.847	0.078	0.192	0.505
	group	1	4.900	0.047*	0.290	0.530
RER	exercise protocol	1.198‡	3.402	0.088	0.274	0.419
	protocol*group	1.198‡	8.689	0.011*	0.491	0.805
	group	1	1.110	0.320	0.110	0.157
Heart Rate ($beats.min^{-1}$)	exercise protocol	2	0.035	0.966	0.003	0.055
	protocol*group	2	1.52	0.860	0.012	0.071
	group	1	27.722	0.000*	0.681	0.998
Blood Pressure (systolic) ($mm.Hg^{-1}$)	exercise protocol	2	1.759	0.192	0.119	0.334
	protocol*group	2	1.772	0.190	0.120	0.337
	group	1	14.966	0.002*	0.535	0.946
Blood Lactate ($mmol.L^{-1}$)	exercise protocol	2	11.831	0.000*	0.476	0.989
	protocol*group	2	0.515	0.603	0.038	0.126
	group	1	1.872	0.194	0.126	0.245

* $P \leq 0.05$. § Follow-up t-tests with Bonferroni adjustment were not significant ‡Greenhouse Gaesser correction applied for non-spherical data

Follow-up t-tests with Bonferroni adjustment (3 comparisons; α level $P \leq 0.0167$ = significant)

Dependent variable		t statistic	df	Significance (*P* value)
Blood Lactate ($mmol.L^{-1}$)	CON vs LOW	-1.297	13	0.216
	CON vs HIGH	-4.487	13	0.001*
	LOW vs HIGH	-3.292	13	0.005*

* $P \leq 0.0167$

Non-parametric tests

Friedman's Test (difference between CON, LOW & HIGH)

Dependent variable		df	Chi-Square	*P* value
Rating of Perceived Exertion	exercise protocol	2	4.863	0.088

Mann Whitney U Test (difference between Controls and CHF in CON, LOW & HIGH)

Dependent variable			df	Z score	*P* value
Rating of Perceived Exertion	CON	group	1	-2.525	0.012*
	LOW	group	1	-2.577	0.011*
	HIGH	group	1	-1.415	0.157

* $P \leq 0.05$.

3-way mixed design ANOVA (difference between CON, LOW and HIGH and Controls and CHF over time)

Dependent variable		df	F value	significance (*P* value)	partial η^2	observed power
Average VO_2 ($ml.min^{-1}$)	exercise protocol	2	0.189	0.830	0.019	0.075
	protocol*group	2	0.854	0.441	0.079	0.176
	time	1.593‡	86.611	0.000*	0.896	1.000
	time*group	3	6.178	0.002	0.382	0.938
	time*protocol	6	7.403	0.000*§	0.425	1.000
	time*protocol*group	6	0.844	0.541	0.078	0.308
	group	1	4.676	0.056	0.319	0.498
Blood lactate concentration ($mmol.L^{-1}$)	exercise protocol	2	6.737	0.004*	0.341	0.882
	protocol*group	2	0.913	0.414	0.066	0.190
	time	1.207‡	32.352	0.000*	0.713	1.000
	time*group	2	3.779	0.064	0.225	0.484
	time*protocol	4‡	7.488	0.001*	0.364	0.971
	time*protocol*group	4‡	0.608	0.606	0.045	0.161
	group	1	1.237	0.286	0.087	0.178

* $P \leq 0.05$. ‡Greenhouse Gaesser correction applied for non-spherical data. § Follow-up tests with Bonferroni adjustment (4 comparisons; α level $P \leq 0.0125$ = significant) showed that average VO_2 at 0-5 min was significantly lower in HIGH than CON (t = 4.158, P = .006). No other significant differences were found.

Follow-up t-tests with Bonferroni adjustment (3 comparisons; α level $P \leq 0.01667$ = significant)

Dependent variable		t statistic	df	significance (*P* value)
Blood Lactate (mmol.L^{-1})	Controls: values @ 10 min			
	CON vs LOW	-1.062	4	0.337
	CON vs HIGH	-1.798	4	0.132
	LOW vs HIGH	-1.064	4	0.336
	Controls: values @ 20 min			
	CON vs LOW	-1.549	4	0.182
	CON vs HIGH	-3.978	4	0.011*
	LOW vs HIGH	-1.616	4	0.167
	CHF: values @ 10 min			
	CON vs LOW	0.573	8	0.582
	CON vs HIGH	-2.377	8	0.132
	LOW vs HIGH	-6.194	8	0.000*
	CHF: values @ 20 min			
	CON vs LOW	-0.429	8	0.680
	CON vs HIGH	-2.701	8	0.027
	LOW vs HIGH	-3.257	8	0.012*

* $P \leq 0.01667$

Statistical Results: Study 4 (Chapter 7)

Dependent variable		df	F value	significance (*P* value)	effect size (partial $\eta^{2)}$	observed power
Test duration (s)	training	1	3.340	0.084	0.157	0.409
	training*group	1	0.454	0.509	0.025	0.098
	group	1	0.004	0.950	0.000	0.050
Peak work rate (W)	training	1	6.194	0.023*	0.256	0.653
	training*group	1	0.854	0.368	0.045	0.141
	group	1	0.135	0.717	0.007	0.135
VO_{2peak} ($L.min^{-1}$)	training	1	3.416	0.081	0.159	0.417
	training*group	1	0.687	0.418	0.037	0.123
	group	1	0.337	0.569	0.018	0.085
VO_{2peak} (ml.kg-1.min^{-1})	training	1	3.880	0.064	0.177	0.462
	training*group	1	1.726	0.205	0.088	0.238
	group	1	0.001	0.976	0.000	0.050
VO_2 at VT ($L.min^{-1}$)	training	1	11.564	0.008*	0.562	0.856
	training*group	1	0.019	0.893	0.002	0.052
	group	1	0.111	0.747	0.012	0.060
VO_2 at VT ($ml.kg^{-1}.min^{-1}$)	training	1	10.769	0.010*	0.545	0.831
	training*group	1	0.342	0.573	0.037	0.082
	group	1	0.406	0.540	0.043	0.088
VE/VCO_2 slope	training	1	0.273	0.614	0.029	0.076
	training*group	1	0.024	0.880	0.003	0.052
	group	1	2.174	0.174	0.195	0.262
BNP ($pg.ml^{-1}$)	training	1	0.119	0.738	0.013	0.061
	training*group	1	0.950	0.355	0.096	0.141
	group	1	0.357	0.565	0.038	0.084

*$P \leq 0.05$

Non-parametric tests

Wilcoxon Signed Ranks (difference between pre- and post-training)

Dependent variable		df	Z score	*P* value
MLHFQ total score	Circuit group	1	-2.383	0.017*
MLHFQ physical component		1	-2.077	0.038*
MLHFQ emotional component		1	-1.278	0.201
MLHFQ total score	Intermittent group	1	-1.947	0.050*
MLHFQ physical component		1	-1.101	0.271
MLHFQ emotional component		1	-0.496	0.024*
SF-36 Physical Functioning	Circuit group	1	-.949	0.343
SF-36 Role-Physical		1	-1.414	0.157
SF-36 Bodily Pain		1	-0.000	1.000
SF-36 General Health		1	-0.355	0.723
SF-36 Vitality		1	-0.691	0.091
SF-36 Social Functioning		1	-0.136	0.892
SF-36 Role-Emotional		1	-1.604	0.109
SF-36 Mental health		1	0.736	0.461
SF-36 Physical Functioning	Intermittent Group	1	-1.219	0.233
SF-36 Role-Physical		1	-1.633	0.102
SF-36 Bodily Pain		1	-1.633	0.102
SF-36 General Health		1	-1.604	0.109
SF-36 Vitality		1	-1.802	0.072
SF-36 Social Functioning		1	-.318	0.750
SF-36 Role-Emotional		1	-1.134	0.257
SF-36 Mental health		1	-.848	0.396

* $P \leq 0.05$.

Mann Whitney U Test (difference in change post-training between Circuit and Intermittent Groups)

Dependent variable	**df**	**Z score**	***P* value**
MLHFQ total score	1	-0.822	0.411
MLHFQ physical component	1	-1.107	0.268
MLHFQ emotional component	1	-0.496	0.620
SF-36 Physical Functioning	1	0.000	1.000
SF-36 Role-Physical	1	-0.791	0.429
SF-36 General Health	1	-0.526	0.599
SF-36 Vitality	1	-0.773	0.440
SF-36 Social Functioning	1	-0.589	0.556
SF-36 Role-Emotional	1	-1.394	0.163
SF-36 Mental health	1	-0.366	0.737

APPENDIX 6: QUALITY OF LIFE QUESTIONNAIRES

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	**No**			**Very Little**		**Very Much**
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

11/10/04

SF-36 QUESTIONNAIRE

Name:_____ Ref. Dr:_____ Date: _____

ID#: _____ Age: _____ Gender: M / F

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

_ Excellent _ Very Good _ Good _ Fair _ Poor

Compared to one year ago, how would you rate your health in general now?

_ Much better now than one year ago
_ Somewhat better now than one year ago
_ About the same
_ Somewhat worse now than one year ago
_ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

_ Yes, Limited a lot _ Yes, Limited a Little _ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

_ Yes, Limited a Lot _ Yes, Limited a Little _ No, Not Limited at all

Lifting or carrying groceries

_ Yes, Limited a Lot _ Yes, Limited a Little _ No, Not Limited at all

Climbing several flights of stairs

_ Yes, Limited a Lot _ Yes, Limited a Little _ No, Not Limited at all

Climbing one flight of stairs

_ Yes, Limited a Lot _ Yes, Limited a Little _ No, Not Limited at all

Bending, kneeling, or stooping

_ Yes, Limited a Lot _ Yes, Limited a Little _ No, Not Limited at all

Walking more than a mile

_ Yes, Limited a Lot _ Yes, Limited a Little _ No, Not Limited at all

Walking several blocks

_ Yes, Limited a Lot _ Yes, Limited a Little _ No, Not Limited at all

Walking one block

_ Yes, Limited a Lot _ Yes, Limited a Little _ No, Not Limited at all

Bathing or dressing yourself

_ Yes, Limited a Lot _ Yes, Limited a Little _ No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

_ Yes _ No

Accomplished less than you would like

_ Yes _ No

Were limited in the kind of work or other activities

_ Yes _ No

Had difficulty performing the work or other activities (for example, it took extra effort)

_ Yes _ No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

_ Yes _ No

Accomplished less than you would like

_ Yes _ No

Didn't do work or other activities as carefully as usual

_ Yes _ No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

_ Not at all _ Slightly _ Moderately _ Severe _ Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

_ None _ Very Mild _ Mild _ Moderate _ Severe _ Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

_ Not at all _ A little bit _ Moderately _ Quite a bit _ Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt downhearted and blue?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
_ Definitely true _ Mostly true _ Don't know _ Mostly false _ Definitely false

I am as healthy as anybody I know
_ Definitely true _ Mostly true _ Don't know _ Mostly false _ Definitely false

I expect my health to get worse
_ Definitely true _ Mostly true _ Don't know _ Mostly false _ Definitely false

My health is excellent
_ Definitely true _ Mostly true _ Don't know _ Mostly false _ Definitely false