THE PHYSIOLOGICAL EFFECTS OF CARDIAC RESYNCHRONISATION THERAPY AND THE ADDITIONAL EFFECTS OF EXERCISE TRAINING IN PATIENTS WITH HEART FAILURE

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Medicine by

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Abbreviations

ACE	Angiotensin converting enzyme
ARB	Angiotensin II receptor blocker
AF	Atrial fibrillation
AT	Anaerobic threshold
BIV	Biventricular
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Blood pressure
ECG	Electrocardiogram
CAD	Coronary artery disease
CHF	Chronic heart failure
CI	Cardiac Index
CO	Cardiac output
CO_2	Carbon dioxide
CPO	Cardiac power output
CPX	Cardiopulmonary exercise
CR	Cardiac reserve
CRT	Cardiac resynchronisation therapy
CRT-P	Cardiac resynchronisation therapy pacemaker
CRT-D	Cardiac resynchronisation therapy with defibrillator
DCM	Dilated cardiomyopathy
EF	Ejection fraction
EPS	Electrophysiology study
EXDU	Exercise duration
HR	Heart rate
HT	Hypertension
ICD	Implantable cardioveter defibrillator
LBBB	Left bundle branch block
LV	Left ventricular
LVEDD	Left ventricular end internal diastolic volume
LVSWI	Left ventricular stroke work index
EF	Left ventricular ejection fraction

MBP	Mean blood pressure
MI	Myocardial infarction
MLWHF	Minnesota living with heart failure
MRI	Magnetic resonance imaging
MUGA	Multi gated acquisition scan
NYHA	New York heart association (functional class)
NT-proBNP	N terminal pro-brain natriuretic peptide
O_2	Oxygen
$PETCO_2$	End-tidal pressure of CO_2
QOL	Quality of life
RER	Respiratory exchange ratio
RHD	Rheumatic heart disease
RR	Respiratory rate
RV	Right ventricular
SBP	Systolic blood pressure
SR	Sinus rhythm
VE	Minute ventilation
VE/VCO_2	Ratio of minute ventilation to carbon dioxide production
VE/VO_2	Ratio of minute ventilation to oxygen consumption
VCO_2	Carbon dioxide production
VO_2	Oxygen consumption
V_t	Tidal volume
VT	Ventricular tachycardia

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Abstract

Chronic heart failure (CHF) is an increasingly common condition. Over the past 10 years the treatment options for heart failure have improved dramatically however despite this many patients remain significantly limited. A proportion of these patients suffer from dyssynchronous ventricular contractions, which lead to further limitation in cardiac function and neurohormal stimulation causing increased symptoms and a worse prognosis. Cardiac resynchronisation therapy (CRT) has been shown to be of benefit in this patient group and leads to a significant improvement in morbidity and mortality. This thesis uses non-invasive methods of measuring functional capacity to investigate several hypotheses in patients suitable for CRT.

The first study evaluated the longitudinal impact of CRT on functional capacity, haemodynamic measures and skeletal muscle function in 40 patients. The study showed cardiopulmonary exercise testing could be safely performed in patients suitable for CRT. It was found that CRT led to significant improvements in symptomatic status, aerobic exercise capacity and cardiac pumping capability. The improvements in most measures were significant 2 weeks after CRT and were maintained untill 3 months. Despite the significant improvements there was no significant changes in peak skeletal muscle function or anaerobic exercise capacity.

The second study was performed in 50 patients to assess whether exercise training in addition to CRT could lead to further improvements. The subjects were followed for 3 months following CRT implantation and then randomised to either a exercise training or a control group. Three months following CRT there were significant improvements in exercise capacity and exercise haemodynamic measures. However there was no significant change in peak skeletal muscle function. The addition of exercise training led to further improvements in exercise capacity, exercise haemodynamic measures and also peak skeletal muscle function. The control group did not show significant changes during this period. The results from this study allow us to achieve the maximum patient benefit following CRT through the addition of exercise training.

The third study was designed to assess the effectiveness of surgically placed CRT in 23 patients with unsuccessful transvenous placement. The results were compared to a control group with successful transvenous CRT. This study showed that both groups showed similar significant improvements at 6 months. The improvement was delayed and of a smaller magnitude in the mini thoracotomy group. Therefore while CRT via a mini thoracotomy is a viable option for patients it could not be regarded as a first line option.

The findings from this thesis help to improve our understanding of the mechanisms behind improvements following CRT and will allow us to maximise the benefit for patients following CRT. This information can be used to help clinical decision-making and improve the quality of care provided in the future.

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CHAPTER 1: INTRODUCTION

1.1 Congestive cardiac failure

1.1.1 Epidemiology

Chronic heart failure (CHF) is an increasingly common condition, which has now reached epidemic proportions. In the United kingdom heart failure affects between 1-3% of the general population (Davies et al., 2001;McMurray and Stewart, 2002) and increases with age to affect 10% of those over 70 (McMurray and Stewart, 2002). This represents only those patients who are symptomatic. In a population based study in England it was shown that the prevalence of left ventricular (LV) systolic dysfunction (defined as an ejection fraction (EF) <40%) in patients aged 45 years and above was 1.8%, and of these 47% had no symptoms (Davies et al., 2001). As the population ages and survival from ischaemic heart disease improves the prevalence is likely to increase further. In a simulation model it was shown that between 1985 and 2010 there was likely to be a 70% increase in absolute numbers of heart failure patients (Bonneux et al., 1994). This hypothesis has been shown to be accurate in a long term study of the Framingham cohort. In this study the 5 year event rate was calculated following a myocardial infarction. The authors showed that the overall rate of chronic heart failure and death combined had stayed similar from 1970 to 1999 ($p=0.25$). This has occurred as the rate of death following a MI has significantly reduced in that time ($p<0.0001$) whilst the risk of developing heart failure has significantly increased ($p=0.02$) (see table 1.1) (Velagaleti et al., 2008).

Table 1.1: Long term trends in chronic heart failure following myocardial infarction (adapted from "Long-term trends in the incidence of heart failure after myocardial infarction" Velageleti et al Circulation 2008)

5-Year events (including 30-day events)	1970–1979	1980–1989	1990–1999	p for Trend
Chronic heart Failure (CHF)				
No. of events/No. at risk (%)	45/230 (19.6)	54/251 (21.5)	66/195 (33.9)	0.02
Death without CHF				
No. of events/No. at risk (%)	66/230 (28.7)	47/251 (18.7)	26/195 (13.3)	<0.01
CHF or death				
No. of events/No. at risk (%)	111/230 (48.3)	101/251 (40.2)	92/195 (47.2)	0.25

1.1.2 Aetiology

The most common cause of chronic heart failure has changed over the past five decades. In the Framingham study the most common aetiology of chronic heart failure was hypertension. Hypertension (HT) preceded almost 75% of all cases of chronic heart failure whereas coronary artery disease (CAD) not accompanied by hypertension was only responsible for 10% of cases. Other causes identified were rheumatic heart disease (RHD) and a miscellaneous group including congential heart disease, thyrotoxic heart disease, atrial fibrillation and inherited cardiomyopathies (see figure 1.1) (McKee et al., 1971). Levy et al assessed the temporal trends in the incidence of heart failure over a 40 year period spanning 1950-1990. They showed no change in annual incidence of cardiac failure in men over that period but showed a 30-40% decline in annual incidence in women over that period. The explanation for this was that the most common aetiology in men was CAD and the improved survival from acute myocardial infarction due to thrombolysis and revascularisation treatments means that there are more people highly susceptible to cardiac failure. In women the most common aetiology was hypertension and whilst this was a common cause in the 1950's medical therapy has declined its importance by the 1990's (Levy

et al., 2002). In one British study from the 1990's only 6% of cases of heart failure were secondary to hypertension whereas 41% were secondary to CAD (Sutton, 1990)

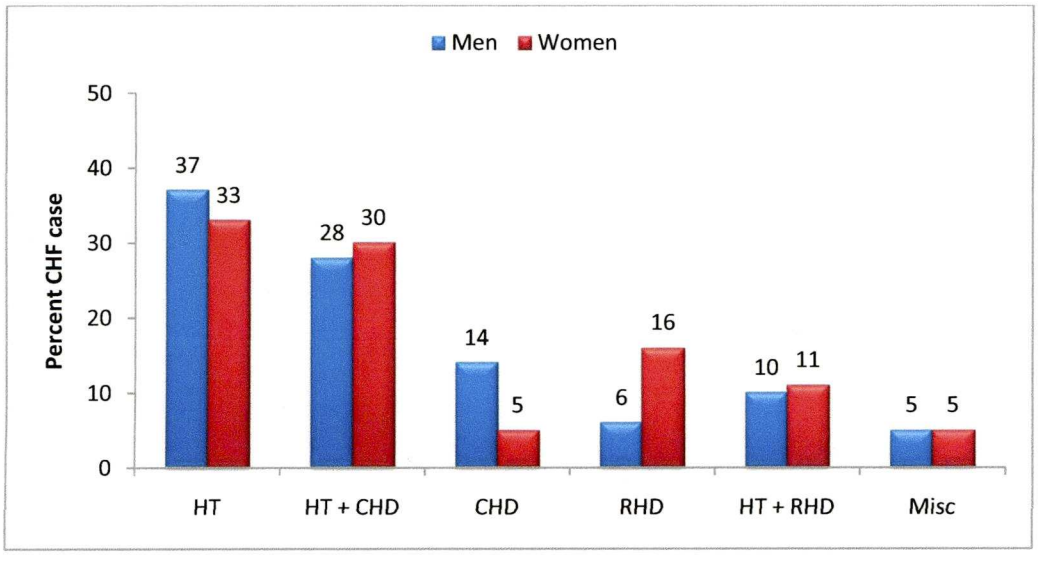

Figure 1.1: Aetiology of chronic heart failure in the Framingham study (adapted from "The natural history of congestive heart failure" Mckee et al NEJM 285(26): 1441-1446)

1.1.3 Pathophysiology of cardiac failure

Chronic heart failure is a progressive syndrome that starts with a left ventricular insult and progresses at variable speed to end stage cardiac failure. The pathophysiology behind this progression has been widely described and treatments aimed at modifying the neurohormonal adaptations have been shown to significantly improve the outcome in patients with heart failure. The initial insult leading to left ventricular dysfunction can be varied and include myocardial infarction, inflammatory myocardial disease and chronic volume or pressure overload. This initial insult increases myocardial wall stress which has a major impact on the expression of local neuroendocrine systems such as the renin angiotensin aldsosterone system. Wall stress also causes a change in baroreceptor mechanisms that impact on the sympathetic parasympathetic balance leading to sympathetic

activation and therefore peripheral vasoconstriction. Sympathetic induced vasoconstriction potentially causes endothelial dysfunction, vascular smooth muscle proliferation and ischaemia. Simultaneously the increased expression of angiotensin II, via the renin angiotensin aldsoterone system, has been shown to trigger myocyte apoptosis (Tan et al., 1991) leading to myocardial thinning and dilation. The above mechanisms cause "forward failure" leading to reduced organ function and "backward failure" leading to oedema and pulmonary congestion (see figure 1.2) (Bohm et al., 2003). The deleterious effects of over activation of the renin angiotensin and the sympathetic nervous systems are the main mechanisms by which the clinical syndrome of heart failure develops. Therefore these are the main target for the medical management of heart failure.

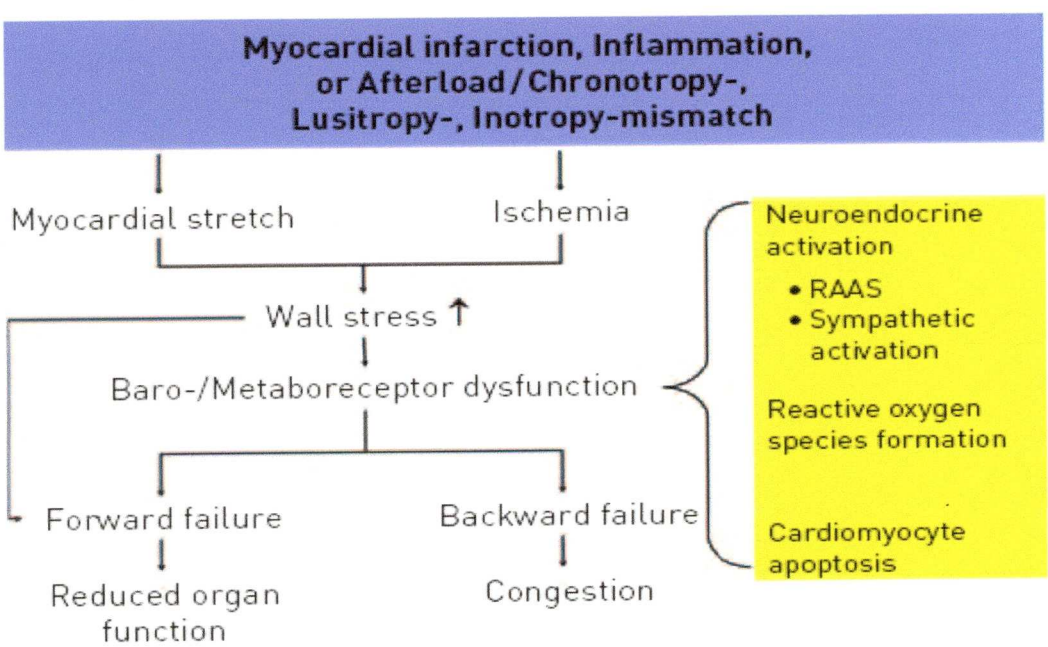

Figure 1.2: The progression from left ventricular dysfunction to advanced heart failure (adapted from Mechanisms contributing to the progression of left ventricular dysfunction to end-stage heart failure Bohm et al EHJ Suppl 2003 5(I);I14-21)

1.1.4 Presentation and Morbidity

Unlike most cardiovascular condition cardiac failure is becoming a more common condition over time. Currently improved survival from CAD has meant that there are nearly 1 million new cases diagnosed annually worldwide. This makes cardiac failure the most rapidly growing cardiovascular disorder. Cardiac failure impairs quality of life significantly, in multiple surveys it has been shown that cardiac failure impairs quality of life more than almost any other chronic medical problem (McMurray and Stewart, 2002). The medical outcomes study (Stewart et al., 1989) showed that self reported quality of life was more impaired by heart failure than by hypertension, diabetes, arthritis, chronic lung disease or angina. In another study nearly half of all the patients with heart failure felt that their quality of life was so poor that they would be willing to trade at least half of their remaining life expectancy in order to feel better (Lewis et al., 2001).

1.1.5 Progression and Mortality

In the last decade there have been many advances in the pharmacological treatment of heart failure, however the condition continues to exact a heavy burden in terms of mortality and morbidity (Cleland et al., 1999). Death due to heart failure may be sudden (usually arrhythmic) or due to progressive heart failure with gradual deterioration in symptoms (MERIT-HF Study Group, 1999). The 1-year mortality has been shown to increase with worsening symptomatic heart failure from 5-15% for NYHA class II and 20-50% for class III to >50% for class IV (Uretsky and Sheahan, 1997;Stellbrink et al., 1999a;Farwell et al., 2000). Despite advances in the treatments available around 38% of patients diagnosed with heart failure die within a year of diagnosis (Cowie et al., 2000). The 5-year mortality following the diagnosis

of heart failure has remained approximately 50% (McKee et al., 1971;Johnson and Palacios, 1982;Levy et al., 2002) and is therefore similar to those from cancer of the colon, and worse than those from cancer of the breast or prostate (Quinn M et al., 2001).

Long term follow up data from the Framingham study has shown that whilst there has been improvement in survival from heart failure in both men and women since the 1950 the 5 year survival was still less than 50% (see figure 1.3) (Levy et al., 2002). In the UK heart failure has been reported to consume more than 2.5% of the total health care expenditure (McMurray and Stewart, 2002). With such continued impact from heart failure we require new modes of treatment in addition to those currently available to improve mortality and morbidity.

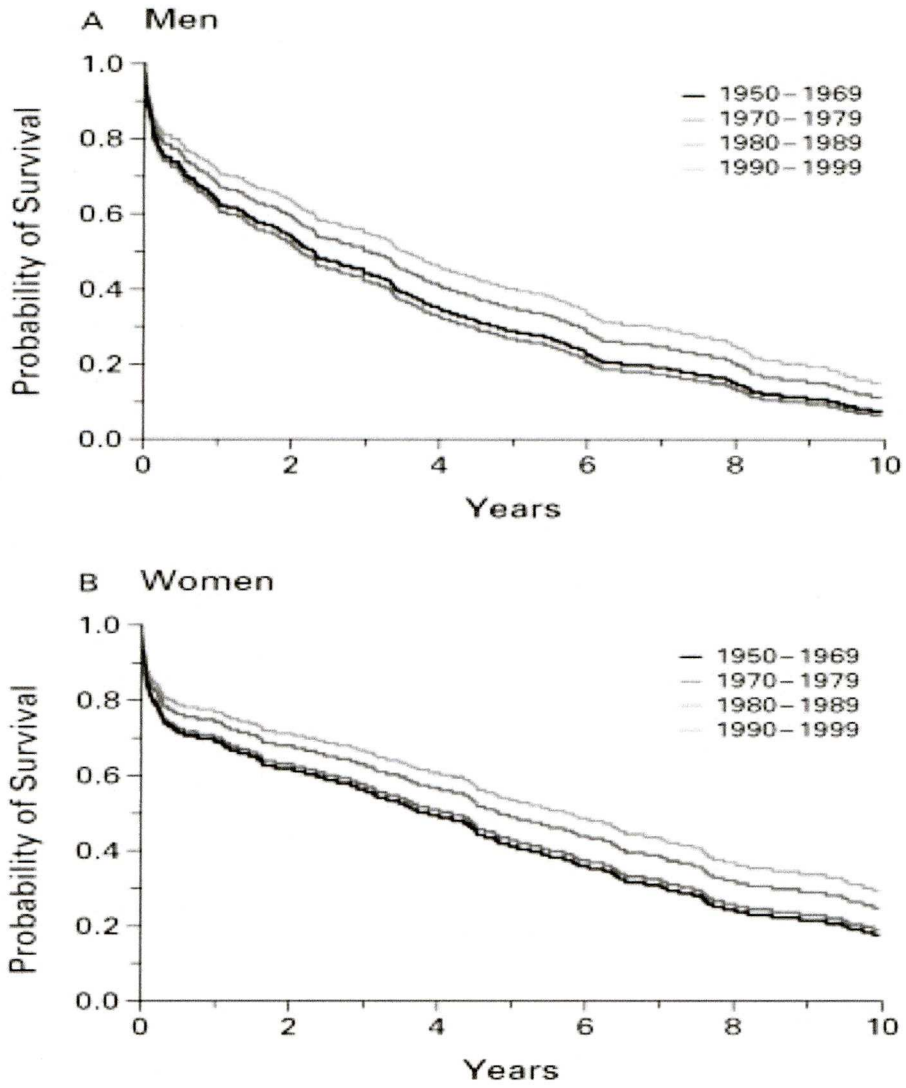

Figure 1.3: Temporal trends in survival from heart failure (adapted from "Long-term trends in the incidence of and survival with heart failure" Levy D NEJM, v. 347, no. 18, p. 1397-1402)

1.1.6 Assessment of cardiac failure

Heart failure is primarily a clinical diagnosis. Patients with heart failure may have a number of symptoms, the most common being breathlessness, fatigue, exercise intolerance, and fluid retention. The degree of exertion required to elicit symptoms such as breathlessness is used to grade the severity of symptoms into one of four functional classes (New York heart association (NYHA) classes see Table 1.2) (New

York Heart Association Criteria Committee, 1979). There is a close relationship between NYHA class and mortality. Ahmed et al showed that as patients functional class worsened so did their prognosis (see figure 1.4) (Ahmed et al., 2006). However none of the symptoms discussed above is specific to heart failure, and several other disorders may present in a similar manner. Therefore, symptoms alone cannot be relied upon to make the diagnosis which depends upon a combination of good clinical skills with history taking and physical examination, supplemented by tests.

Table 1.2:NYHA classification (adapted from Nomenclature and criteria for diagnosis of disease of the heart and great vessels, criteria committee of the New York heart association 1979.)

I	No limitations. Ordinary physical activity does not cause fatigue, breathlessness or palpitation. (Asymptomatic left ventricular dysfunction is included in this category.)
II	Slight limitation of physical activity. Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, breathlessness or angina pectoris (symptomatically 'mild' heart failure).
III	Marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms (symptomatically 'moderate' heart failure).
IV	Inability to carry on any physical activity without discomfort. Symptoms of congestive cardiac failure are present even at rest. With any physical activity increased discomfort is experienced (symptomatically 'severe' heart failure).

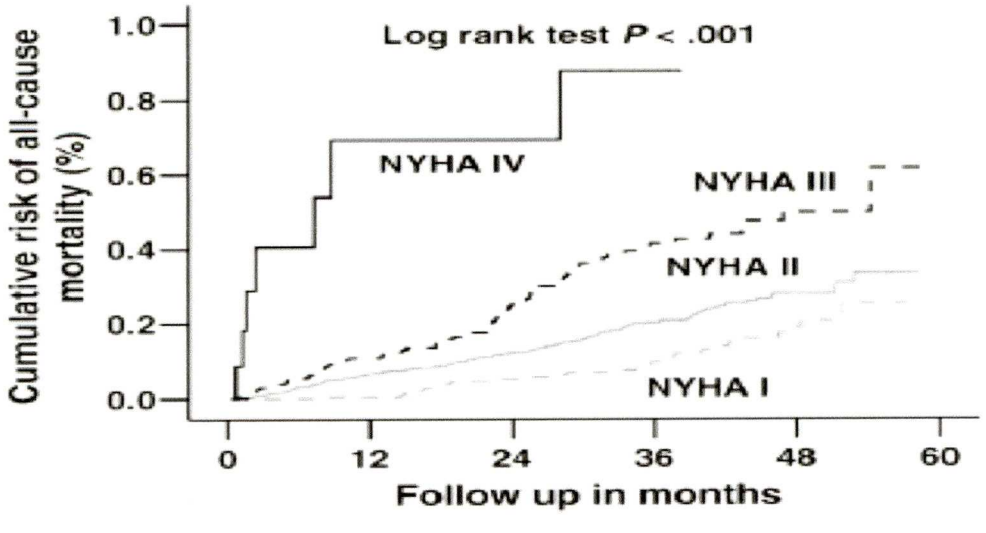

Figure 1.4: NYHA class and mortality (adapted from "Higher New York heart association classes and increased mortality and hospitalization in patients with heart failure" Ahmed A et al Am Heart J 151(2): 444–450.)

There are multiple guidelines on the ideal diagnostic path to an accurate diagnosis of heart failure. The diagnosis of heart failure is initially suspected on clinical grounds. Once there is a suspicion of a diagnosis of heart failure the ideal first two tests are a 12 lead electrocardiogram and measurement of Brain Natriuretic Peptide (BNP) or N terminal pro-Brain Natriuretic peptide (NT-proBNP). A diagnosis of heart failure is very unlikely in a patient with a normal ECG and a normal plasma concentration of BNP or NT-proBNP, given the high sensitivity of these tests (Cowie et al., 2003). Normal results in both tests may therefore indicated that alternative diagnoses need to be considered. If either of these tests is abnormal then a heart failure diagnosis is possible however neither of these tests is a 100% sensitive and therefore further investigation is warranted.

The current gold standard test is a transthoracic echocardiographic examination. This can, in the hands of a good operator, provide detailed views of the heart and left ventricular systolic function (ejection fraction (EF)) can be assessed with either the "eyeball" method or by using mathematical models such as the apical biplane formulae. The latter uses a Simpsons rule assumption based on stacked disks to calculate ejection fraction (Otto, 2004). If there is reduction in ejection fraction seen then the combination of an abnormal echocardiogram, symptoms and signs of heart failure and abnormal ECG and BNP measurement provides strong evidence towards a diagnosis of heart failure. In people whose transthoracic echocardiographic window is poor alternative imaging modalities should be considered including transoesophageal echocardiogram, cardiac magnetic resonance imaging (MRI) and multi gated acquisition (MUGA) scan (full algorithm shown in figure 1.5) (National Institute for Clinical Excellence, 2003)

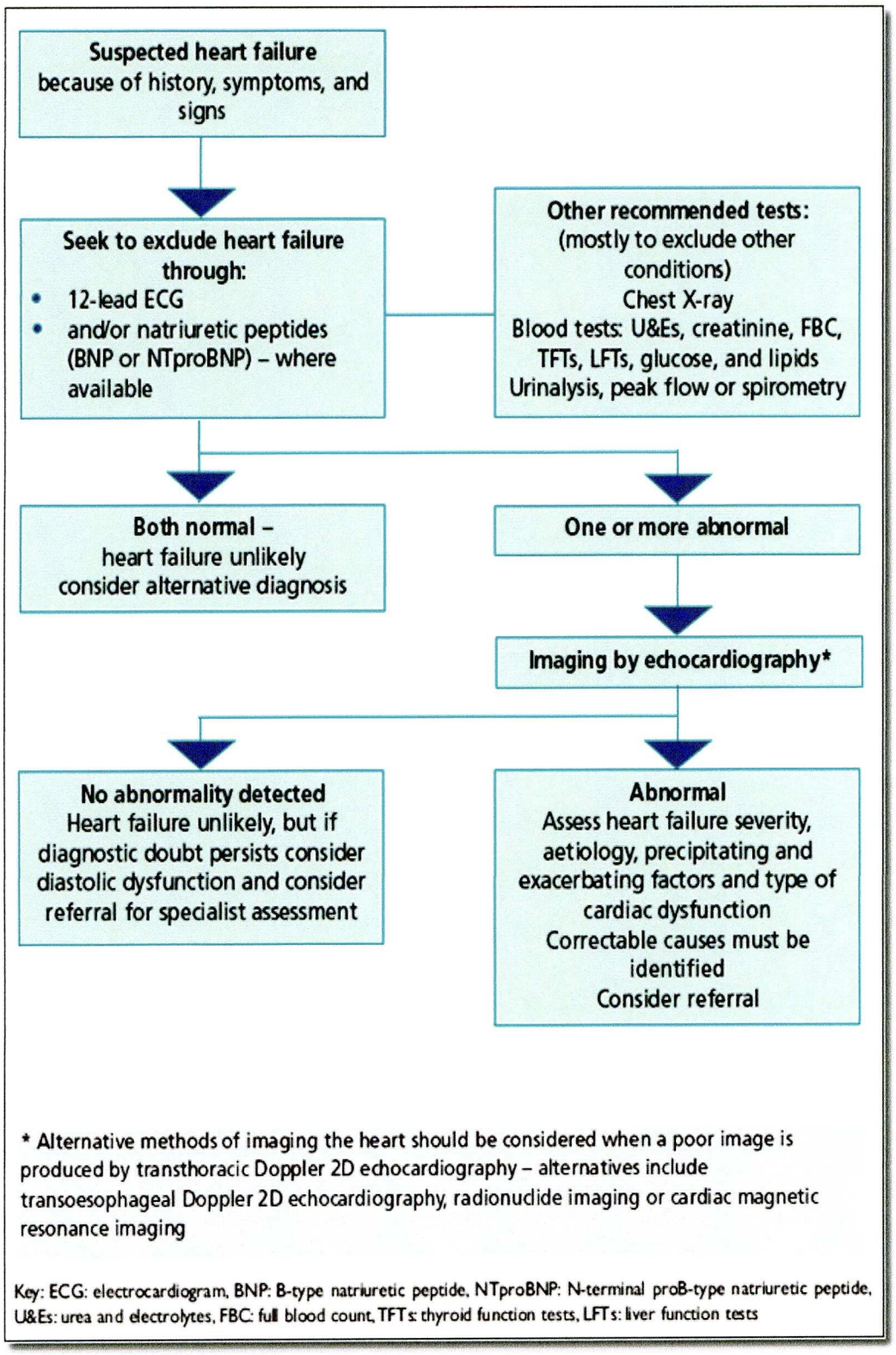

Figure 1.5: Diagnostic alogrithm for heart failure (adapted from the NICE guidelines for chronic heart failure 2003)

1.2 Treatment of cardiac failure

The treatment options available for patients are now extensive and detailed below. The ideal treatment regime would need to be tailored to the individual patient. Treatments are designed to improve symptoms, reduce progression and increase life expectancy. The importance of each of these components will depend on the stage of the disease in any one specific case. The latest American Heart Association guidelines suggested 4 sub groups of patients with heart failure- a group who are currently well but at risk of developing structural heart disease, a group with asymptomatic structural heart disease, a group with symptomatic heart failure and a group with refractory heart failure. The treatments recommended for each group are shown in figure 1.6 (Hunt et al., 2005)

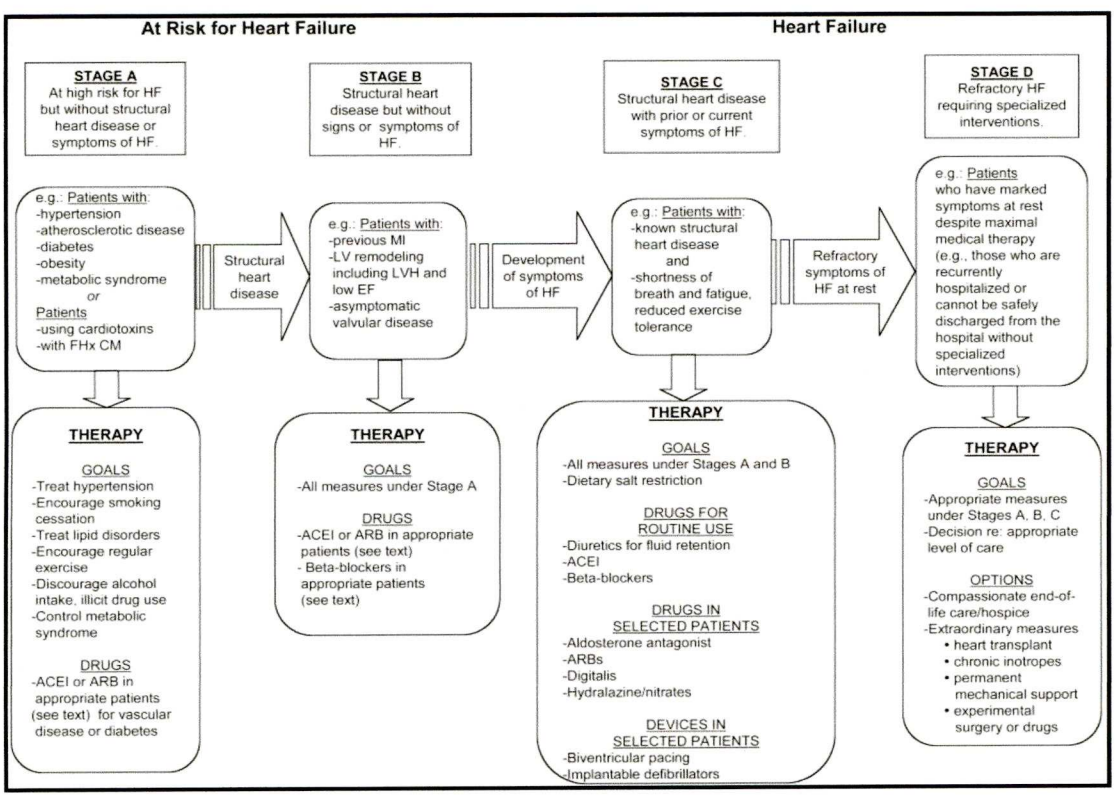

Figure 1.6: Stages in the development of heart failure (adapted from the American heart association guidelines for the management of heart failure (2005))

1.2.1 Lifestyle

Changes in lifestyle are an important treatment aimed at slowing down disease progression. They are particularly important in patients at risk of structural heart disease and patients with asymptomatic structural heart disease. Lifestyle changes are primarily focussed on reducing the risk of ischaemic heart disease, including smoking cessation and good lipid control, and preventing excess fluid accumulation by reducing salt and fluid intake. Patients are also advised to perform regular exercise and if appropriate lose weight to achieve better control of the metabolic syndrome. Good control of hypertension is important and advice is also given to reduce alcohol consumption. Regular innoculations to avoid pneumococcal infections is also important to reduce concomitant illness. Whilst these changes are not specifically designed to improve symptoms they are a very important first step in reducing disease progression (Hunt et al., 2005).

1.2.2 Treatment of reversible causes

The most common cause of heart failure in the modern era is ischaemia (Sutton, 1990). In patients with symptoms of heart failure and reversible ischaemia on functional testing revascularisation may be considered. If the heart failure is secondary to hypertension then adequate treatment may improve symptoms. In patients with valvular heart disease causing heart failure, valve repairs or replacement may improve outcomes. Heart failure can also be secondary to any high output states including hyperthyroidism, Pagets syndrome and atrioventiricular fistulae. In these cases treatment of the underlying condition is paramount in improve the symptoms of heart failure

1.2.3 Exercise training in heart failure

1.2.3.1 Central and peripheral therories of heart failure

The primary initial abnormality in heart failure is the failure of the heart to provide an adequate output. However this central haemodynamic impairment is not the sole cause of the symptoms seen in patients with heart failure. When central cardiac function is suddenly improved (e.g. following cardiac transplantation) there is no immediate improvement in exercise performance but rather a gradual improvement occurs over weeks to months (Savin et al., 1980;Sinoway et al., 1988). This observation has led to the "muscle hypothesis of cardiac failure". This proposes that skeletal muscle is abnormal in CHF. During exercise, muscle has a limited capacity for aerobic metabolism, resulting in fatigue and ergoreflex activation, which causes an increase in the ventilator response to exercise and the sensation of dysopnea. Ergoreflex activation also causes sympathetic nervous system activation, with a consequent increase in afterload and a decrease in blood flow to the periphery, further exacerbating skeletal muscle abnormalities (Clark et al., 1996).

Muscle wasting has been recognised in heart failure. Mancini et al showed that muscle wasting occurs even in mild heart failure and that peak exercise capacity correlated with calf muscle volume (Mancini et al., 1992). Further evidence towards the importance of the peripheries in heart failure was shown in a study by Jondeau et al. In this study the authors performed maximal lower limb cardiopulmonary exercise testing and then added in upper limb exercise in addition, thus increasing the exercising muscle bulk. In normal subjects increasing the exercising muscle bulk led to no further increase in peak VO_2 suggesting that exercise capacity was limited by cardiac function. However in the heart failure group the increase in exercise muscle

bulk led to a further increase in peak VO_2 suggesting that the limitation was at least partly at the skeletal muscle level (Jondeau et al., 1992). The histological appearance of skeletal muscle in chronic heart failure patients has been reported in numerous trials. The majority of these have a shown a reduction in Type 1 (slow twitch, aerobic) fibres and a increase in Type 2 (fast twitch, anaerobic fibres) (Lipkin et al., 1988;Mancini et al., 1989;Sullivan et al., 1990;Drexler et al., 1992). Biochemically there was a reduction in the oxidative capacity of the muscle (Mancini et al., 1989;Drexler et al., 1992). Taken together, the histological and biochemical changes suggest a switch, from aerobic to anaerobic metabolism in the skeletal muscle of patients with chronic heart failure, and a reduction in the activity of oxidative enzymes (Clark et al., 1996).

1.2.3.2 Benefical effects of exercise training

Exercise training is not routinely offered to patients following cardiac resynchronisation therapy in the United Kingdom. However it is now widely accepted that in patients with chronic heart failure a period of exercise training can lead to improvements in exercise capacity, peak VO_2, quality of life and in one trial mortality (Piepoli et al., 2004;van Tol et al., 2006). The mechanism behind the improvement in peak VO_2 is likely to be a combined improvement in central cardiac output and skeletal muscle function. However, the majority of trials evaluating exercise training have focussed on patients with mild heart failure (New York Heart Association (NYHA) I-II). Most recently HF-Action showed that exercise training was safe in patients with more severe heart failure (NYHA II-IV) and led to an improvement in peak VO_2. Despite this there were no significant improvements in mortality or morbidity in this group (O'Connor et al., 2008). Patients suitable for

CRT are of a comparable functional status to those in HF-Action. The combination of exercise training and CRT has not been well investigated with only one small scale study suggesting possible benefit (Conraads et al., 2007). Previous trials looking at exercise in CHF have had varying intensity and frequency. In the ExtraMatch meta analyses the trials varied from 2 to 7 times a week and 50% to 80% of the peak heart rate (Piepoli et al., 2004) and in HF-Action, the largest trial of exercise training in heart failure so far, the exercise programme was 30 minutes 3 times a week in the supervised stage. However, by the end of the trial the average duration of exercise was only 50 minutes per week (O'Connor et al., 2008). Therefore it is still unclear what the ideal training programme should be and whether the addition of exercise training to CRT is beneficial.

1.2.4 Medical therapy

In heart failure there is compensatory up regulation of components of the renin-angiotensin-aldosterone and sympathetic nervous systems due to a reduced cardiac output. This has been shown to suppress myocardial function, cause myocardial hypertrophy and myocyte apoptosis leading to mural thinning and progressive dilation (Bohm et al., 2003). Therefore modulation of these neurohormonal changes has become the cornerstone of treatment. Three main classes of drugs have been shown to improve mortality and symptoms namely drugs blocking the over expression mechanisms (including angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARB)), beta-adrenoceptor blockers and aldosterone antagonists.

There have been 34 trials assessing ACE inhibitors in heart failure. A review of all 34 trials showed a statistically significant reduction in total mortality ($p<0.001$) and combined endpoint of mortality or hospitalisation ($p<0.001$) (Garg and Yusuf, 1995). In animal models it has been shown that despite adequate ACE inhibition there is still near normal production of angiotensin II, via ACE independent pathways, within the myocardium (van Kats et al., 1998). It was therefore postulated that blockade of the renin-angiotensin system at the angiotensin II type 1 receptor level would be more beneficial than ACE inhibition. However this has not been borne out in clinical trials. In a meta-analysis of 17 trials looking at ARBs the results showed that when ARB were compared to placebo there was a non-significant trend towards improved survival ($p=0.19$) and decreased hospitalisation ($p=0.33$) with ARB treatment. When ARB were compared to ACE Inhibitors there was no difference in survival or hospitalisation and when ARB were added to ACE inhibitors and compared to ACE inhibitors alone there was no difference in mortality but there was a statistically significant reduction in hospitalisation ($p<0.0001$) (Jong et al., 2002).

Beta-adrenoceptor blockers have been shown to significantly improve the functional status ($p=0.04$) (CIBIS Investigators, 1994), reduce hospitalisation (($p<0.01$) (CIBIS Investigators, 1994), ($p=0.036$) (Packer et al., 1996)), reduce all cause mortality (($p=0.0062$) (MERIT-HF Study Group, 1999), ($p<0.001$) (Packer et al., 1996), ($p<0.0001$) (CIBIS-II Investigators, 1999)) and reduce sudden death (($p=0.0002$) (MERIT-HF Study Group, 1999), ($p=0.0011$) (CIBIS-II Investigators, 1999)).

Two main aldosterone antagonists, namely Spironolactone and Eplerenone, have been studied in addition to standard therapy, and both produced a significant

reduction in mortality ((p<0.001) (Pitt et al., 1999), (p=0.008) (Pitt et al., 2003)) and morbidity ((p<0.001) (Pitt et al., 1999), (p=0.002) (Pitt et al., 2003)). Further symptomatic treatment is achieved using diuretics and digoxin (The Digitalis Investigation Group, 1997), however neither of these treatments have any impact on mortality.

A combination of the above drugs is now widely accepted as being the optimum medical therapy for heart failure however it has been shown that full implementation of evidence-based doses is rarely achieved in clinical practice (Packer et al., 1996;Philbin et al., 1996;Smith et al., 1998). This is despite the fact that clinical studies have shown that ACE inhibitors at maximum doses are well tolerated by around 80-90% of patients with chronic heart failure (Kjekshus and Swedberg, 1988;O'Connell and Bristow, 1994). The ATLAS trial showed the importance of achieving the maximum tolerated dose, in this large-scale trial it was shown that there was a greater benefit to be gained from high dose (32.5-35mg) versus low dose (2.5-5mg) Lisinopril in patients with heart failure (Packer et al., 1999). Unfortunately in a substantial number of patients despite being on optimal medical treatment they continue to suffer with poorly controlled symptoms and a high risk of death (Cohn et al., 1986;The CONSENSUS Trial Study Group, 1987;Cohn et al., 1991;Packer et al., 1996;Bradley, 2003).

1.2.5 Device based treatments

The mechanism of sudden death in heart failure patients was assessed in a sub-study of the ATLAS trial. In this study 51% of patients with sudden death were thought to have had a primary arrhythmic event (Uretsky et al., 2000). In view of this high

incidence of potentially reversible arrhythmia many trials have evaluated ways of preventing sudden death.

Initially anti-arrhythmic drugs were used in post myocardial infarction (MI) patients with impaired LV function. CAST and CAST II used class I anti-arrhythmic agents (encainide, flecainide or moricizine) versus placebo. Both trials were terminated prematurely due to increased mortality ((p=0.0004) (Echt et al., 1991) (p=0.40) (The Cardiac Arrhythmia Suppression Trial II Investigators, 1992)) in the anti-arrhythmic group. In view of these results the focus switched to amiodarone, and to date there have been 13 randomised trials performed (Hockings et al., 1987;Hamer et al., 1989;Burkart et al., 1990;Cairns et al., 1991;Nicklas et al., 1991;Ceremuzynski et al., 1992;Navarro-Lopez et al., 1993;Doval et al., 1994;Garguichevich et al., 1995;Singh et al., 1995;Julian et al., 1997;Cairns et al., 1997;Elizari et al., 2000). Only three of these have reported a significant reduction in overall mortality (Burkart et al., 1990;Doval et al., 1994;Garguichevich et al., 1995). A meta-analysis of all 13 trials showed that there was a 13% reduction in mortality with amiodarone (p=0.03) and a 29% reduction in arrhythmic death (p=0.0003). There was virtually no effect of amiodarone on non-arrhythmic death (Connolly, 1999).

1.2.6 Implantable cardioverter defibrillator

In the mid 1990's attention began to switch towards implantable cardioverter defibrillators (ICD). Initially ICDs were compared against anti-arrhythmic agents (mainly Amiodarone) in patients who had been resuscitated from ventricular arrhythmias. Three large scale multi-centre trials were carried out in this patient group. The antiarrhythmics versus implantable defibrillators (AVID) trial found a

significant reduction in mortality in the ICD group ($p<0.02$) (The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators, 1997), the Canadian implantable defibrillator study (CIDS) found a non-significant 19.7% reduction in all cause mortality ($p=0.142$) and a non-significant 32.8% reduction in the risk of arrhythmic mortality with ICD therapy ($p=0.094$) (Connolly et al., 2000b), and the cardiac arrest study Hamburg (CASH) which found a non-significant 23% reduction in all cause mortality in the ICD group ($p=0.081$) (Kuck et al., 2000). A meta-analysis showed that there was an overall 28% reduction in mortality ($p=0.0006$) and that this was entirely due to a 50% reduction in arrhythmic deaths ($p<0.0001$). The meta-analysis also showed that patients with a LVEF >35% had significantly less benefit from ICD than those with a EF <35% ($p=0.011$) (Connolly et al., 2000a).

ICDs were thus established as the treatment of choice in preventing sudden death in patients post resuscitation for ventricular arrhythmias. The next step was to decide whether high-risk patients who had not yet suffered a cardiac arrest would benefit from ICD's. The high-risk group initially identified were patients with LV dysfunction post MI with a history of non-sustained ventricular tachycardia (at least 3 beats) and a positive electrophysiological study (EPS) (defined as inducible non-suppressible ventricular tachy-arrhythmias). The two trials looking at this were the multicenter automatic defibrillator implantation trial (MADIT) I and the multicenter unsustained tachycardia trial (MUSTT). Both studies randomised patients to treatment with either an ICD or conventional treatment (including amiodarone). MADIT I found a 54% reduction in mortality with ICD treatment ($p=0.009$) (Moss et al., 1996) whilst MUSTT showed a 76% reduction in cardiac arrest or death from arrhythmia in patients treated with an ICD ($p<0.001$) (Buxton et al., 1999). The

MUSTT trial also showed treatment with serial electrophysiologic drug testing without ICD back up, even when a drug was found that effectively suppressed VT induction, had no significant benefit compared to no treatment (Klein and Reek, 2000).

In the MUSTT trial the patients who were not inducible at baseline (and hence not entered into the trial) were entered into a MUSTT registry. These patients had lower death rates than the randomised, inducible patients. The effect of EF on mortality and inducibility over the course of the trial in both groups of patients (inducible and non inducibility) was examined. The subgroup with the worst mortality rates had low EF and inducibility, followed by the subgroup with low EF and non inducibility and then the group with a normal EF and inducibility. The group with a normal EF and non inducibility VT had the best prognosis. Thus, in MUSTT, EF was a more important predictor of sudden death than inducibility (Buxton et al., 2007).

The MADIT II trial researchers therefore reasoned that in patients with a prior MI and advanced LV dysfunction, the scarred myocardium would serve as a substrate for ventricular arrhythmia, and therefore EPS testing or 24 hour holter monitoring would not be required for risk stratification (Moss et al., 2002a). They therefore took 1232 patients with a history of a previous myocardial infarction and an EF <30% and randomised them, without any further testing, to either implantation of a ICD or conventional treatment. In the group with an ICD there was a 31% relative reduction in mortality compared to optimal conventional treatment (p=0.016). The greatest reduction was seen in a sub group of patients whose QRS width was greater than 150ms (Moss et al., 2002b). Despite EPS inducibility not being an inclusion criteria

593 patients in the ICD arm underwent EPS testing at the time of ICD implantation. EPS inducibility at baseline did not differentiate between those who were more likely to require ICD therapy for termination of ventricular tachycardia or fibrillation from those who were not (Moss, 2003).

More recently the results from Sudden Cardiac Death in Heart Failure trial (SCD-HeFT) were reported. This study took 2521 patients with ischaemic and non-ischaemic NYHA class II and III chronic heart failure and EF <35%. Patients were randomised to an ICD versus amiodarone versus placebo with a primary end-point of all-cause mortality. There was no statistically significant difference between the placebo and amiodarone group, however the ICD group had a significant 23% reduction in mortality ($p=0.007$). The improvement in mortality was independent of the heart failure aetiology and the benefit was greater in the group with NYHA class II, rather than class III, heart failure (Bardy et al., 2005).

ICD therapy has therefore become the treatment of choice in primary and secondary prevention of ventricular arrhythmias. However whilst it is known that ICDs reduce sudden death, it has now been shown that recurrent ICD discharges are associated with psychological disturbances (Dougherty, 1995). Therefore the combination of anti-arrhythmic drugs and ICDs are currently being investigated. In the only double blinded trial looking at the addition of an anti-arrhythmic to an ICD, it was shown that the addition of Sotalol led to a 48% reduction in death or first ICD shock ($p<0.001$) (Pacifico et al., 1999). The evidence for amiodarone is less robust, the conventional versus amiodarone drug evaluation (CASCADE) study was designed to compare amiodarone versus EPS guided drug therapy. However during the course of

the trial ICD placement became standard to both groups and in the amiodarone group there were significantly fewer shocks associated with syncope (p=0.032) and a non-significant reduction in total number of shocks (p=0.14) (The CASCADE Investigators, 1993)

1.2.7 Cardiac resynchronisation therapy

Conduction system delay (evidenced by QRS prolongation) occurs as a consequence of the underlying pathophysiological disease in patients with chronic heart failure and results in dyssynchronous ventricular contractions. This triggers adaptive chamber dilation and neurohormal stimulation (Kass, 2003) leading to diminished contractile reserve of the heart (Nelson et al., 2000) and inefficient myocardial contraction (Hare, 2002). The mean QRS duration increases as the severity of chronic heart failure increases. The percentage of people with a QRS >120ms has been shown to be 9.7% for New York Heart Association (NYHA) class 0-I, 32% for NYHA class II and 53% for NYHA class III (Cohn et al., 1986). In a sub-study of the VEST trial increased QRS width was a independent predictor of mortality ($p<0.0001$) (Gottipaty et al., 1999) (see figure 1.7).

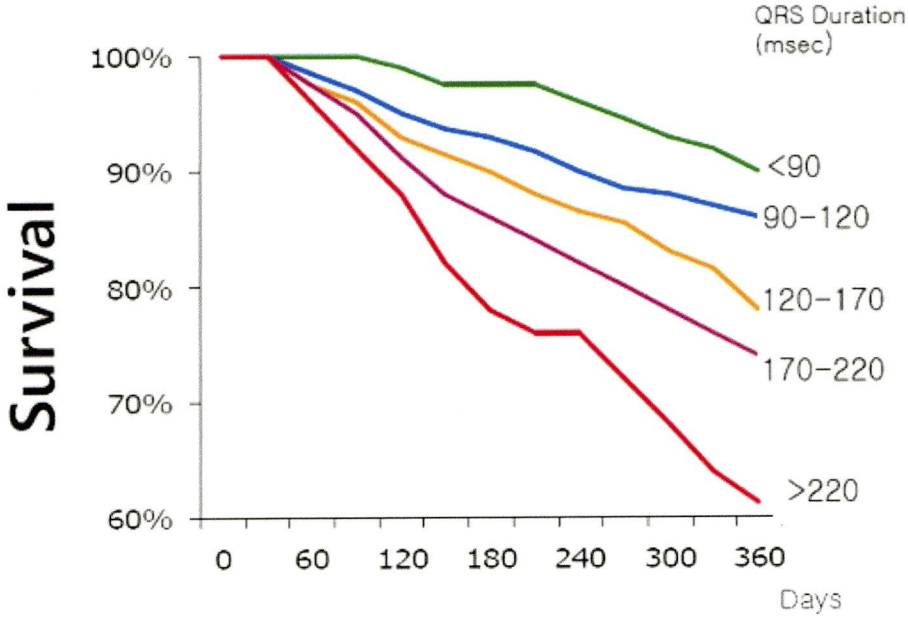

Figure 1.7: QRS duration predicts mortality (adapted from Gottipaty et al 1999)

Studies were devised to reverse LBBB using temporary pacing wires connected to an external pacemaker box, delivering right ventricular (RV), left ventricular (LV) or biventricular (BiV) pacing. These studies showed RV pacing led to no significant improvement over no pacing (Cazeau et al., 1996;Blanc et al., 1997;Kass et al., 1999). BiV and LV pacing was shown to increase the mean cardiac index ($p<0.006$) (Cazeau et al., 1996), decrease the pulmonary capillary wedge pressure ($p<0.01$) (Cazeau et al., 1996;Blanc et al., 1997), decrease mean V wave (($p<0.004$) (Cazeau et al., 1996), ($p<0.001$) (Blanc et al., 1997)), increase the systolic blood pressure (($p<0.03$) (Blanc et al., 1997), ($p<0.0001$) (Auricchio et al., 1999b)) and increase the maximum LV pressure derivative (($p<0.01$) (Kass et al., 1999), ($p<0.0001$) (Auricchio et al., 1999b)). In some of these studies LV pacing had a more beneficial effect than BiV pacing (($p<0.05$) (Kass et al., 1999), ($p<0.01$) (Auricchio et al., 1999b)). This may have been due to the fact that in the BiV pacing group there was synchronous stimulation of both ventricles however this does not recapture the

normal activation of the two ventricles and therefore may be sub-optimal. However the studies had small patient numbers thus preventing firm conclusions (Leclercq and Kass, 2002).

In view of these acute haemodynamic changes CRT devices were developed with right atrial and ventricular leads as seen in a dual chamber pacemaker and an additional lead which is passed through the coronary sinus to the LV free wall (see figure 1.8). The pacemaker can then mimic the intrinsic conduction system and ensure that atrial and synchronised ventricular contractions occur in order to achieve optimal cardiac function and thereby improve symptoms.

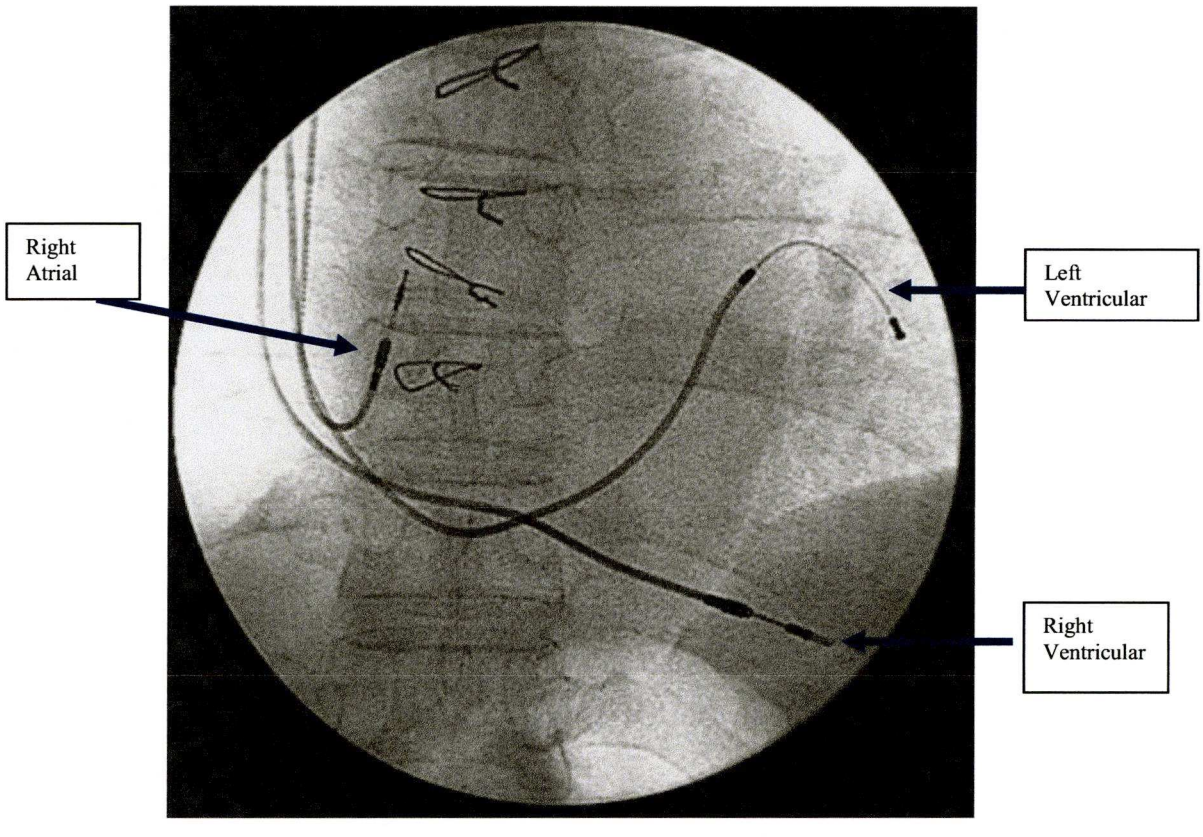

Figure 1.8: Xray showing lead position in a CRT pacemaker

Initially small-scale observational studies, including the pacing therapies for congestive heart failure (PATH-CHF) (n=41) (Auricchio et al., 2002), multisite stimulation in cardiomyopathies (MUSTIC) (n=67) (Cazeau et al., 2001) and the multicenter insync (InSync) study(n=103) (Gras et al., 2002), were carried out to assess the effects of CRT on symptoms and functional capacity. All the patients were on optimal medical treatment but still had severe persistent symptoms (NYHA III-IV), a prolonged QRS duration (>120ms in PATH-CHF, >150ms in MUSTIC and InSync) and a dilated LV (>60mm in InSync). Treatment with a CRT device led to an improvement in quality of life scores ($p<0.001$) (Cazeau et al., 2001;Auricchio et al., 2002;Gras et al., 2002), NYHA class ($p<0.001$) (Auricchio et al., 2002;Gras et al., 2002), 6 minute walk test distance ($p<0.001$) (Cazeau et al., 2001;Auricchio et al., 2002;Gras et al., 2002), peak VO2 (($p<0.001$) (Auricchio et al., 2002), ($p<0.03$) (Cazeau et al., 2001)) and decreased hospitalisations ($p<0.05$) (Cazeau et al., 2001).

In addition CRT therapy was shown to reduce myocardial oxygen consumption (Nelson et al., 2000), which is most likely due to decreased LV wall stress through improved co-ordination of the wall contractions (Toussaint et al., 1999;Curry et al., 2000). This is significant as most heart failure therapies directly enhancing systolic function do so whilst also increasing myocardial oxygen consumption. The only other therapy shown to reduce myocardial oxygen consumption but improve systolic function is beta-blockade (Nelson et al., 2000). Corresponding to these haemodynamic and functional benefits, studies have also shown that CRT leads to a reduction in the LV end-diastolic and end-systolic volumes and also to improved myocardial performance index (Breithardt et al., 1999;Stellbrink et al., 1999b;Gras et al., 2002).

The multicenter insync randomised clinical evaluation (MIRACLE) trial was the first large scale randomised clinical trial looking at CRT in heart failure. 453 patients with moderate to severe heart failure, ejection fraction <35%, and QRS durations >130ms were recruited following successful implantation of a CRT device. The patients were randomised to have the device switched on or off to act as controls. In the active treatment group there was a statistically significant improvement in the 6-minute walk distance ($p=0.005$), the functional class ($p<0.001$), quality of life scores ($p=0.001$), treadmill exercise time ($p=0.001$) and ejection fraction ($p<0.001$). The active treatment group also required less hospitalisation or intravenous medication ($p<0.05$) (Abraham et al., 2002). In a sub-study echocardiograms were performed pre and post treatment with a CRT device. In the active treatment group the echocardiograms showed reduced end diastolic and end systolic volumes ($p<0.001$), decreased LV mass ($p<0.01$), reduced mitral regurgitation ($p<0.001$), improved ejection fraction ($p<0.001$), and improved myocardial performance index ($p<0.001$) (St John Sutton et al., 2003). Therefore the MIRACLE trial showed that CRT treatment improved both symptoms and echocardiographic appearance in patients with moderate to severe heart failure.

It was hypothesised that CRT might improve prognosis in patients with chronic heart failure. The largest trial to date to assess this was the cardiac resynchronisation in heart failure (CARE-HF) trial. This trial enrolled 813 patients and randomised them to either medical treatment or a CRT device. There was a 36% reduction in death from any cause ($p<0.002$) and 52% reduction in hospitilisation from heart failure ($p<0.001$). The CRT group also had a decreased incidence of death from worsening heart failure. This suggests that the improvement in all cause mortality is most likely

due to an improvement in cardiac function following CRT. However in this trial 35% of the deaths occurring in the CRT arm were due to sudden cardiac death (Cleland et al., 2005b). It was therefore postulated that a combination device with CRT and ICD functions may improve outcomes further.

When a meta-analysis of the initial trials (not including CARE-HF) was carried out it showed that CRT led to a significant 51% reduction in deaths from progressive heart failure (Odds Ratio (OR) 0.49, 95% Confidence Intervals (CI) 0.25-0.93), a significant 29% reduction in heart failure hospitalisations (OR 0.71, 95%CI 0.53-0.96) and a non-significant 23% reduction in all cause mortality (OR 0.77, 95%CI 0.51-1.18). It also showed that CRT had no effect on non-heart failure mortality (OR 1.15, 95%CI 0.65-2.02) and was not associated with a reduction in ventricular tachycardia or fibrillation (OR 0.92, 95%CI 0.67-1.27) (Bradley et al., 2003).

Attention thus began to focus on combination devices with both CRT and ICD functions, the latter having been shown to have the greatest impact on mortality in patients fitting selection criteria for the former in MADIT II. Two multicenter randomised trials have evaluated the effect of a combination cardiac resynchronisation and defibrillator device in patient with heart failure, namely the comparison of medical therapy, pacing, and defibrillation in heart failure (COMPANION) trial and the multicenter insync ICD randomised clinical evaluation (MIRACLE ICD) trial.

The COMPANION trial was a three-arm study of 1520 patients with NYHA class III/IV heart failure despite optimal treatment. The inclusion criteria were evidence of

a conduction system delay on 12 lead ECG (with a PR interval >150ms and a QRS interval >120ms), LVEF <35%, end-diastolic LV size >60mm, and hospitalisation for heart failure in the past year. The patients were randomised to drug treatment only, insertion of a CRT device, or insertion of a combination (CRT+ICD) device (Bristow et al., 2000). The results showed that the primary end-point (all cause mortality and all cause hospitalisation) was reduced by 19% in the CRT only group ($p=0.014$) and by 20% in the CRT+ICD group ($p=0.01$). Total mortality was reduced by a non-significant 24% in patients receiving CRT alone ($p=0.059$) and by a significant 36% in the CRT+ICD group ($p=0.003$) (Bristow et al., 2004). The rate of sudden death in the CRT only group was 36% in the COMPANION trial, which is in keeping with the CARE-HF study where the rate was 35% (Cleland et al., 2005b).

Interestingly the rates of sudden death were higher in both the CARE-HF and COMPANION trials when compared to the SCD-HEFT trial. In SCD-HEFT, where the inclusion criteria required symptomatic heart failure (NYHA class II or III) and a low left ventricular ejection fraction (EF<35%) but no need for conduction system delay, the sudden death rates were 29% in the placebo group and 28% in the group receiving amiodarone treatment alone (Bardy et al., 2005). This is in keeping the previously mentioned VEST substudy which showed that QRS duration is a independent predictor of mortality (Gottipaty et al., 1999). The addition of an ICD improved sudden death rates in both the SCD-HEFT trial (22%) (Bardy et al., 2005) and also in the COMPANION trial (16%). Therefore in all the trials the lowest sudden death rate achieved was in the CRT+ICD group in the COMPANION trial (Bristow et al., 2004). However with a rate of 16% it must be noted that an ICD therefore does not guarantee a non sudden death.

The MIRACLE ICD trial also assessed a combination CRT and ICD device . This trial assessed 369 patients with NYHA III/IV heart failure on optimal treatment, with an EF <35% and a QRS interval >130ms. All the patients had a combination device placed, in the control group (n=182) the CRT portion of the device was switched off, in the active treatment group (n=187) the CRT portion was switched on. All of the patients had the ICD facility switched on. At 6 months post device implantation, the active treatment group showed improved quality of life scores (p=0.02), improved functional class (p=0.007), improved peak O_2 consumption (p=0.04) and improved exercise function on a treadmill (p<0.001). No pro-arrhythmiathic tendencies were observed in the active treatment group. In this group there was also no impairment of arrhythmia termination capabilities by the ICD portion. However the MIRACLE ICD trial was not powered or designed to evaluate an effect on mortality (Young et al., 2003).

These trials therefore showed that combination devices could be used safely to provide a significant improvement in both symptoms and mortality. CRT is now an accepted treatment for suitable patients with a wide QRS and severe symptoms of heart failure on stable optimal medical treatment. There is now interest in exploring the effects of CRT in a wider population. Initially a study (RethinQ) was performed to see if patients with severe heart failure and a normal QRS duration would benefit from CRT. In this study there was no significant benefit following CRT in patients with a normal QRS (Beshai et al., 2007). Interest has therefore turned to patients with a wide QRS but only mild symptoms of heart failure. Preliminary results from two recent trials, resynchronisation reverses remodelling in systolic left ventricular dysfunction (REVERSE) and the multicenter automatic defibrillator implantation

trial with cardiac resynchronisation therapy (MADIT CRT), have shown that in patients with a low ejection fraction and a wide QRS but with mild symptoms of heart failure (NYHA I or II) CRT reduces the risk of future heart failure hospitalisation and improved echocardiographic parameters but did not have any effect on mortality (Linde et al., 2008;Moss et al., 2009). CRT pacemakers (CRT-P) and combination devices with CRT and ICD functions (CRT-D) have now been included in the NICE guidelines (National Institute for Clinical Excellence, 2007) and are now routine treatments for suitable patients.

1.2.7.1 Technical aspects of CRT implanation

For patients in sinus rhythm successful implantation of CRT devices requires three transvenous leads in the right atrium, right ventricle and on the epicardial surface of the posterolateral wall of the left ventricle. Patients with atrial fibrillation have a similar procedure but with only right ventricular and left ventricular leads. Initial studies evaluating CRT placed the epicardial left ventricular leads via a full thoracotomy. These patients exhibited significant improvements in peak VO_2, functional class and quality of life scores (Auricchio et al., 2002). However during these studies there were significant complications related to the thoracotomy procedure and subsequent studies therefore used transvenous left ventricular leads. Transvenous leads have the advantage of being done under a local anaesthetic and without a thoracotomy, leading to a significantly reduced peri-operative risk. The epicardial surface of the left ventricle is accessed retrogradely via the coronary sinus. Different areas of the left ventricle can be accessed via the tributaries to the coronary sinus.

Several multi-centre trials have shown that CRT via the transvenous route is an effective procedure (Abraham et al., 2002;Bristow et al., 2004;Cleland et al., 2005b). However a significant operator learning curve exists in all the major trials which exhibit a historic 8-10% failure rate for placement of the left ventricular lead via the transvenous route (Abraham et al., 2002;Cleland et al., 2005b). This failure of implantation can be due to multiple factors including operator inexperience, failure to cannulate the coronary sinus, diaphragmatic stimulation and recurrent displacements due to low stability of some leads. As transvenous CRT has evolved there has been a vast improvement in the delivery catheters, and a wider variety of left ventricular leads, which should mean an improved success rate in the future.

There is also an overall 30% non-responder rate which may reflect compromised lead positioning, for example due to high thresholds, diaphragmatic twitching or lack of an appropriate target vein (Young et al., 2003;Rivero-Ayerza et al., 2003). Transvenous left venticular lead position is limited by the fact the final postion is dependent on the coronary sinus venous anatomy. In multiple studies it had been showed that the ideal pacing site for the left ventricular lead was the mid lateral wall accessed via a posterolateral branch of the coronary sinus (Auricchio et al., 1999a) (Butter et al., 2001) (see figure 1.9), whilst this is the first choice when implanting CRT devices, some patients do not have an appropriate vein going to this site. In this circumstance an alternative less haemodynamically beneficial site may be used which may lead to clinical non response.

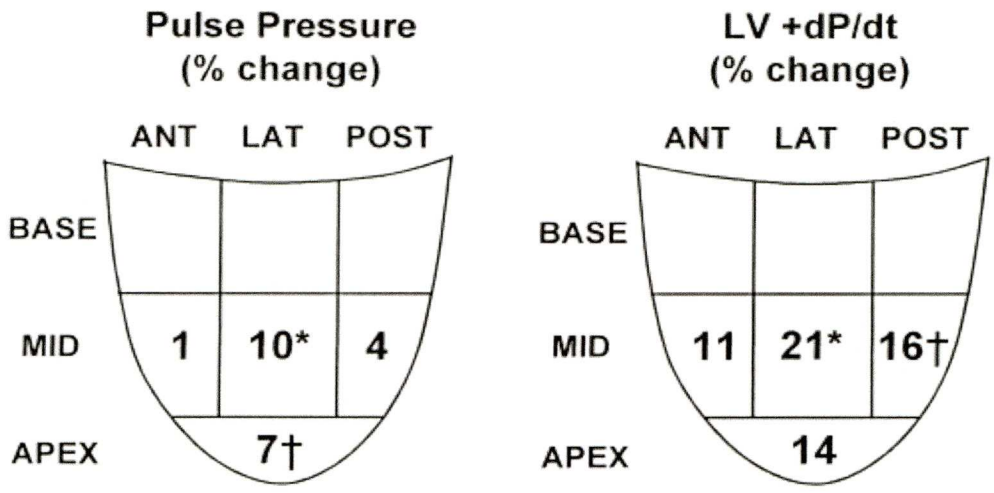

Figure 1.9: Average percentage change from baseline in systolic parameters at different left ventricular pacing sites (adapted from Auricchio et al 1999a)

The options for patients in whom a suitable target vein is not available are unclear and may include epicardial placement of the left ventricular lead on to the lateral wall (see section1.2.7.2). Following successful implantation there is currently no consensus on whether optimisation is beneficial and no standard guidelines exist on the best method to optimise patients following CRT.

1.2.7.2 Non responders to CRT

The rate of responders and non-responders to CRT is hard to define accurately as currently no consensus is held on the definition of a non-responder to CRT. Multiple trials have reported results from CRT and assessed predictors of response. Unfortunately each of these have used different criteria for response. Alonso et al used a improvement of 1 NYHA class and a 10% increase in peak VO_2 (Alonso et al., 1999), Oguz et al used only a improvement of 1 NYHA class (Oguz et al., 2002) and Stellbrink et al suggested a left ventricular end stroke volume decrease of greater than 15% (Stellbrink et al., 2001) . From a device perspective the primary role of resynchronisation therapy is to provide a more co-ordinated ventricular contraction,

therefore it could be argued that the purest response to CRT would be to show an improved contraction such as a increased ejection fraction. However from a patients' perspective response can only be defined if the improved ventricular contraction leads to an improvement in exercise capacity and symptoms. Therefore using only one variable to assess response is likely to be inaccurate. A combination of variables which takes both the more co-ordinated ventricular contraction and an improved exercise performance may therefore provide a more accurate basis for assessing response. This may be achieved by defining a postive response as being an improvement in both peak VO_2 and ejection fraction.

It is also important to remember that advanced heart failure is often a progressive disease and that maintaing the patients current level may still be an improved outcome. The cause behind non-response is likely to be multifactorial and may include poor patient selection and technical compromise of left ventricular lead implantation.

1.2.7.3 Implanation of the left ventricular lead via a thoracotomy

The initial studies evaluating the acute response to CRT placed the epicardial left ventricular lead via a thoracotomy. The mid-lateral wall was shown to be the ideal pacing site in the LV (Butter et al., 2001;Auricchio et al., 2002). The lateral wall was accessed via a full thoracotomy. These studies showed signficant improvements in functional class and exercise haemodynamic measures. However there was a signficant complication rate related to the thoracotomy procedure and a concern about long term lead performance (Butter et al., 2001;Auricchio et al., 2002). At that time therefore interest shifted towards transvenous leads which were associated with

lower procedural complications. As described in section 1.1.11 transvenous lead has been shown to lead to signficant improvements however in a small percentage of people the coronary venous anatomy is not ideal for a transvenous approach. The options for this group till recently were either a compromised transvenous placement or a full thoracotomy with the attached higher procedural risks. Recently case reports and case series have suggested epicardial lead placement via a lateral mini thoracotomy as an alternative to allow delivery of CRT (Mair et al., 2005). This potentially has the advantage of reducing operative risk compared to a full thoracomy and therefore may be a viable option for patients in whom transvenous implanation is not ideal. However the published case series looking at epicardial placement via a minin thoracotomy have involved small numbers and there is no long term data on the haemodynamic effects compared to standard transvenous lead implantation.

1.3 Exercise testing in the evaluation of cardiac failure patients

There is no universally accepted definition of chronic heart failure. A broad definition is that chronic heart failure is the inability of the heart to provide the required cardiac output to meet the metabolic requirements (Denolin et al., 1983). The primary goal of chronic heart failure management is therefore to improve the cardiac function and hence allow better physical performance. Exercise testing is now an accepted investigational tool for patients suffering from heart failure. Its major advantage over traditional cardiac tests is that it assesses the heart at exercise rather than just at rest. Exercise testing provides a objective functional assessment of a patient's condition and has been shown to be accurate at predicting prognosis. In one study (Myers et al., 2002) peak exercise capacity was shown to be the strongest

predictor of all-cause mortality amongst both normal subjects and those with cardiovascular disease. Exercise capacity outperformed other traditional markers of cardiovascular risk, including smoking, hypertension, diabetes, previous history of a myocardial infarction or chronic heart failure and hyperlipidaemia. The authors concluded that, in terms of reducing mortality from any cause, improving exercise tolerance warranted at least as much attention from physicians as other traditional risk factors (Myers et al., 2002). Serial exercise testing is also a very useful tool to assess response to treatment.

Exercise tests are conducted on either a treadmill or bicycle ergometer and there is considerable debate as to which best suits patients with heart failure. It is important to take into account the exercise protocol as this can significantly affect the results. When different protocols are used peak VO_2 varies considerably whereas VO_2 at the anaerobic threshold remains reproducible (Pina and Karalis, 1990). Patient motivation is another factor that can significantly affect the overall VO_2 measured. It is important to reduce the effect of external variables on the measurement of haemodynamic measures. To ensure reliable results repeated testing should be performed at same time of the day and should be at a controlled temperature. It is also important to ensure that food and caffeine intake are kept to a minimum for at least 4 hours prior to testing. A separate familiarisation test is usually performed to ensure that familiarisation bias is eliminated. Treadmill testing produces a 10-15% higher peak VO_2 and ventilation threshold compared to bicycle testing. This is due to the greater mass of skeletal muscle used (Page et al., 1994). The protocol used is of equal importance to the method of exercise testing. When performing exercise testing in patients with severe heart failure, such as those being investigated in this

thesis, it is generally considered safer to investigate patients using gentle protocols with small increments in speed and incline, for example the modified Bruce or Naughton scale.

1.3.1 Peak VO_2

Oxygen consumption (VO_2) (mls/min) is a measurement of an individual's ability to transport and utilize oxygen during exercise. For a given individual the relationship between work and oxygen consumption is linear until a level after which further increases in work load do not lead to further increases in oxygen consumption. This plateau is defined as the maximal oxygen consumption (VO_{2Max}). To achieve a reproducible plateau VO_{2Max} requires significant subject determination and is often impossible to achieve in patients with significant cardiac dysfunction. In these patients a peak VO_2, defined as the highest oxygen consumption measured at peak exercise, is a more reproducible measure. The measured value of VO_2 is dependent on a combination of factors including pulmonary ventilation and gas diffusion, cardiac output and skeletal muscle oxygen utilisation.

Peak VO_2 is a more reliable index of functional capacity than exercise duration or workload as it represents a more precise, reproducible and physiological measure of cardiopulmonary function (Myers and Gullestad, 1998;Francis et al., 2001). Numerous studies published in the last two decades demonstrate peak VO_2 to be an independent predictor of mortality (Szlachcic et al., 1985;Cohn et al., 1993;Myers et al., 1998;Pardaens et al., 2000). Szlachcic et al were the first group to suggest a cut off value, of 10mls/min/kg, that was useful in risk stratisfication of patients with severe heart failure. Subsequently a cut off value of 14mls/min/kg has been shown to

confer an equal 1 year mortality compared to cardiac transplantation (Mancini et al., 1991). This value is currently accepted as a threshold for consideration of cardiac transplantation however there is currently some debate as to whether this cut off is helpful. Wilson et al tested a group of patients being referred for cardiac transplantation. They showed that there was a poor correlation between peak VO_2 and invasive cardiac haemodynamic measurements. In fact 44% of patients with mild to moderate haemodynamic abnormalities had a peak VO_2 <14mls/min/kg and 25% of patients with severe haemodynamic impairment had a peak VO_2 >14mls/min/kg (Wilson et al., 1995). Following this study it was suggested that a peak VO_2 <10mls/min/kg was associated with a poor prognosis and should be considered for transplantation, a peak VO_2 >18mls/min/kg was associated with a good pronosis and transplantation should be deferred and further haemodynamic testing is required for the group with a peak VO_2 between 10 and 18mls/min/kg (Pina, 1995).

1.3.1.1 Limitation of peak VO_2

Peak VO_2 is widely used in many of the clinical trials assessing cardiac patients. It is often described as being indicative of cardiac function. However peak VO_2 can be influenced by many non-cardiac factors including skeletal muscle function, physical size and hyperventilation (Fleg and Lakatta, 1988;Wilson et al., 1995;Coats, 2001). A recent study showed that peak VO_2 reproducibility within subjects is poor, and therefore different tests done on different days are likely to give different values (Bensimhon et al., 2008). This has implications on testing for heart failure especially when using a cut off value of 14mls/min/kg for transplantation. It would therefore be more reliable to use peak VO_2 as continuous variable rather than having a discrete cut off. A large study consisting of 664 patients during a 10-year period of follow up

showed that peak VO_2 was an independent predictor of mortality above and below a range of 10-17 mls/min/kg, rather than at a cut-off point of 14 mls/min/kg (Myers et al., 2000). These limitations have encouraged researchers to move to more cardiac specific markers such as cardiac power output and cardiac reserve (Tan, 1987;Tan and Littler, 1990).Williams et al showed cardiac output reserve to be the best prognostic indicator of all cardiopulmonary variables at predicting mortality at 10 years (Williams et al., 2005) and also in a separate study peak cardiac power output was the only independent predictor of prognosis in chronic heart failure patients (Williams et al., 2001)

1.4 Cardiac power output and cardiac reserve

1.4.1 Theoretical model of cardiac power output and cardiac reserve

The heart is, at its most basic, the pump responsible for generating flow and pressure around the body. In chronic heart failure the symptoms seen are due to failure of the pressure and flow generating capabilities. The cardiac pump has a potential output between zero and infinity. To adequately describe the capabilities of the heart both the resting and peak cardiac function have to be assessed. For most patients with heart failure the symptoms are mainly related to exertion and therefore resting cardiac output may be fairly normal. If only resting cardiac output is measured then it is possible to get a false impression in this scenario. Therefore two important terms can be applied to cardiac performance:

(a) Cardiac pumping capability – the maximum performance that can be achieved.

(b) Cardiac pumping reserve – the difference in performance between resting and maximal states.

This concept was initially proposed by in 1916 (Barringer, 1916) and has since been re-evaluated and modified (Tan, 1986;Tan, 1987;Tan, 1991). The primary job of the heart is to deliver oxygen to organs and peripheral tissues. The delivery of oxygen is dependent on the rate of blood flow into the vascular bed of an organ. Therefore the first demand placed on the heart is the production of an adequate cardiac output (CO). The blood flow to the tissues can also be increased by reducing the systemic vascular resistance or by increasing the arterial perfusion pressure. Increasing the arterial perfusion pressure assumes greater importance in skeletal muscle during exercise because of higher tissue pressure during muscular contraction, in particular during isometric exercise. Hence, the second demand imposed on the heart is the maintenance of an adequate arterial pressure. The product of cardiac output and arterial pressure is defined as cardiac power output (CPO). This term represents the demand imposed by metabolising tissues on the cardiac pump.

Cardiac pumping capability can thus be defined as the maximum cardiac power output achieved by the heart's during maximal stimulation, and cardiac reserve as the increase in power output as the hearts performance is increased from the resting state to the maximally stimulated state. It is important to distinguish between direct and indirect measurements of cardiac function. Cardiac output is by its very nature a direct measurement of cardiac function. Other commonly used measures such as peak VO_2 and exercise duration are strongly affected by cardiac function, however they are also affected by non cardiac factors such as skeletal muscle function, and therefore have to be classified as indirect measures. Schlosshan et al suggested a hierarchy of cardiac function measures ranging from resting measures such as ejection fraction to peak cardiac power (Schlosshan, 2007) (see figure 1.10)

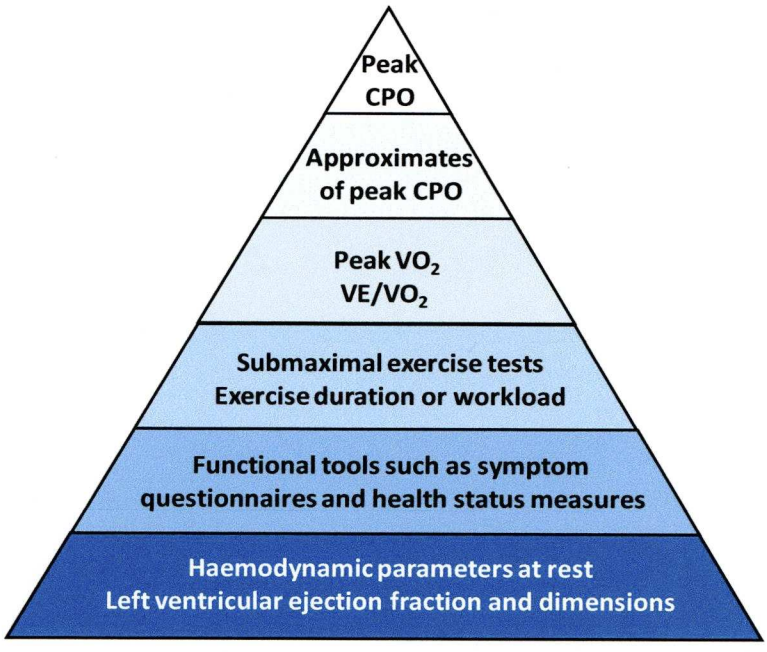

Figure 1.10: Hierarchy of indices of cardiac function (adapted from D. Schlosshan et al 2007)

CRT aims to improve both the flow and pressure generating capabilities of the heart by resynchronisation of the ventricular contractions. Resynchronisation is the mechanism of action of CRT but cannot be viewed as the end goal. Electrical resynchronisation in a heart that is scarred from previous myocardial infarction and therefore non-contractile, would not lead to any significant increase in haemodynamic function. Therefore to assess patients fully following CRT both the pressure and flow generating capabilities have to be tested. The major trials to date have used peak VO_2 as the main outcome measure, however peak VO_2 is significantly affected by both pulmonary and skeletal muscle function and is therefore not a ideal marker of cardiac function. When assessing the effect of CRT on cardiac function direct measurement of cardiac function should be considered the gold standard.

1.4.2 Clinical application of Cardiac power output and Cardiac Reserve

Cardiac power output is defined as the product of cardiac output (CO), mean arterial pressure (MAP) and a conversion factor of 2.22 $x10^{-3}$ (Tan, 1986) (see appendix 1). It is expressed in watts (W). Cardiac power output (CPO) can be calculated at a resting state and maximal exercise. The difference between resting cardiac power output and peak cardiac power output is the cardiac reserve (CR) (see figure 1.11).

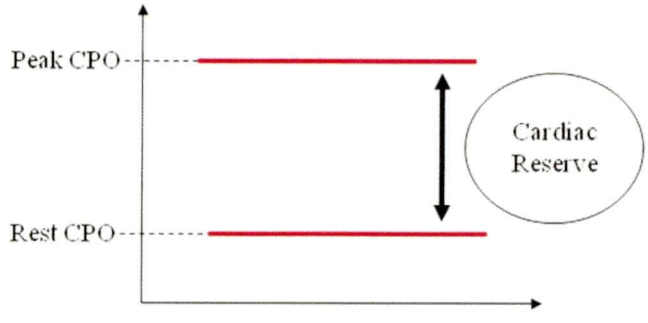

Figure 1.11: Relationship of peak CPO and cardiac reserve

The initial studies looking at cardiac power output and cardiac reserve were carried out using invasive catheters to measure cardiac output and mean arterial pressure. The first such study was done by Tan in 1986. In this study sixty three patients with a mean left ventricular ejection fraction of 24.2% and severe heart failure (NYHA III-IV) were studied. Invasive haemodynamic measurements were recorded at rest. Dobutamine was then infused as a stress agent increasing in increments of 5mcg/kg/min to a maximum of 40mcg/kg/min. The hypothesis tested was that a maximal CPO of <1 watt (assumed to be normal resting value for average sized male) could discriminate between survivors and non-survivors at one year follow up. Of the 23 patients with a maximal CPO <1 watt, 19 died of progressive heart failure. Four patients died in the group of 40 with a maximal CPO of ≥1 watt. No pattern was

seen with any resting haemodynamic parameter. Conclusions were drawn therefore that a maximal CPO <1 watt was indicative of a poor 1-year survival (Tan, 1986).

Two further studies done using invasive measurement and dobutamine stress were subsequently carried out. The first studied the application of cardiac power output in patients with acute cardiogenic shock. The study showed differences between survivors and non-survivors in resting and maximal left ventricular stroke work index (LVSWI), maximal cardiac index (CI) and maximum CPO. All patients with a resting CPO <0.35 watts died, as did all patients with a maximum CPO of <1 watt or a LVSWI <0.25 J/m^2 (Tan and Littler, 1990). In the second study a group of critically ill patients on an intensive care unit were studied. No patient with a maximal CPO <1.5 watts survived. Survivors also had considerably higher values of LVSWI (resting and stress) and resting CPO (Timmins et al., 1992). These 3 studies helped to establish cardiac power output and cardiac reserve as useful measures in the assessment of cardiac patients.

All the above studies were performed using dobutamine as the stressor agent. Tan et al showed that exercise induced stress produced comparable maximal CPO to dobutamine testing (Tan et al., 1989). However dobutamine has peripheral effect in addition to its inotropic and chrontropic effects. Therefore a more physiological method of stress would be exercise. Roul et al were the first group to evaluate the prognostic value of peak CPO during maximal exercise testing in patients with CHF. This group assessed 50 patients with NYHA class II-III CHF using invasive measurements of haemodynamic parameters during maximal supine exercise with a mean follow up of 21.2 ± 1.2 months. Multivariate analysis revealed peak CPO to be an

statistically significant independent predictor of death or a major cardiac event ($p<0.00001$) and a peak CPO <2 watts was found to accurately identify patients with a poor short term prognosis ($p<0.003$) (Roul et al., 1995).

1.4.3 Non-invasive assessment of cardiac power output and cardiac reserve.

The initial trials using cardiac power output had shown it to be a useful prognostic marker in patients. The trials had so far used invasive methods to calculate cardiac output using the direct Fick method (see figure 1.12). However invasive haemodynamic measurement is not without its risks and is not suitable for routine clinical use or for serial testing. The major difficulty in measuring CPO and CR non-invasively is the need for accurate cardiac output measurement. Mean arterial pressure can be accurately measured using a standard sphygmomanometer.

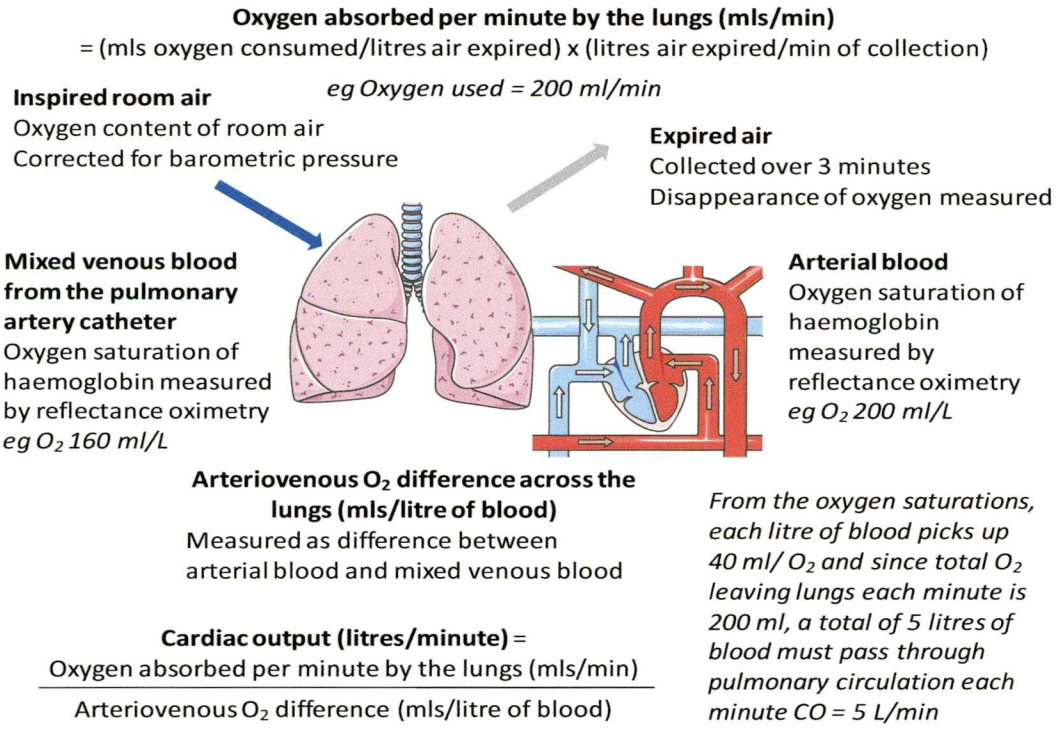

Figure 1.12: Schematic example of cardiac output calculation from the direct Fick method (Guyton, Medical Textbook of Physiology, 1991)

Several techniques have been previously used to measure cardiac output non invasively and these included impedance cardiography (Kinnen et al., 1964), transcutaneous doppler (Feigenbaum et al., 1967) and radionuclide ventriculography (Slutsky et al., 1979). However, these techniques are impractical for the measurement of CO at peak exercise. The current versions of cardiopulmonary exercise test machines now come with the capabilities to measure cardiac output. These use the indirect Fick equation (Cardiac output (L/min) = CO_2 production (L/min) / (venous - arterial CO_2 concentration) to work out cardiac output. During cardiopulmonary exercise testing, CO_2 production is measured directly, along with O_2 consumption. The arterial CO_2 partial pressure can be extrapolated from the end-tidal pressure of CO_2 ($PETCO_2$), assuming that equilibrium exists between the gas in the alveolar space and the pulmonary vein capillary bed (Campbell and Howell, 1960). Computerised dissociation tables then convert partial pressure to concentration (McHardy, 1967). To complete the indirect Fick equation required the calculation of venous CO_2 concentration. This involves re-breathing gas containing pre-determined concentrations of CO_2 using the lung as a tonometer for the equilibrium of CO_2. The two most widely reported methods of calculating venous CO_2 concentration are Defares's (Defares, 1958) and Collier's (Collier, 1956). Both these use rebreathing of a constant concentration of CO_2 to estimate venous CO_2 concentration. Initial comparison showed good agreement between the methods ($r=0.97$, $p<0.001$), and a good correlation between Colliers method and direct dye-dilution ($r=0.94$, $p<0.001$) at rest (Muiesan et al., 1968). Comparison of Defares method and dye-dilution at rest was disappointing ($r=0.22$) though the correlation gradually improved with increasing workload ($r=0.87$) at maximum exercise (Ferguson et al., 1968).

Following this early work further studies have evaluated both these methods in different patient groups. Wilmore et al, employed the automated "Beckman metabolic measurement cart" to measure cardiac output by the Collier method in 6 healthy subjects during exercise, and 11 patients with coronary artery disease during cardiac catheterisation. The rebreathe value for cardiac output exhibited an almost linear relationship with VO_2 ($r=0.9$), and correlated well with the cardiac output measured using the thermodilution method during rest ($r=0.87$) (Wilmore et al., 1982).

Reybrouck et al compared the Defares method with the invasive Fick method in 16 hypertensive patients at rest and during exercise. There was a good overall correlation ($r=0.96$, $p<0.001$). However, at rest the cardiac output was overestimated using the rebreathing method by an average 0.5 l/min, ($p<0.05$). During exercise the mean difference was negligible ($p>0.25$) and the limits of agreement were substantially improved. It was thus concluded that the Defares rebreathing measurement of cardiac output was acceptable during exercise, but not at rest (Reybrouck and Fagard, 1990).

Russell et al measured the cardiac output at rest in 25 patients with valvular heart disease or dilated cardiomyopathy. Duplicate recordings were made by three techniques; the Collier rebreathing, invasive dye-dilution and invasive thermodilution. The reproducibility of measurements in individual patients was satisfactory with dye-dilution but was poor with Collier rebreathing and thermodilution, only 50% and 70% of the differences being within 20% of the mean respectively. Measurements of cardiac output by the Collier rebreathing method were

not significantly different from those obtained with dye-dilution (mean difference – 0.3 l/min). Unfortunately correlation coefficients were not calculated on the available data. Thermodilution significantly overestimated cardiac output by a mean of 2.2 l/min ($p<0.001$) compared with rebreathing and by a mean of 1.9 l/min ($p<0.001$) compared with dye-dilution. It was concluded that the Collier method of measuring cardiac output was acceptable at rest, providing duplicate recordings were made in order to correct for the inherent variability. The commercially available thermodilution method of measuring cardiac output was found to be unsatisfactory because of variable results and overestimation compared with dye-dilution (Russell et al., 1990).

Nugent et al compared the Collier rebreathing method of measuring cardiac output at rest with the direct Fick and thermodilution techniques in 11 patients under investigation for suspected coronary artery disease. The rebreathing results were consistently lower than the other two methods (mean difference –0.73, 95% confidence interval –0.95 to –0.5 l/min with the direct Fick, and -0.72, 95% confidence interval –1.19 to –0.26 l/min with thermodilution). In the same study 11 healthy subjects underwent Collier rebreathing cardiac output measurements at rest and during two levels of steady state exercise, on three consecutive days. Reproducibility of results between replicates at rest (coefficient of variation 9.1%) improved with exertion (coefficients of variation 5.6% and 5.4% respectively at each exercise level) (Nugent et al., 1994).

In summary, the indirect rebreathing methods of Collier and Defares are less accurate and less reproducible than dye dilution or direct Fick techniques for measuring

cardiac output at rest. The Collier method although providing a slight underestimation, is more consistent and accurate than the Defares method. During exertion however, both methods provide acceptable and reproducible results. For practical reasons it is simpler to perform the Defares method during maximal exercise. It was therefore proposed to adopt the Collier method for measuring cardiac output at rest and the Defares method during exercise testing. Numerous studies have now been completed with this protocol and have shown it to be a safe and effective method of calculating cardiac output (Cooke et al., 1998;Williams et al., 2001;Wright et al., 2003;Schlosshan et al., 2006).

1.5 Aims and objectives

This review has highlighted the importance of obtaining objective measures in the evaluation of cardiac resynchronisation therapy. With the development of non-invasive techniques to assess cardiac power output, it is now possible to obtain measurements of cardiac functional capacity using cardiopulmonary exercise testing. This thesis applies these methods to investigate several hypotheses in patients with chronic heart failure suitable for cardiac resynchronisation therapy, in order to further our understanding of complex mechanisms in these disease areas and to realise the importance of the application of these measures in clinical practice. The hypotheses tested in this thesis are:

(1) That cardiac resynchronisation therapy leads to improvements in central haemodynamics but has no effect on the peripheral effects of heart failure.

(2) That exercise training in addition to cardiac resynchronisation therapy will improve the overall outcome by reversing skeletal muscle deconditioning.

(3) That epicardial lead placement via a mini-thoracotomy was a safe technique and provided similar improvements to transvenous left ventricular lead placement.

These hypothesis were tested using three studies. The objectives of these studies were:

1.5.1 Study I: The longitudinal improvement in exercise haemodynamic measures following cardiac resynchronisation therapy

1) To assess the impact of cardiac resynchronisation therapy on cardiopulmonary indices, exercise haemodynamics, cardiac pump function and skeletal muscle function. More specifically, to evaluate:
   - The rate of improvement in functional class, exercise haemodynamic measures and skeletal muscle torque.
   - To identify which variables or patient characteristics predict significant improvement in exercise capacity following technically successful CRT.

2) To assess the impact of cardiac resynchronisation therapy on symptoms and quality of life using the Minnesota living with heart failure questionnaire (MLWHF).

1.5.2 Study II. The effects of exercise rehabilitation in addition to cardiac resynchronisation therapy

1) To assess whether a formal exercise rehabilitation programme in addition to cardiac resynchronisation therapy leads to a further improvement in functional class, exercise capacity and exercise haemodynamic measures.

2) To assess whether exercise rehabilitation reverses skeletal muscle deconditioning in patients following CRT.

3) To assess the effect of exercise training in non responders to CRT.

1.5.3 Study III. The effectiveness of cardiac resynchronisation therapy placed via a mini thoracotomy in patients with previously failed transvenous placement

1) To examine the whether left ventricular lead placement via a mini thoracotomy was feasible in patients with previously failed transvenous placement.

2) To assess the improvement in functional class, exercise capacity and exercise haemodynamic measures in patients following left ventricular lead placement via a mini thoracotomy

3) To compare the difference in response following lead placement via mini thoracotomy and transvenous lead placement

CHAPTER 2: METHODS

2.1 Background

The methodology using cardiopulmonary exercise testing described in this thesis is based on work previously carried out (Cooke et al., 1998;Williams et al., 2001;Wright et al., 2003). A non-invasive method of evaluating cardiac power output was developed and validated by Cooke et al (Cooke et al., 1998). Seventy subjects, with a wide range of cardiac function (from athletes to patients with severe CHF), were studied in the development and validation of non-invasive measurements of various exercise parameters and CPO (Cooke et al., 1998). Using these methods I studied the impact of CRT alone, CRT with exercise training and CRT placed epicardially in appropriately selected patients.

2.2 Exercise testing protocol

The exercise tests were performed over two days. On the first day a transthoracic echocardiogram was performed after 30 minutes rest. This was followed by triplicate measurements of resting cardiac output using Collier's method (Collier, 1956). Following this an incremental cardiopulmonary exercise test was performed and peak cardiac output measured using Defares method (Defares, 1958). The second day a second exercise test was performed and peak cardiac output measurement. After at least 30 minutes rest peak lower limb skeletal muscle function was measured.

2.2.1 Familiarisation and standardisation

Patients were made familiar with the exercise equipment and introduced to the staff prior to recruitment for any of the studies. The purpose of the studies and the procedures were explained in full before written consent was obtained. All patients performed a preliminary cardiopulmonary exercise test and non-invasive

measurements of cardiac output were made at rest and during exercise. The findings from this test were discarded and not used in the final results. Familiarisation identified patients not able to complete any part of the studies in this thesis – e.g. patients not able to exercise maximally due to non-cardiac limitation, not willing to give blood etc. These screened patients were not entered into the studies.

Exercise testing was conducted on the same Cosmos treadmill (Cosmos, Nussdorf-Traustein, Germany) throughout the studies using a modified Bruce protocol. The same supervisors (me and a sport scientists) conducted the tests throughout. All patients were exercised after a two-hour postprandial period and were asked not to consume alcohol or caffeine for the preceding 12 hours. The room in which the tests were carried out was maintained at a constant temperature of 22°C using an air conditioning system controlled by a thermostat. Follow-up tests were performed at the same time of day for each individual.

2.2.2 Calibration

The gas analysis system was calibrated before each test. The pneumotach, which was used to measure gas volumes was calibrated manually with a 3 litre syringe (Cardiokinetics, Salford, UK) by five injections and withdrawals, representing fluctuations in respiration, after a baseline was established (no flow). The O_2 and CO_2 analysers were also calibrated using bottled gases, and the manual sphygmomanometer was checked against a standard mercury column manometer every month.

2.2.3 Day One – Echocardiogram

Transthoracic echocardiograms were performed prior to any testing and after at least 30 minutes rest. All the echocardiograms were performed by myself in the same room at John Moores University. All echocardiograms were performed using a Acuson Cypress echocardiography system (Siemens medical solutions, Malvern, USA). The scans were performed in the left lateral position. Parasternal long axis, parasternal short axis and apical views were obtained. Left ventricular dimensions were measured in systole and diastole using m-mode in the parasternal long axis. Ejection fraction was calculated using the Simpson's rule (Otto, 2004) from the apical 4 chamber and apical 2 chamber views.

2.2.4 Minnesota living with heart failure questionnaire.

The Minnesota living with heart failure questionnaire was first designed in 1984. It measures the effects of heart failure and treatments for heart failure on an individual's quality of life. The questionnaire assesses the impact of frequent physical symptoms - shortness of breath, fatigue, peripheral oedema, and difficulty sleeping - and psychological symptoms of anxiety and depression. In addition it also measures the effects of heart failure on physical and social functioning. Since treatments might have side effects in addition to ameliorating symptoms and functional limitations produced by heart failure, questions about side effects of medications, hospital stays and costs of care are also included to help measure the overall impact of a treatment on quality of life. To measure the effects of heart failure symptoms, functional limitations and psychological distress on an individual's quality of life, the MLHFQ asks each person to indicate using a 6-point

(zero to five) scale how much each of 21 questions prevents them from living as they desire (see appendix 3 for trial questionnaire).

2.2.5 Day one – Resting Cardiac Output

Resting CO was measured using the CO_2 re-breathing method of Collier (Collier, 1956), as previously described in section 1.4.3. Patients sat at rest for five minutes, until respiratory values were stable, with respiratory monitoring and a 12 ECG lead for heart rate measurement. A 5 litre anaesthetic bag was connected to the pneumotach with a three-way tap in between. The bag was filled to 2 times the resting V_t, with a CO_2 concentration calculated by the computer from the following equation:

$$\text{Bag } CO_2 = (48.5 + 0.007 \times VCO_2 = 0.7 \times ETpCO_2) \times 100 / \text{P Bar}$$

The bag determined concentration was attained by manual mixing of O_2, CO_2 and nitrogen using Bassett and Fitton's method (Bassett, Jr. and Fitton, 1995). After expiration, the three-way tap was altered so the subject breathed from the gas in the closed anaesthetic bag. The concentration of CO_2 in the bag exceeded the patient's concentration of CO_2 in their venous (pulmonary capillary) blood and the diffusion gradient between the venous blood and alveolar space was reversed. Equilibrium was achieved during several breaths (see figure 2.1). The computer recognised equilibrium at the point where the difference between inspired and expired CO_2 was less than 0.1% in two successive breaths. Calculation of the partial pressure of CO_2 in the venous blood was made by the computer and CO was calculated using the indirect Fick equation (see section 1.4.3). At least three measurements of CO were

made in order to calculate an average. Respiratory values were allowed to go back to baseline between each measurement.

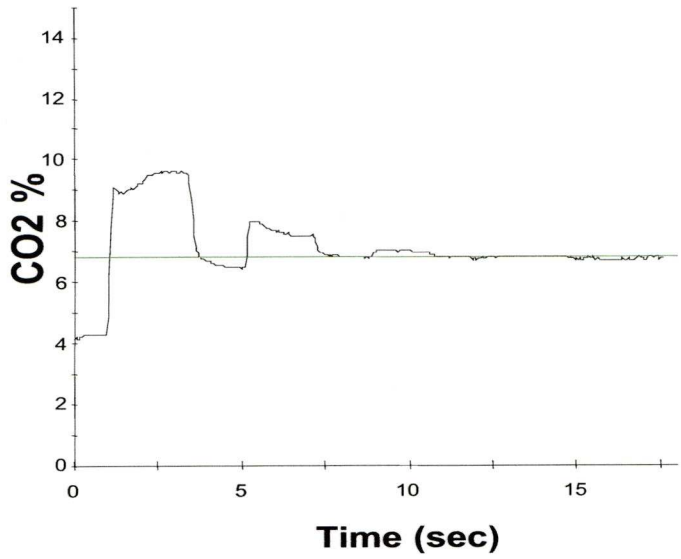

Figure 2.1: Equilibrium method to calculate cardiac output at rest using Collier's method

2.2.6 Day one – Incremental cardiopulmonary exercise test

After the resting measurements, an incremental exercise test using a modified Bruce protocol was performed (see table 2.1). A 12-lead electrocardiogram (ECG) was recorded at baseline and then every 3 minutes. Blood pressure was measured using a sphygmomanometer at baseline (first Korotkoff sound used for systolic BP and fifth sound for diastolic BP), two minutes into each stage, at peak exercise and during recovery. A mask attached to a counterweighted headgear was placed around the patients head. A silicone seal gel was positioned around the mask to achieve an airtight seal. Prior to starting the exercise the seal was checked by asking the patient to blow out with the pneumotach sealed. A few minutes were given before starting the incremental test to allow the patients to get used to the mask and headgear (see figure 2.2).

Table 2.1 The seven stages of Bruce and Modified Bruce protocols

	Bruce		Modified Bruce	
Time (mins)	Speed (mph)	Incline (%)	Speed (mph)	Incline (%)
0-3	1.7	10	1.7	0
3-6	2.5	12	1.7	5
6-9	3.4	14	1.7	10
9-12	4.2	16	2.5	12
12-15	5.0	18	3.4	14
15-18	5.5	20	4.2	16
18-21	6.0	22	5.0	18

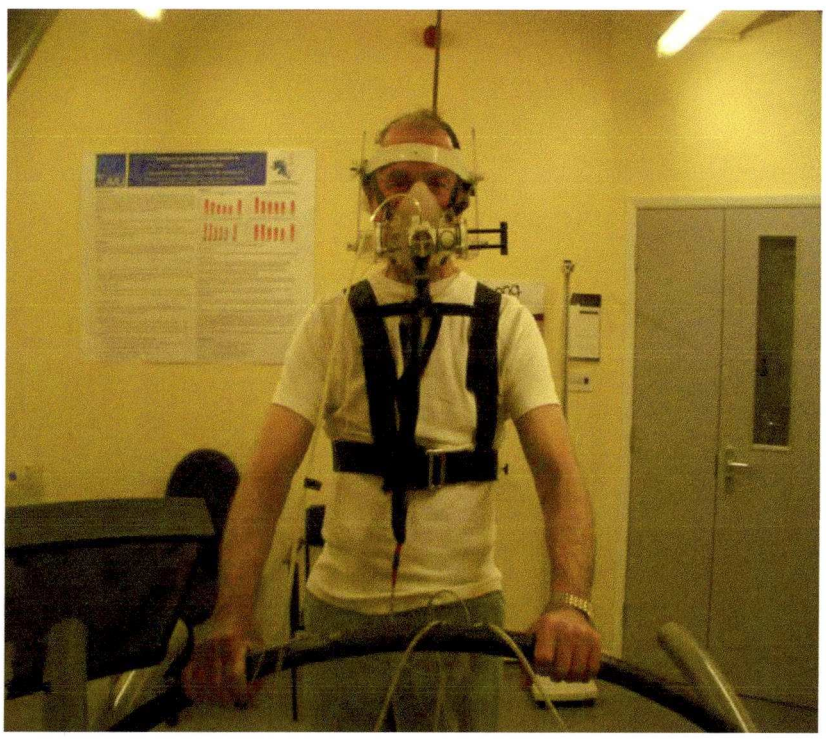

Figure 2.2: Set up for a incremental exercise test (published with the permission of the subject)

VO_2 (mls/min), VCO_2 (mls/min), end tidal partial pressure of carbon dioxide ($PETCO_2$, mm Hg), tidal volume (V_t, l), and respiratory rate (RR, min^{-1}) were recorded breath by breath using the Medgraphics CPXD analytic system (Medical graphics corporation, St Paul, Minnesota, USA). Respiratory exchange ratio (RER =

VCO_2/VO_2), minute ventilation (VE = V_t x RR, L/min), and VO_2/kg (VO_2/weight, mls/min/kg) were calculated from the above variables. Predicted peak VO_2 was calculated by the Wasserman technique (Wasserman et al., 1994): Peak VO_2 = weight x [56.36 – (0.413 x age)] – males and: weight x [44.37 – (0.413 x age)] - females. Various ventilatory indexes were calculated from the above data: ratio of minute ventilation to O_2 consumption at peak exercise (peak VE/VO_2), ratio of minute ventilation to CO_2 production at peak exercise (peak VE/VCO_2). The regression slopes relating minute ventilation to O_2 consumption (VE/VO_2 slope) and CO_2 production (VE/VCO_2 slope) were also calculated. The V-slope method (Beaver et al., 1986), was used to calculate anaerobic threshold (AT).

At peak exercise a peak cardiac output measurement was made. Defares method (Defares, 1958) was used to calculate cardiac output at peak exercise, again using the indirect Fick equation. The anaesthetic bag was filled with 4% CO_2, with the volume being above a physiological tidal volume. The three-way tap was adjusted so the patient breathed from the bag for 15 seconds in order for the computer to construct a graph of end tidal points. The computer applied a best-fit exponential curve to the points according to the technique of Heigenhauser (Heigenhauser and Jones, 1989), rejecting the first point, and using 8 seconds of re-breathing to create an exponential curve. End tidal points could then be manually modified to create a better fitting curve (see figure 2.3).

Patients were encouraged to exercise to exhaustion, and their limiting symptom (e.g. breathlessness, fatigue or chest pain) was recorded. All patients performed symptom-limited exercise tests unless termination was indicated for safety reasons e.g.

exercise-induced hypotension, significant cardiac arrhythmia, or other clinical end points indicating compromised safety of continued exercise. Attainment of an age-predicted heart rate was not used as a criterion for stopping the test

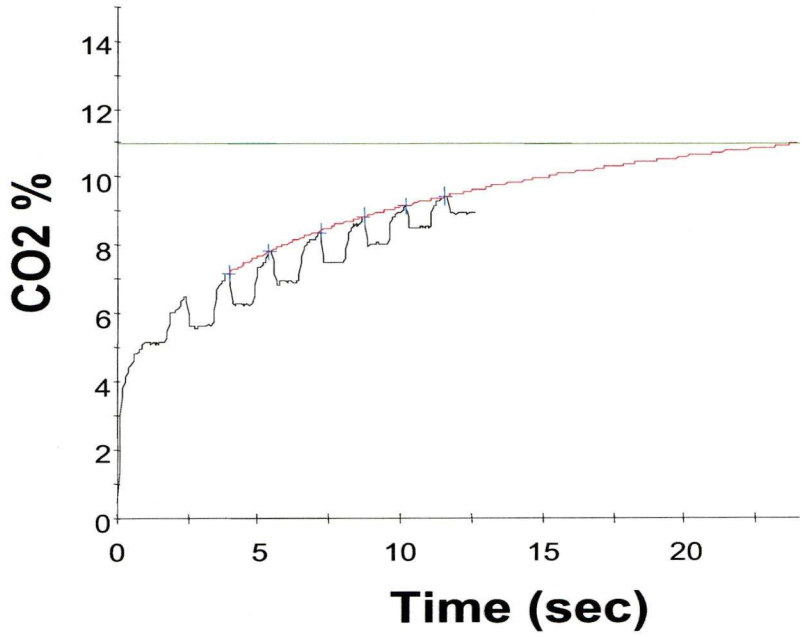

Figure 2.3: Exponential curve obtained at peak exercise using Defares' method

2.2.7 Day two – Second cardiac output measurement

A repeat cardiopulmonary exercise test was performed using the same equipment, exercise protocol and headgear as detailed in section 2.2.5. The subject was exercised until the VO_2, VCO_2, RER and HR were similar to that achieved on day one. At this point a second cardiac output measurement was performed in the same fashion as day one.

2.2.8 Cardiac power output and Cardiac reserve

The three resting cardiac output readings were averaged as were the two separate peak cardiac outputs. Cardiac power output was calculated at rest and peak exercise from the equation:

$$\text{Cardiac power output (watts)} = (CO \times MBP) \times K$$

Where MBP is the mean arterial blood pressure in mm Hg, CO is the cardiac output in L/min and K the conversion factor 2.22×10^{-3} (Tan, 1986) (see appendix 1). MBP was calculated from the equation:

$$MBP = (\text{systolic pressure} + 2 \times \text{diastolic pressure}) / 3$$

Mean arterial blood pressure is defined as the average pressure throughout the cardiac cycle. It has physiologic and clinical importance as it represents the tissue perfusion pressure (Ira, 1996). Cardiac reserve is defined as the difference between cardiac power output at peak exercise and rest.

2.2.9 Day two-Lower limb peak skeletal muscle torque

On the second day of each visit, after a minimum of 30 minutes rest following the cardiac output test, peak skeletal muscle torque was measured in each leg. Testing was performed at the knees using a Biodex isokinetic dynamometer (Biodex medical systems Inc, New York, USA) (see figure 2.4). Each leg was measured in full extension and flexion to 90 degrees using a 60-degree/sec protocol. Five measurements were taken in each leg with the peak value being taken.

Figure 2.4: Lower limb peak skeletal muscle torque measurement using a Biodex Isokinetic dynamometer (published with subjects permission)

2.3 Definition of non responders to CRT.

As metioned in section 1.2.7.1 there is currently no universally accepted definition for a responder to CRT. For the purposes of this thesis we defined a responder as someone who showed an improvement in both ejection fraction and peak VO_2 following CRT. The mechanism of CRT implies that there will be a more co-ordinated ventricular contraction and therefore an improvement in ejection fraction should be part of any definition of positive response. However the main aim of CRT is to improve functional capacity. The main objective marker of functional capacity is peak VO_2 and therefore this should also be incorporated into any definition of positive response.

2.4 Study I: The longitudinal improvement in exercise haemodynamic measures following Cardiac Resynchronisation Therapy

2.4.1 Patient population and study design

Forty patients were prospectively recruited from the CRT referral clinic at the Cardiothoracic Centre in Liverpool between July 2004 and November 2005. Patients were not eligible if they had contraindications to exercise testing, or had non-cardiac conditions that would limit their exercise capacity e.g. chronic pulmonary disease, neurological or rheumatological disabilities. All patients were given an information sheet and provided informed consent (illustrated in appendix 2). The study was approved by the Liverpool adult research ethics committee.

Following a preliminary familiarisation test, all patients performed cardiopulmonary exercise testing, with non-invasive measurements of cardiac output before, 2 weeks, 6 weeks and 3 months after successful CRT. No alteration in treatment occurred as a result of this study. At 6 months the subjects were classified as either a responder or non responder, as defined in section 2.3, and the baseline parameters were assessed to look for predictors of response.

2.4.2 Cardiopulmonary exercise testing

All patients performed cardiopulmonary tests, with assessment of cardiac output and cardiac power output as described previously in section 2.2. All patients exercised according to the modified Bruce protocol. The same supervisors carried out the tests (AYP, PW) throughout the study.

2.4.3 Echocardiography

Transthoracic echocardiography was performed in all patients at each visit on day one as per the methods described in section 2.2.3

2.4.4 Peak skeletal muscle torque

On the second day of each visit peak skeletal muscle torque was measured in the quadriceps and hamstring muscles as per the methods described in section 2.2.8

2.4.5 Quality of life and symptom assessment

The New York heart association functional classification (NYHA criteria committee, 1964) and the Minnesota living with heart failure (Minnesota, USA) (see appendix 3) were assessed when the patients attended for each visit.

2.4.6 Statistical analysis

Linear regression analysis was used to look for relationships between the baseline cardiopulmonary data and peak skeletal muscle function. A goodness of fit value (r^2) was calculated for all the regression analysis. A p value of <0.05 was considered as showing a significant coorelation between two variables. Group data for continuous variables was expressed as mean ± standard error of the mean (SEM). Haemodynamic data and cardiopulmonary exercise test results (continuous data) before and after CRT were compared using the repeated measures ANOVA with a Bonferroni post-hoc test. Discrete data was expressed as modes and compared using the Chi-square (χ^2) test. Baseline variables were assessed for the ability to predict response to CRT using logistic regression with a univariate analysis. A responder was defined as per section 2.3.

2.5 Study II. The effects of exercise rehabilitation in addition to cardiac resynchronisation therapy

2.5.1 Patient population and study design

Fifty patients referred for CRT between June 2004 and August 2005 were recruited. Exclusion criteria included inability to perform an exercise test, reduced exercise tolerance due to non-cardiac causes (e.g. chronic obstructive airways disease, neurological or orthopaedic disability) and recent or planned revascularisation. All patients received a written information sheet and gave informed consent (see appendix 2). The study was approved by the Liverpool adult research ethics committee.

2.5.2 Study protocol

All patients underwent cardiopulmonary exercise testing, a resting transthoracic echocardiogram, quality of life assessment using the Minnesota living with heart failure questionnaire and measurement of peak skeletal muscle torque. All measurements were taken at baseline and repeated 3 months and 6 months after CRT. Prior to the study a separate familiarisation test was performed and the results discarded.

After the 3 month assessment patients were randomised (as described in section 2.5.3) into either an exercise group (n=25) or a control group (n=25). The exercise group underwent a programme of physician supervised exercise training consisting of three 30 minutes visits per week. Each session consisted of 10 minutes treadmill walking followed by 10 minutes cycling and then a further 10 minutes treadmill walking. The intensity was 80% of the peak heart rate achieved at the 3 month test

for the first four weeks, 85% for the next four weeks and 90% for the final four weeks. This was performed at a non-clinical setting (Liverpool John Moores University) away from the base hospital. Patients were supervised by an advanced life support trained physician not involved in the CRT implant or follow up at the base hospital (Liverpool heart and chest hospital). Clinical follow up was organised at the base hospital for both groups. The exercise group were not provided with any specific instruction or guidance to perform exercise outside the study. The control group were given no specific advice on exercise training and underwent no supervised training. No change in cardiac medication occurred as part of the study protocol.

2.5.3 Randomisation

Randomisation occurred at 3 months. It was not performed at baseline to eliminate the potential for bias due to pre-emptive training in the exercise group. Randomisation was performed using a simple sealed envelope method. Fifty sealed envelopes, 25 with exercise training and 25 with control were placed into a box. After the 3 month assessment for each patient an envelope was picked by a person not involved in the study.

2.5.4 Cardiopulmonary exercise testing

The patients performed an incremental cardiopulmonary exercise test on each occasion, as previously described in section 2.2. All patients were exercised according to a modified Bruce protocol. The same supervisors carried out all tests (AYP, PW), on the same equipment.

2.5.5 Echocardiography

Transthoracic echocardiography was performed in all patients at each visit on day one as per the methods described in section 2.2.3

2.5.6 Peak Skeletal Muscle Torque

On the second day of each visit peak skeletal muscle torque was measured in the quadriceps and hamstring muscles as per the methods described in section 2.2.8.

2.5.7 Statistical analysis

Group data for continuous variables was expressed as mean ± standard error. Discrete data was expressed as modes. For in-group analyses paired samples t-tests were used to look for statistical significance in continuous variables and Chi-square (χ^2) tests were used for discrete variables. To look for differences between the exercise and control groups at 6 months, change scores were calculated and independent sample t-tests were used. Analyses were carried out using SPSS version 12.0.1 for Windows (SPSS Inc, Chicago, Illinois). Statistical significance was set at the 5% level.

2.6 Study III. The effectiveness of left ventricular lead placement via a mini thoracotomy to achieve cardiac resynchronisation therapy in patients with previously failed transvenous placement.

2.6.1 Patient population and study design

Twenty-three patients with previously unsuccessful transvenous placement (5 (22%) with failure to cannulate coronary sinus, 12 (52%) with excessive thresholds at all positions attained, 4 (17%) with diaphragmatic twitching and 2 (9%) with recurrent displacements) were recruited. The control group was made up of thirty-five consecutive patients who had received CRT via the transvenous route. Standard clinical guidelines (National Institute for Clinical Excellence, 2003;Hunt et al., 2005) were used to assess suitability for CRT. All patients were in New York heart association (NYHA) functional class III, had a QRS width >120 ms on their surface ECG and a left ventricular ejection fraction (EF) <35%. Exclusion criteria for the study included non-cardiac physical limitation e.g. arthritis, pulmonary disease, myocardial infarction within the last 3 months, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty within the last 3 months, or planned for the future and significant untreated valvular heart disease. All patients received a written information sheet and gave informed consent (see appendix 2). The study was approved by the Liverpool adult research ethics committee.

2.6.2 Study protocol

All patients were assessed at baseline, 3 and at 6 months post CRT with echocardiography, NYHA classification, Minnesota living with heart failure (MLWHF) scoring and cardiopulmonary exercise testing with measurement of

cardiac function. Prior to the baseline test a separate familiarisation test was performed, the results of which were discarded. Pacemakers were set at manufacture default settings and optimisation of pacemaker intervals was not performed during the study period. Pacemaker follow up was performed at the implanting centre at 6 weeks and 6 months post CRT implantation.

2.6.3 Cardiopulmonary exercise testing

The patients performed an incremental cardiopulmonary exercise test on each occasion, as previously described in section 2.2. All patients were exercised according to a modified Bruce protocol. The same supervisors carried out all tests (AYP, PW), on the same equipment.

2.6.4 Echocardiography

Transthoracic echocardiography was performed in all patients at each visit on day one as per the methods described in section 2.2.3

2.6.5 Implantation and programming of cardiac resynchronisation therapy device

2.6.5.1 Mini thoracotomy group:

This group had right ventricular and right atrial leads placed via the transvenous route and the CRT pacemaker placed in a subcutaneous pre pectoral pocket using the standard technique. The LV lead was implanted using a left lateral mini thoracotomy under a general anesthetic. A 3cm incision was made through the left 5th intercostal space and the left lung was retracted. A Medtronic (model 5071) epicardial lead was implanted using the Medtronic (model 10626) implantation tool. The lead was

positioned in the posterolateral portion of the LV epicardium, using an active fixation screw. Standard testing of R wave sensing, impedance and pacing threshold were undertaken. The epicardial lead was then tunnelled back to the previously implanted pacemaker box.

2.6.5.2 Transvenous group

Implantation was performed using the standard technique of transvenous lead insertion. Local anesthetic was delivered with the patient awake but sedated where necessary. Lead testing and antibiotic prophylaxis were identical to the epicardial group.

In both groups the pacemaker was programmed to a base rate of 60 bpm and upper limit 85% of the age–gender maximum predicted heart rate. Atrio-Ventricular delays were programmed to standard settings (120ms paced, 100ms sensed). No V-V offset was utilised during this study. Patients in atrial fibrillation received biventricular VVIR pacemakers. For this study patients received CRT-P and CRT-D devices as appropriate and no distinction was made between them.

2.6.6 Statistical analysis

All continuous variables are presented as mean ± standard error. Analyses were carried out using SPSS version 12.0.1 for Windows (SPSS Inc, Chicago, Illinois). A repeated measures ANOVA with a Bonferroni post hoc test was used to look for intra-group differences between the baseline and post CRT results. All discrete variables are presented as modes and analysed using Chi-Square (χ^2) test. To assess intergroup differences mean change scores were calculated and an independent

samples t-test was used. A p value of <0.05 was considered to be statistically significant.

CHAPTER 3: RESULTS

3.1 Study I: The longitudinal improvement in exercise haemodynamic measures following cardiac resynchronisation therapy

3.1.1 Baseline data

3.1.1.1 Baseline characteristics of study population

Baseline characteristics of the patients are shown in table 3.1. Mean (± SEM) age was 65.3 ± 1.6 (range: 38-80) years and 36 (90%) patients were male. The mean and mode NYHA class was 3 and there was evidence of a dilated cardiomypoathy with a LV end diastolic dimension of 7.01 cm ± 0.15 and a ejection fraction of 21.7 % ± 1.5. Thirty (75%) of the patients were in sinus rhythm at baseline, the rest (25%) were in atrial fibrillation. The primary cause of the dilated cardiomypathy was ischaemic in 29 (72.5%), valvular heart disease in 4 (10%) and idiopathic in 7 (17.5%).

3.1.1.2 Baseline cardiopulmonary haemodynamic data

The baseline cardiopulmonary haemodynamic data are shown in table 3.2. Resting heart rate was 79 ± 3/min and increased to 124 ± 4/min at peak exercise. This was coupled with a increase in mean arterial pressure from 88.7 ± 1.9 mmHg to 106.0 ± 1.8 mmHg. Total exercise duration was 322 ± 27 seconds and patients did achieve a true maximal cardiopulmonary exercise test manifest by a peak RER greater than 1.0 (1.04 ± 0.02). The subjects were significantly impaired in their cardiopulmonary exercise capacity with a peak VO_2 of 15.51 ± 0.54 mls/kg/min, which was 66.9 ± 2.8 % of their predicted peak VO_2. Cardiac power output increased from a resting value of 0.65 ± 0.02 watts to a peak value of 2.53 ± 0.10 watts, therefore giving a cardiac reserve of 1.89 ± 0.09 watts.

Table 3.1: Baseline characteristics of study population

Male, n (%)	36 (90%)
Female, n (%)	4 (10%)
Age (yrs, range)	65.3 ± 1.6 (38-80)
NYHA class	3
Height (cm, range)	171.2 ± 1.2 (154-186)
Weight (kg, range)	84.5 ± 2.8 (58-139)
BMI (kg/m^2, range)	28.7 ± 0.8 (20-44)
QRS duration (msec, range)	158.0 ± 2.9 (124-192)
Sinus rhythm, n(%)	30 (75%)
Atrial Fibrillation, n(%)	10 (25%)
Left ventricular end diastolic dimensions (cm)	7.01 ± 0.15
Ejection fraction (%)	21.71 ± 1.5
Aetiology	
Ischaemic	29 (72.5%)
Valvular	4 (10%)
Idiopathic	7 (17.5%)
Medication	
ACE inhibitors/ARB	39 (97.5%)
Diuretics	40 (100%)
Beta-blockers	33 (82.4%)
Digoxin	17 (42.5%)
Spironolactone	18 (45%)

All continuous values are expressed as mean ± SEM

Table 3.2: Baseline cardiopulmonary haemodynamics and skeletal muscle measurements of study population

Resting HR (min^{-1})	79 ± 3
Resting MBP (mm Hg)	88.7 ± 1.9
Resting SBP (mmHg)	116.9 ± 2.3
Resting VO_2 (mls/kg/min)	5.18 ± 0.19
Resting CO (L/min)	3.30 ± 0.11
Resting CPO (watts)	0.65 ± 0.02
Resting VE (L/min)	14.5 ± 0.7
Exercise duration (secs)	322 ± 27
AT (mls/kg/min)	10.76 ± 0.55
AT % peak VO_2 (%)	68.1 ± 2.8
Peak RER	1.04 ± 0.02
Peak HR (min^{-1})	124 ± 4
Peak MBP (mm Hg)	106.0 ± 1.8
Peak SBP (mm Hg)	154.5 ± 3.2
Peak VO_2 (mls/kg/min)	15.51 ± 0.54
% predicted peak VO_2 (%)	66.9 ± 2.8
Peak CO (L/min)	10.75 ± 0.35
Peak CPO (watts)	2.53 ± 0.10
Cardiac reserve (watts)	1.89 ± 0.09
Peak VE (L/min)	54.0 ± 2.2
Peak VE/VCO_2	41.6 ± 1.4
Peak VE/VO_2	43.6 ± 2.1
VE/VCO_2 slope	40.8 ± 1.6
VE/VO_2 slope	45.9 ± 2.5
Right extension (N-M)	119.8 ± 9.0
Right flexion (N-M)	63.5 ± 4.7
Left extension (N-M)	123.2 ± 9.8
Left flexion (N-M)	64.2 ± 5.5

All values expressed as mean ± SEM.

3.1.1.3 Relationship between cardiopulmonary and skeletal muscle parameters at baseline

Full relationship between all of the baseline parameters are given in table 3.3.

3.1.1.3.1 Baseline relationship to exercise duration

At baseline there was a significant correlation between overall exercise duration and peak VO_2 (R^2=0.45, p<0.001), peak CPO (R^2=0.25, p=0.001), cardiac reserve (R^2=0.35, p<0.001) and the ventilatory equivalents for oxygen uptake (peak VE/VO_2 (R^2=0.13, p=0.024), VE/ VO_2 slope (R^2=0.22, p=0.002)) and carbon dioxide output (peak VE/VCO_2 (R^2=0.20, p=0.04), VE/ VCO_2 slope (R^2=0.24, p=0.001)) see figure 3.1.

There was no signficant correlation with peak RER (R^2=0.00 p=0.895), the percentage of peak VO_2 at the anaerobic threshold (R^2=0.09 p=0.066), LV end diastolic dimension (R^2=0.01 p=0.676), ejection fraction (R^2=0.10 p=0.073), Minnesota living with heart failure scores (R^2=0.01 p=0.518) and peak skeletal muscle torque in extension (right: R^2=0.07 p=0.104, left: R^2=0.01 p=0.484) or flexion (right: R^2=0.04 p=0.21, left: R^2=0.03 p=0.292)

3.1.1.3.2 Baseline relationship to peak VO_2

At baseline there was a significant correlation between peak VO_2 and exercise duration (see section 3.1.1.3.1), peak CPO (R^2=0.24 p=0.002), cardiac reserve (R^2=0.27 p=0.001) and the ventilatory equivalents for oxygen uptake (peak VE/VO_2 (R^2=0.36 p<0.001), VE/ VO_2 slope (R^2=0.35 p<0.001)) and carbon dioxide output

(peak VE/VCO_2 (R^2=0.44 p<0.001), VE/ VCO_2 slope (R^2=0.48 p<0.001)) see figure 3.2.

There was no signficant correlation with peak RER (R^2=0.05 p=0.161), the percentage of peak VO_2 at the anaerobic threshold (R^2=0.00 p=0.739), LV end diastolic dimension (R^2=0.01 p=0.599), ejection fraction (R^2=0.05 p=0.213), Minnesota living with heart failure scores (R^2=0.00 p=0.993) and peak skeletal muscle torque in extension (right: R^2=0.02 p=0.459, left: R^2=0.02 p=0.426) or flexion (right: R^2=0.07 p=0.116, left: R^2=0.02 p=0.358).

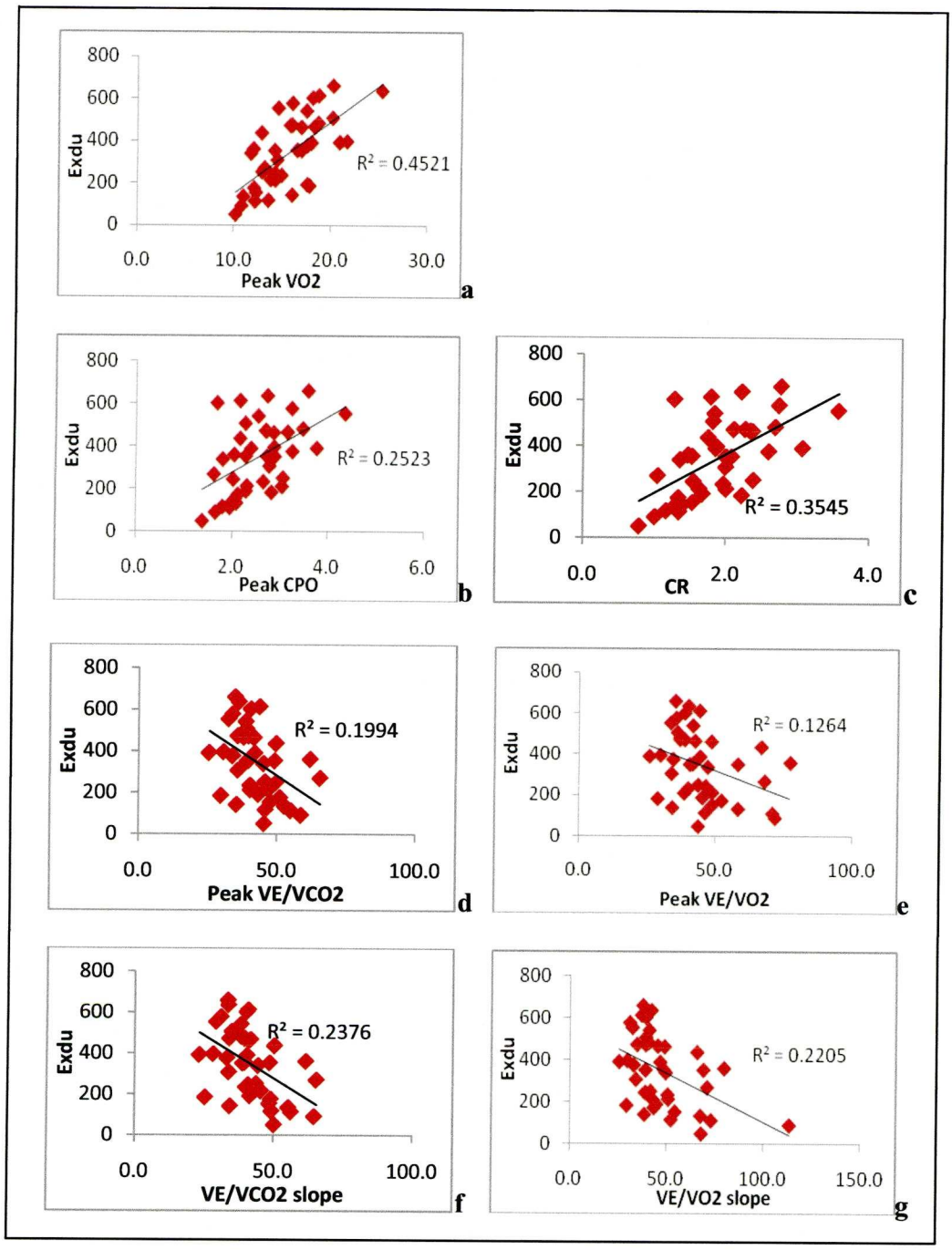

Figure 3.1(a-g) Significant correlelations with exercise duration for peak VO_2 (a), peak CPO (b), CR (c), peak VE/VCO_2 (d), peak VE/VO_2 (e), VE/VCO_2 slope (f) and VE/VO_2 slope (g).

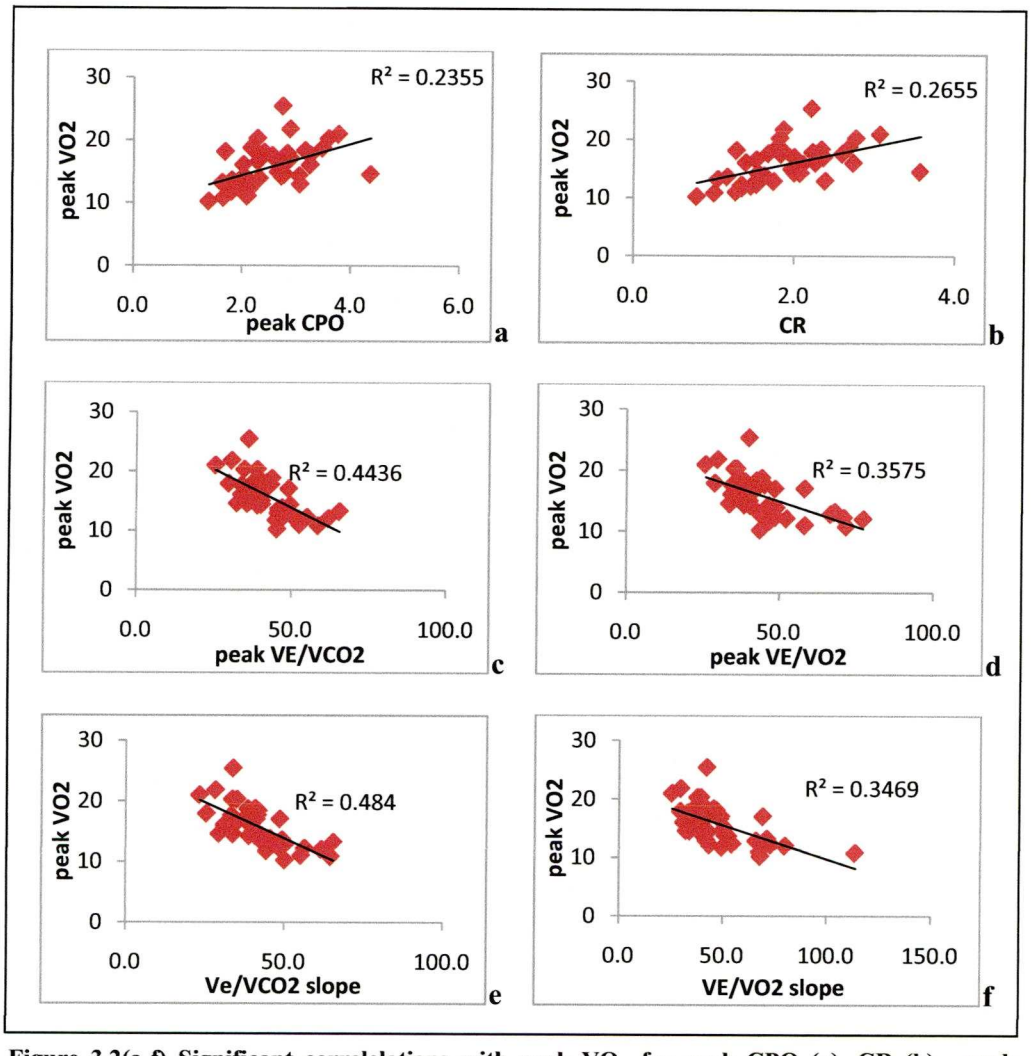

Figure 3.2(a-f) Significant correlelations with peak VO_2 for peak CPO (a), CR (b), peak VE/VCO_2 (c), peak VE/VO_2 (d), VE/VCO_2 slope (e) and VE/VO_2 slope (f).

3.1.1.3.3 Baseline relationship to peak cardiac power output

At baseline there was a significant correlation between peak CPO and exercise duration (see section 3.1.1.3.1) and peak VO_2 (see section 3.1.1.3.2). There was also signficant correleation between peak cardiac power output and cardiac reserve (R^2=0.94 p<0.001), ejection fraction (R^2=0.23 p=0.004), peak skeletal muscle torque in extension (right: R^2=0.29 p<0.001, left: R^2=0.23 p=0.002) and flexion (right:

R^2=0.19 p=0.006, left: R^2=0.11 p=0.036), and the ventilatory equivalents for oxygen uptake (peak VE/VO_2 (R^2=0.33 p<0.001), VE/VO_2 slope (R^2=0.33 p<0.001)) and carbon dioxide output (peak VE/VCO_2 (R^2=0.45 p<0.001), VE/VCO_2 slope (R^2=0.45 p<0.001)) see figure 3.3. There was no signficant correlation with peak RER (R^2=0.03 p=0.333), the percentage of peak VO_2 at the anaerobic threshold (R^2=0.06 p=0.140), LV end diastolic dimension (R^2=0.01 p=0.570), Minnesota living with heart failure scores (R^2=0.04 p=0.233)

3.1.1.3.4 Baseline relationship to cardiac reserve

At baseline there was a significant correlation between cardiac reserve and exercise duration (see section 3.1.1.3.1), peak VO_2 (see section 3.1.1.3.2) and peak CPO (see section 3.1.1.3.2). There was also signficant correleation between cardiac reserve and ejection fraction (R^2=0.20 p=0.009), peak skeletal muscle torque in extension (right: R^2=0.27p=0.001, left: R^2=0.20 p=0.004) and right sided flexion (R^2=0.17 p=0.009). There was a trend towards a correlation in left sided flexion but this did not reach statistical significance (R^2=0.10 p=0.052). Cardiac reserve also showed significant correlation with the ventilatory equivalents for oxygen uptake (peak VE/VO_2 (R^2=0.33 p<0.001), VE/VO_2 slope (R^2=0.38 p<0.001)) and carbon dioxide output (peak VE/VCO_2 (R^2=0.47 p<0.001), VE/VCO_2 slope (R^2=0.50p<0.001)) see figure 3.4. There was no signficant correlation with peak RER (R^2=0.02 p=0.401), the percentage of peak VO_2 at the anaerobic threshold (R^2=0.04 p=0.240), LV end diastolic dimension (R^2=0.00 p=0.768), Minnesota living with heart failure scores (R^2=0.05 p=0.184).

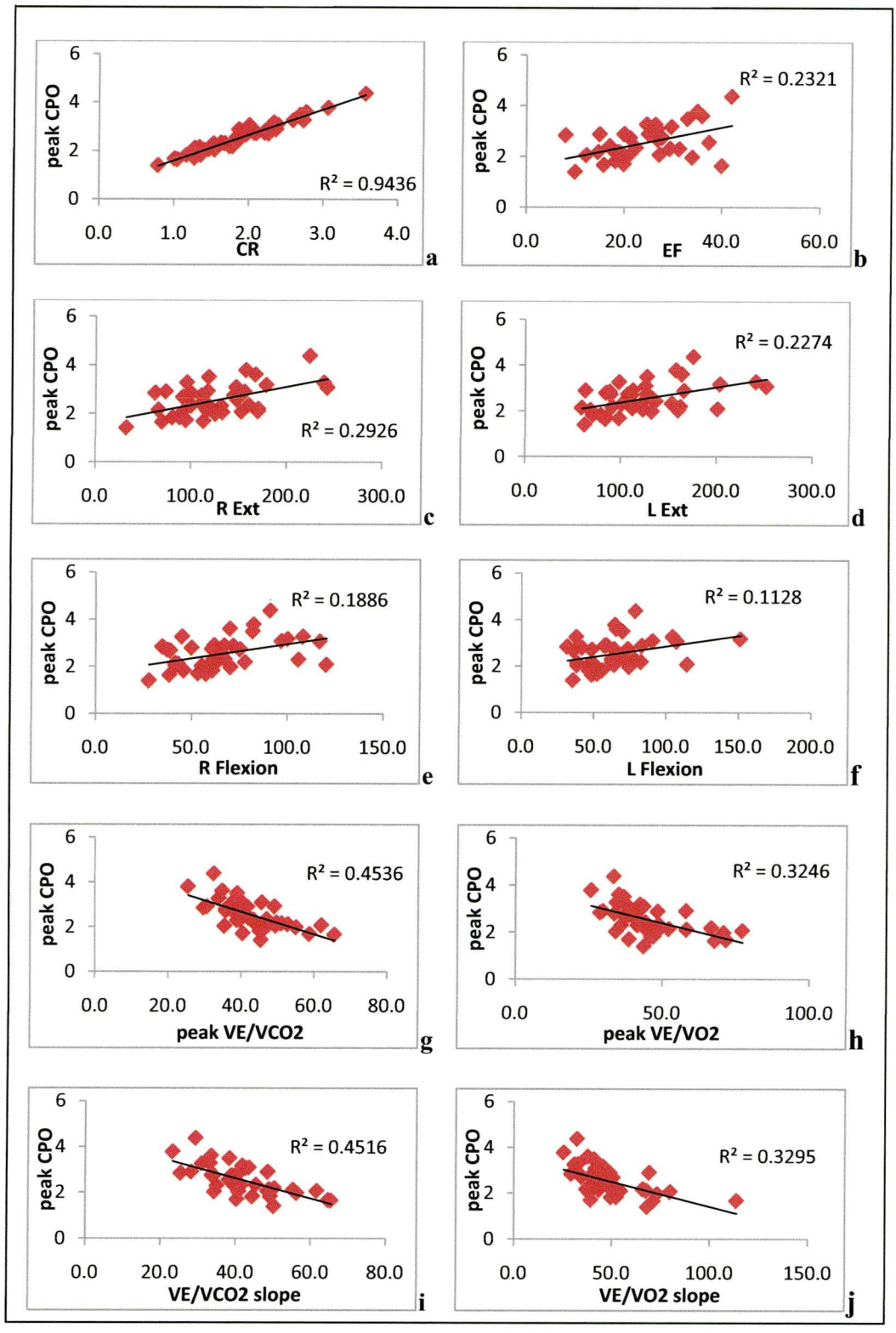

Figure 3.3(a-j) Significant correlelations with peak cardiac power output for CR (a), EF (b), R extension (c), L extension (d), R Ffexion (e), L flexion (f), peak VE/VCO_2 (g), peak VE/VO_2 (h), VE/VCO_2 slope (i) and VE/VO_2 slope (j).

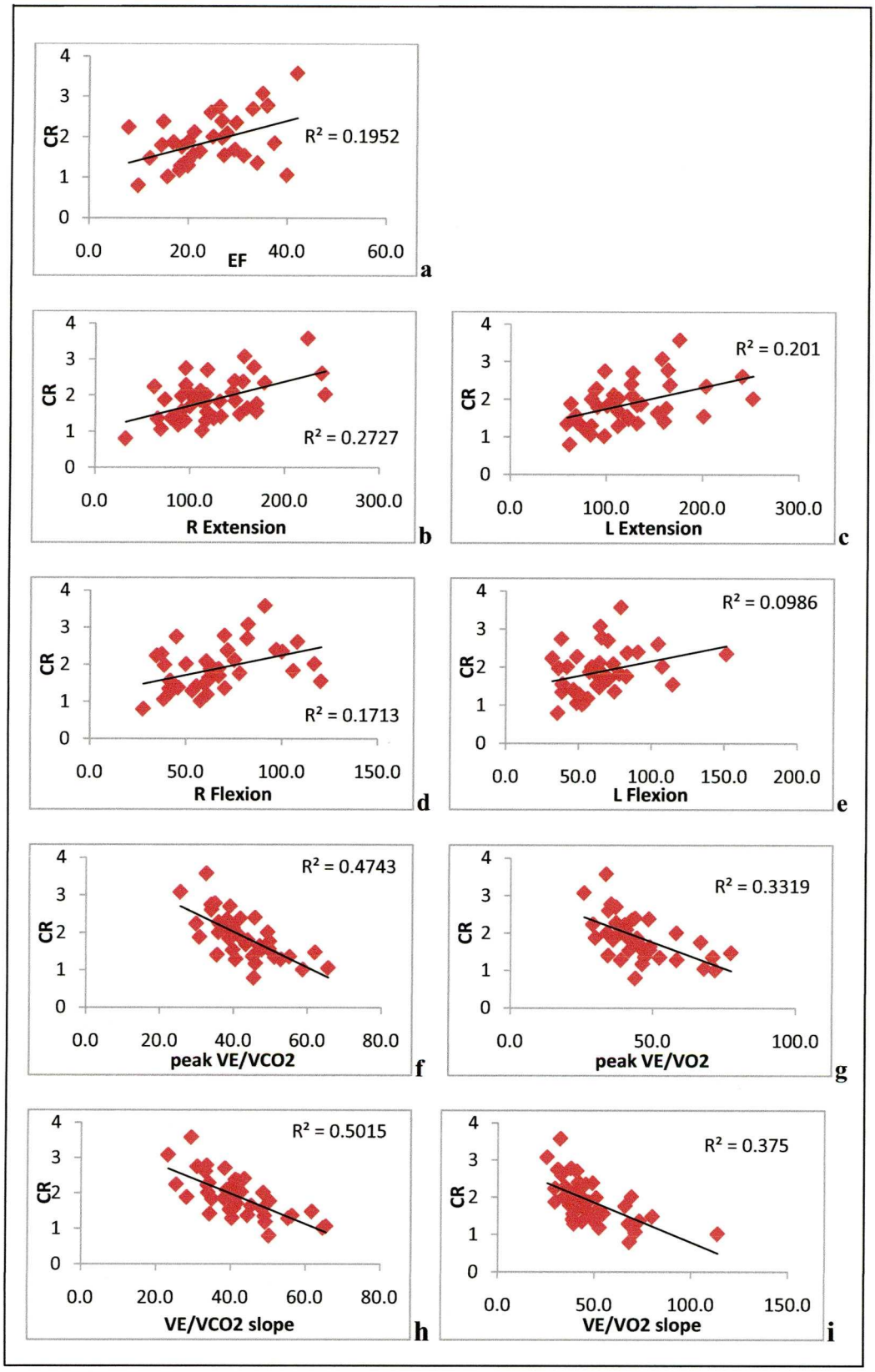

Figure 3.4(a-i) Correlelations with cardiac reserve for EF (a), R extension (b), L extension (c), R flexion (d), L flexion (e), peak VE/VCO_2 (f), peak VE/VO_2 (g), VE/VCO_2 slope (h) and VE/VO_2 slope (i).

3.1.1.3.5 Baseline relationships for ejection fraction and left ventricular end diastolic dimension.

Ejection fraction showed a signficant correlation with peak CPO (see section 3.1.1.3.3), cardiac reserve (see section 3.1.1.3.4), peak skeletal muscle torque during extension (right: R^2=0.16 p=0.013, left: R^2=0.13 p=0.027) and flexion on the right side (R^2=0.14 p=0.018). There was a trend towards a signficant correlation with left sided flexion but this failed to reach statistical signifcance (R^2=0.09 p=0.057) see figure 3.5.

Ejection fraction showed no signficant correlation with peak VO_2 (see section 3.1.1.3.2) or any of the ventilatory equivalents for oxygen uptake (peak VE/VO_2 (R^2=0.02 p=0.360), VE/VO_2 slope (R^2=0.04 p=0.192)) and carbon dioxide output (peak VE/VCO_2 (R^2=0.02 p=0.344), VE/ VCO_2 slope (R^2=0.03 p=0.320)). There was no signficant correlation between the left ventricular end-diastolic dimension and ejection fraction (R^2=0.03 p=0.307). Left ventricular end-diastolic dimension showed no signficant correlation with any variable (see table 3.3

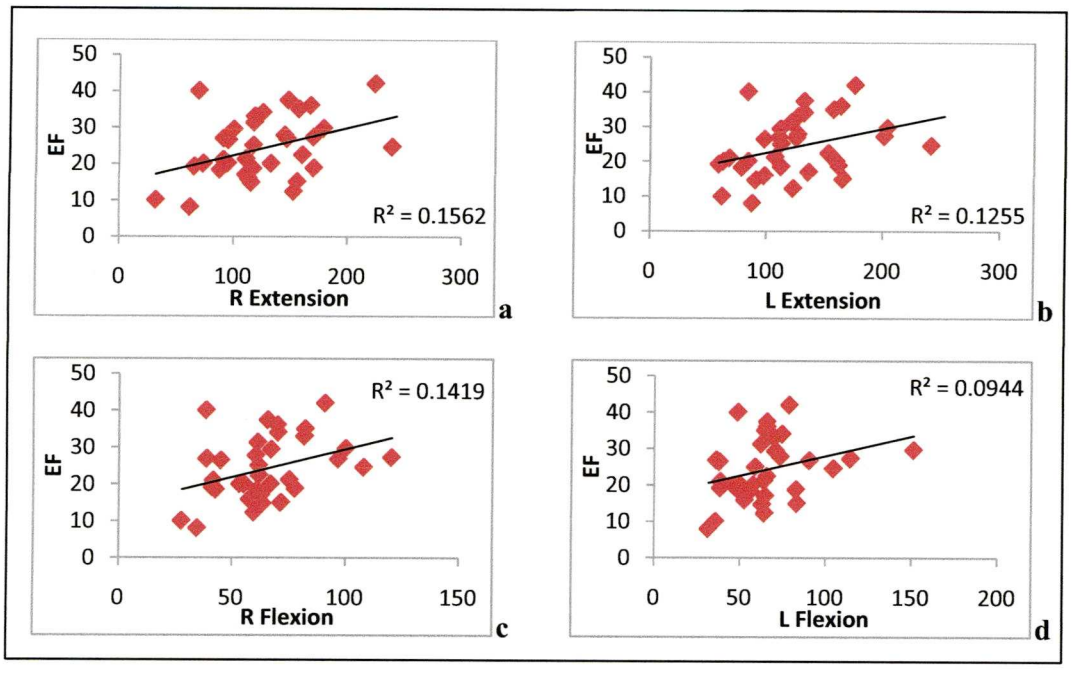

Figure 3.5(a-d) Correlelations with ejection fraction for R extension (a), L extension (b), R flexion (c), L flexion (d).

3.1.1.3.6 Baseline relationships for ventilatory equivalents, peak RER and the percentage of peak VO_2 at the anaerobic threshold

The ventilatory equivalents for oxygen uptake and carbon dioxide production showed signficant correlation with exercise duration (see section 3.1.1.3.1), peak VO_2 (see section 3.1.1.3.2), peak CPO (see section 3.1.1.3.3) and cardiac reserve (see section 3.1.1.3.4). There was significant correlation between peak RER and the ventilatory equivalents for oxygen uptake (peak VE/VO_2 (R^2=0.56 $p<0.001$), VE/VO_2 slope (R^2=0.42 $p<0.001$)) and carbon dioxide output (peak VE/VCO_2 (R^2=0.23 p=0.002), VE/VCO_2 slope (R^2=0.27 p=0.001)) (see figure 3.6). Peak RER did not show any correlation with any other parameter (see table 3.3).

At baseline there was no significant correlation between the percentage of peak VO_2 at the anaerobic threshold and any variable (see table 3.3).

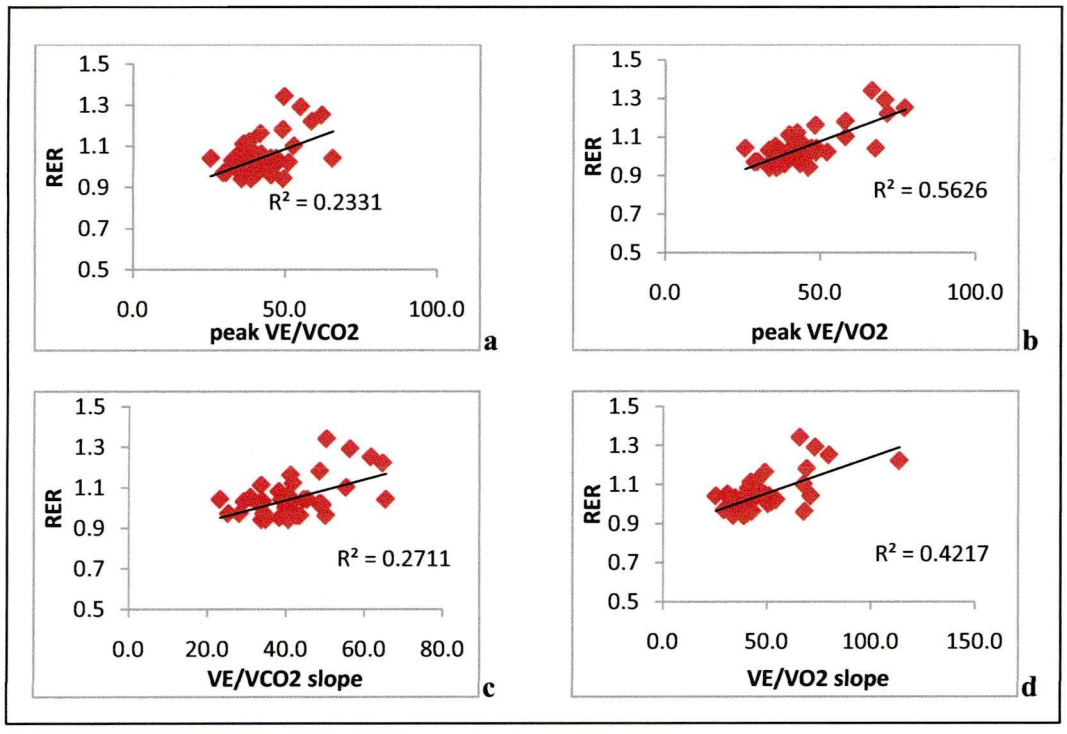

Figure 3.6(a-d) Correlelations with peak respiratory exchange ratio for peak VE/VCO_2 (a), peak VE/VO_2 (b), VE/VCO_2 slope (c), VE/VO_2 slope (d).

3.1.1.3.7 Baseline relationship for Minnesota living with heart failure scores

At baseline there was no signficant correlation with Minnesota living with heart failure scores and exercise duration (see section 3.1.1.3.1), peak VO_2 (see section 3.1.1.3.2), peak CPO (see section 3.1.1.3.3), CR (see section 3.1.1.3.4), echocardiographic parameters (see section 3.1.1.3.5) and any measure of skeletal muscle function (right extension (R^2=0.05 p=0.176), right flexion (R^2=0.04 p=0.244), left extension (R^2=0.06 p=0.139) and left flexion (R^2=0.01 p=0.630)).

The only parameter that MLWHF showed a mild correlation with was the peak ventilatory equivalents for carbon dioxide production (R^2=0.10 p=0.045

	EXDU	Peak VO2	Peak CPO	CR	RER	LV	EF	AT	Right Ext	Left Ext	MLWHF	Right Flexion	Left Flexion	Peak VE/VCO2	Peak VE/VO2	VE/VCO2slope	VE/Vo2 slope
EXDU		R^2=0.45 p=0.000	R^2=0.25 p=0.001	R^2=0.35 p=0.000	R^2=0.00 p=0.895	R^2=0.01 p=0.676	R^2=0.10 p=0.073	R^2=0.09 p=0.066	R^2=0.07 p=0.104	R^2=0.01 p=0.484	R^2=0.01 p=0.518	R^2=0.04 p=0.210	R^2=0.03 p=0.292	R^2=0.20 p=0.004	R^2=0.13 p=0.024	R^2=0.24 p=0.001	R^2=0.22 p=0.002
Peak VO2	R^2=0.45 p=0.000		R^2=0.24 p=0.002	R^2=0.27 p=0.001	R^2=0.05 p=0.161	R^2= 0.01 p=0.599	R^2=0.05 p=0.213	R^2=0.00 p=0.739	R^2=0.02 p=0.459	R^2=0.02 p=0.426	R^2=0.00 p=0.993	R^2=0.07 p=0.116	R^2=0.02 p=0.358	R^2=0.44 p=0.000	R^2=0.36 p=0.000	R^2=0.48 p=0.000	R^2=0.35 p=0.000
Peak CPO	R^2=0.25 p=0.001	R^2=0.24 p=0.002		R^2=0.94 p=0.000	R^2=0.03 p=0.333	R^2=0.01 p=0.570	R^2=0.23 p=0.004	R^2=0.06 p=0.140	R^2=0.29 p=0.000	R^2=0.23 p=0.002	R^2=0.04 p=0.233	R^2=0.19 p=0.006	R^2=0.11 p=0.037	R^2=0.45 p=0.000	R^2=0.33 p=0.000	R^2=0.45 p=0.000	R^2=0.33 p=0.000
CR	R^2=0.35 p=0.000	R^2=0.27 p=0.001	R^2=0.94 p=0.000		R^2=0.02 p=0.401	R^2=0.00 p=0.768	R^1=0.20 p=0.009	R^2=0.04 p=0.240	R^2=0.27 p=0.000	R^2=0.20 p=0.004	R^2=0.05 p=0.184	R^2=0.17 p=0.009	R^2=0.10 p=0.052	R^2=0.47 p=0.000	R^2=0.33 p=0.000	R^2=0.50 p=0.000	R^2=0.38 p=0.000
RER	R^2=0.00 p=0.895	R^2=0.05 p=0.161	R^2=0.03 p=0.333	R^2=0.02 p=0.401		R^2=0.03 p=0.328	R^2=0.00 p=0.837	R^2=0.00 p=0.823	R^2=0.04 p=0.211	R^2=0.03 p=0.269	R^2=0.02 p=0.392	R^2=0.00 p=0.940	R^2=0.04 p=0.221	R^2=0.23 p=0.002	R^2=0.56 p=0.000	R^2=0.27 p=0.001	R^2=0.42 p=0.000
LV	R^2=0.01 p=0.676	R^2=0.01 p=0.599	R^2=0.01 p=0.570	R^2=0.00 p=0.768	R^2=0.03 p=0.328		R^2=0.03 p=0.307	R^2=0.02 p=0.377	R^2=0.02 p=0.345	R^2=0.03 p=0.309	R^2=0.04 p=0.229	R^2=0.02 p=0.455	R^2=0.02 p=0.417	R^2=0.01 p=0.605	R^2=0.00 p=0.976	R^2=0.00 p=0.847	R^2=0.00 p=0.889
EF	R^2=0.10 p=0.073	R^2=0.05 p=0.213	R^2=0.23 p=0.004	R^2=0.20 p=0.009	R2=0.00 p=0.837	R^2=0.03 p=0.307		R^2=0.01 p=0.476	R^2=0.16 p=0.013	R^2=0.13 p=0.027	R^2=0.00 p=0.688	R^2=0.14 p=0.018	R^2=0.09 p=0.057	R^2=0.02 p=0.344	R^2=0.02 p=0.360	R^2=0.03 p=0.320	R^2=0.04 p=0.192
AT	R^2=0.09 p=0.066	R^2=0.00 p=0.739	R^2=0.06 p=0.140	R^2=0.04 p=0.240	R^2=0.00 p=0.823	R^2=0.02 p=0.377	R^2=0.01 p=0.476		R^2=0.01 p=0.562	R^2=0.01 p=0.630	R^2=0.00 p=0.869	R^2=0.00 p=0.907	R^2=0.00 p=0.796	R^2=0.01 p=0.610	R^2=0.01 p=0.645	R^2=0.00 p=0.736	R^2=0.03 p=0.329
REXT	R^2=0.07 p=0.104	R^2=0.02 p=0.459	R^2=0.29 p=0.000	R^2=0.27 p=0.001	R^2=0.04 p=0.211	R^2=0.02 p=0.345	R^2=0.16 p=0.013	R^2=0.01 p=0.562		R^2=0.85 p=0.000	R^2=0.05 p=0.176	R^2=0.64 p=0.000	R^2=0.58 p=0.000	R^2=0.04 p=0.245	R^2=0.01 p=0.680	R^2=0.02 p=0.377	R^2=0.01 p=0.463
LEXT	R^2=0.01 p=0.484	R^2=0.02 p=0.426	R^2=0.23 p=0.002	R^2=0.20 p=0.004	R^2=0.03 p=0.269	R^2=0.03 p=0.309	R^2=0.13 p=0.027	R^2=0.01 p=0.630	R^2=0.85 p=0.000		R^2=0.06 p=0.139	R^2=0.59 p=0.000	R^2=0.63 p=0.000	R^2=0.05 p=0.183	R^2=0.01 p=0.539	R^2=0.02 p=0.410	R^2=0.01 p=0.536
MLWHF	R^2=0.01 p=0.518	R^2=0.00 p=0.993	R^2=0.04 p=0.233	R^2=0.05 p=0.184	R^2=0.02 p=0.392	R^2=0.04 p=0.229	R^2=0.00 p=0.688	R^2=0.00 p=0.869	R^2=0.05 p=0.176	R^2=0.06 p=0.139		R^2=0.04 p=0.244	R^2=0.01 p=0.630	R^2=0.10 p=0.045	R^2=0.08 p=0.073	R^2=0.06 p=0.141	R^2=0.02 p=0.367
R Flex	R^2=0.04 p=0.21	R^2=0.07 p=0.116	R^2=0.19 p=0.006	R^2=0.17 p=0.009	R^2=0.00 p=0.940	R^2=0.02 p=0.455	R^2=0.14 p=0.018	R^2=0.00 p=0.907	R^2=0.64 p=0.000	R^2=0.59 p=0.000	R^2=0.04 p=0.244		R^2=0.77 p=0.000	R^2=0.04 p=0.205	R^2=0.02 p=0.347	R^2=0.02 p=0.340	R^2=0.03 p=0.306
L Flex	R^2=0.03 p=0.292	R^2=0.02 p=0.358	R^2=0.11 p=0.036	R^2=0.10 p=0.052	R^2=0.04 p=0.221	R^2=0.02 p=0.417	R^2=0.09 p=0.057	R^2=0.00 p=0.796	R^2=0.58 p=0.000	R^2=0.63 p=0.000	R^2=0.01 p=0.630	R^2=0.77 p=0.000		R^2=0.01 p=0.654	R^2=0.00 p=0.963	R^2=0.00 p=0.960	R^2=0.00 p=0.793
Peak VE/VCO2	R^2=0.20 p=0.04	R^2=0.44 p=0.000	R^2=0.45 p=0.000	R^2=0.47 p=0.000	R^2=0.23 p=0.002	R^2=0.01 p=0.605	R^2=0.02 p=0.344	R^2=0.01 p=0.610	R^2=0.04 p=0.245	R^2=0.05 p=0.183	R^2=0.10 p=0.045	R^2=0.04 p=0.205	R^2=0.01 p=0.654		R^2=0.88 p=0.000	R^2=0.94 p=0.000	R^2=0.69 p=0.000
Peak VE/VO2	R^2=0.13 p=0.024	R^2=0.36 p=0.000	R^2=0.33 p=0.000	R^2=0.33 p=0.000	R^2=0.56 p=0.000	R^2=0.00 p=0.976	R^2=0.02 p=0.360	R^2=0.01 p=0.645	R^2=0.01 p=0.680	R^2=0.01 p=0.539	R^2=0.08 p=0.073	R^2=0.02 p=0.347	R^2=0.00 p=0.963	R^2=0.88 p=0.000		R^2=0.87 p=0.000	R^2=0.79 p=0.000
VE/VCO2 slope	R^2=0.24 p=0.001	R^2=0.48 p=0.000	R^2=0.45 p=0.000	R^2=0.50 p=0.000	R^2=0.27 p=0.001	R^2=0.00 p=0.847	R^2=0.03 p=0.320	R^2=0.00 p=0.736	R^2=0.02 p=0.377	R^2=0.02 p=0.410	R^2=0.06 p=0.141	R^2=0.02 p=0.340	R^2=0.00 p=0.960	R^2=0.94 p=0.000	R^2=0.87 p=0.000		R^2=0.81 p=0.000
VE/Vo2 slope	R^2=0.22 p=0.002	R^2=0.35 p=0.000	R^2=0.33 p=0.000	R^2=0.38 p=0.000	R^2=0.42 p=0.000	R^2=0.00 p=0.889	R^2=0.04 p=0.192	R^2=0.03 p=0.329	R=0.01 p=0.463	R^2=0.01 p=0.536	R^2=0.02 p=0.367	R^2=0.03 p=0.306	R^2=0.00 p=0.793	R^2=0.69 p=0.000	R^2=0.79 p=0.000	R^2=0.81 p=0.000	

Table 3.3: Relationship between cardiopulmonary and skeletal muscle parameters at baseline (highlighted sections show statistically significant correlations)

3.1.2 Longitudinal results from baseline to 3 months

3.1.2.1 Functional measures and exercise duration

At baseline the mode New York heart association classification was 3. This showed a signficant improvement to 2 at 2 weeks post (χ^2 $p<0.001$). The mode NYHA was maintained at 2 between 2 and 6 weeks post (χ^2 $p=0.360$). Between 6 weeks and 12 weeks post the mode NYHA class stayed at 2 however there was a significant improvement during that time using the chi squared test (χ^2 $p<0.001$) (see figure 3.7).

Exercise duration increased from a baseline of 323 ± 27 seconds to 477 ± 33 seconds ($p<0.001$). The improvement in exercise duration was maintained at 6 weeks with no further signficant improvement in exercise duration between 2 and 6 weeks post (2 weeks: 477 ± 33, 6 weeks: 527 ± 33 seconds, $p=0.396$). Between 6 and 12 weeks the mean exercise duration showed no further change (6 weeks: 527 ± 33, 12 weeks: 558 ± 36, $p=1.0$) (see figure 3.8)

Minnesota living with heart failures also showed a significant improvement from baseline at the 2 weeks post stage (baseline: 61.6 ± 3.7, 2 weeks: 37.3 ± 4.0, $p<0.001$). The improvement seen was maintained but not increased at the 6 weeks stage (2 weeks: 37.3 ± 4.0, 6 weeks: 33.1 ± 4.0 $p=1.0$). At 12 weeks post the initial improvement has been maintained but again no further improvement was seen compared to the 6 weeks post test (6 weeks: 33.1 ± 4.0, 12 weeks: 32.3 ± 3.6 $p=1.0$) (see figure 3.9).

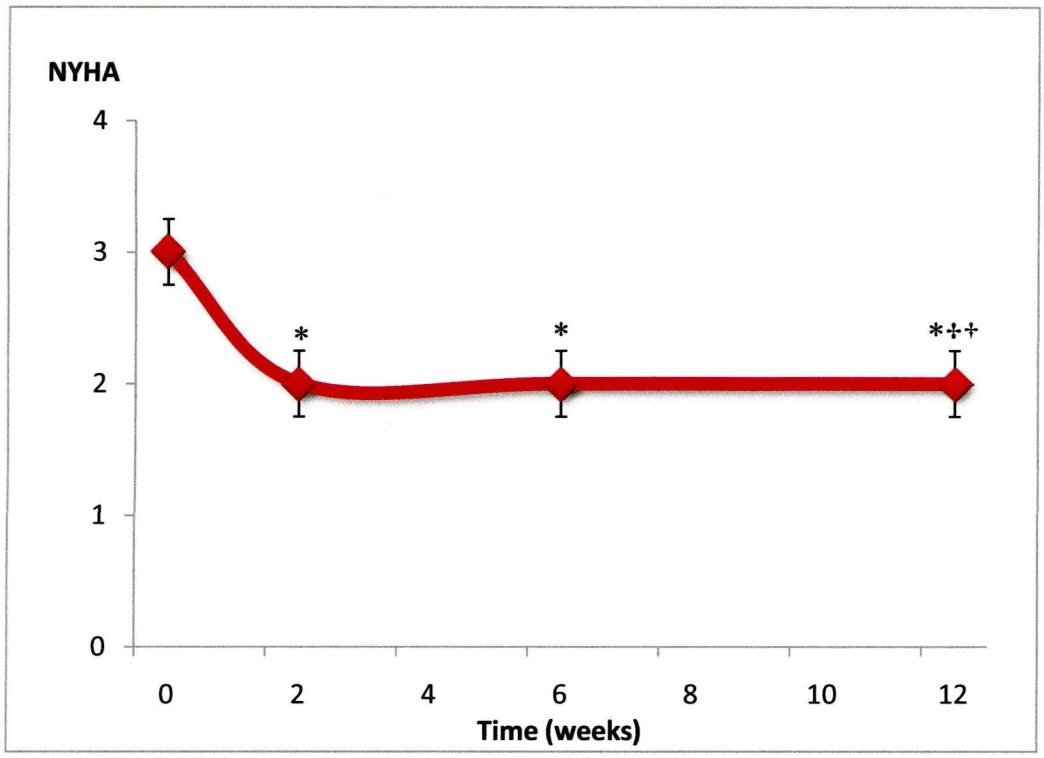

Figure 3.7: Longitudinal change in New York heart association class.

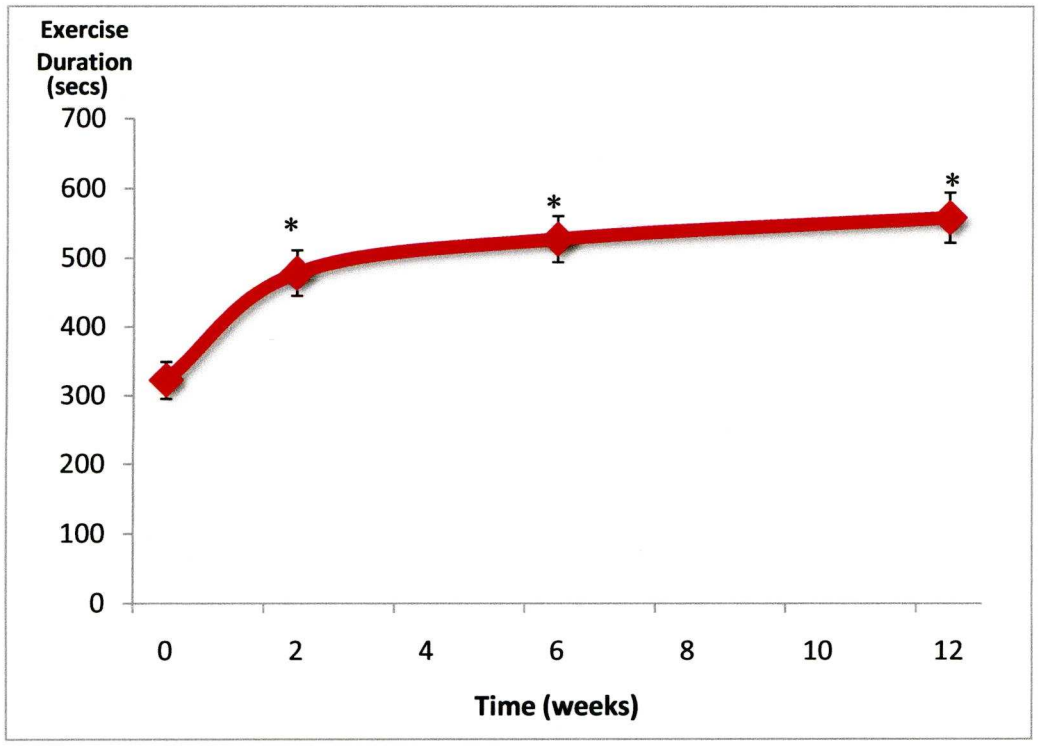

Figure 3.8: Longitudinal improvement in exercise duration

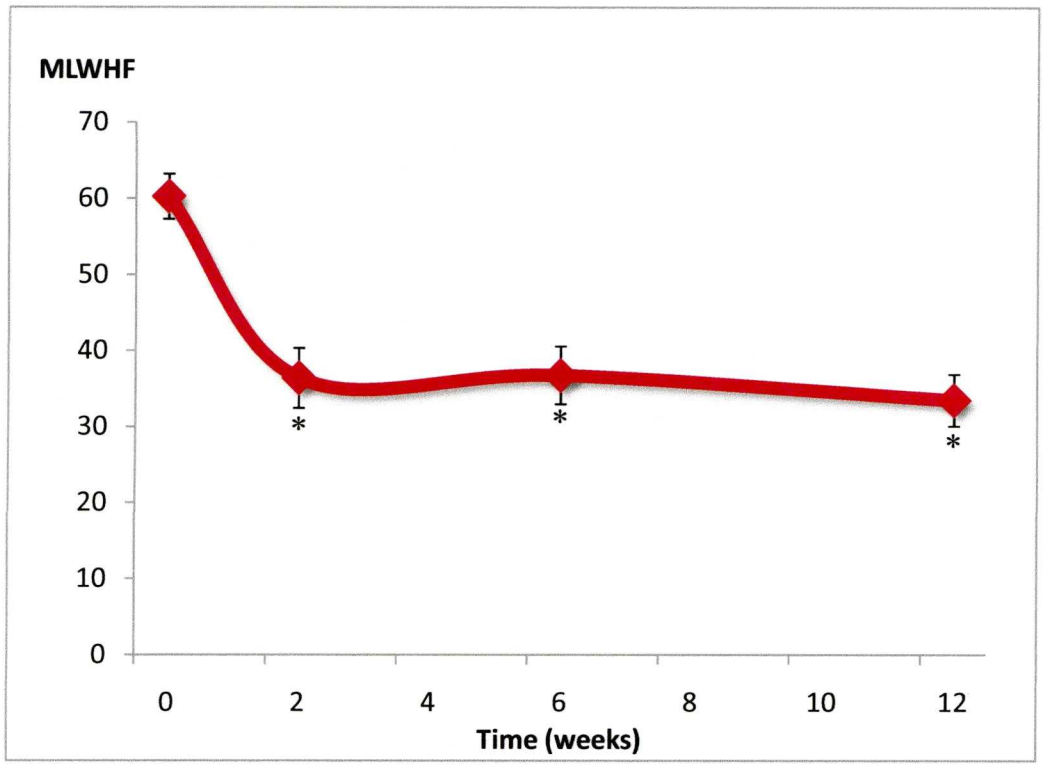

Figure 3.9: Longitudinal improvement in Minnesota living with heart failure.

3.1.2.2 Peak VO_2

There was a signficant increase in the peak VO_2 at the 2 weeks post test (baseline: 15.51 ± 0.54, 2 weeks: 17.76 ± 0.55 p=0.003). This improvement was maintained but not increased at 6 weeks (2 weeks: 17.76 ± 0.55, 6 weeks: 17.54 ± 0.56 p=1.0). Between 6 and 12 weeks post the initial improvement was maintined but no further improvement was seen (6 weeks: 17.54 ± 0.57, 12 weeks: 18.48 ± 0.62 p=0.177) (see figure 3.10).

3.1.2.3 Ventilatory equivalents for oxygen and carbon dioxide

There was no significant change in the ventilatory equivalents for oxygen or carbon dioxide between baseline and 2 weeks (peak VE/VCO_2: baseline 41.6 ± 1.4, 2 weeks: 39.4 ± 1.2 p=0.163, VE/VCO_2 slope: baseline 40.8 ± 1.6, 2 weeks: 37.4 ± 1.2

p=0.082, peak VE/VO_2: baseline 43.6 ± 2.1, 2 weeks: 41.4 ± 1.6 p=0.758, VE/VO_2 slope: baseline 45.9 ± 2.5, 2 weeks: 41.8 ± 1.9 p=0.323).

Between the 2 and 6 weeks test there was no signficant change (peak VE/VCO_2: 2 weeks: 39.4 ± 1.2, 6 weeks: 39.2 ± 1.3 p=1.0, VE/VCO_2 slope: 2 weeks: 37.4 ± 1.2, 6 weeks: 37.4 ± 1.3 p=1.0, peak VE/VO_2: 2 weeks: 41.4 ± 1.6, 6 weeks: 42.2 ± 1.6 p=1.0, VE/VO_2 slope: 2 weeks: 41.8 ± 1.9, 6 weeks: 43.0 ± 1.9 p=1.0).

Between the 6 and 12 week test there were also no significant changes in any of the ventilatory equivalents for oxygen (peak VE/VO_2: 6 weeks: 42.2 ± 1.6, 12 weeks: 41.3 ± 1.4 p=1.0, VE/VO_2 slope: 6 weeks: 43.0 ± 1.9, 12 weeks: 42.5 ± 1.8 p=1.0) or for carbon dioxide (peak VE/VCO_2: 6 weeks: 39.2 ± 1.3, 12 weeks: 38.3 ± 1.2 p=1.0, VE/VCO_2 slope: 6 weeks: 37.4 ± 1.3, 12 weeks: 37.1 ± 1.3 p=1.0).

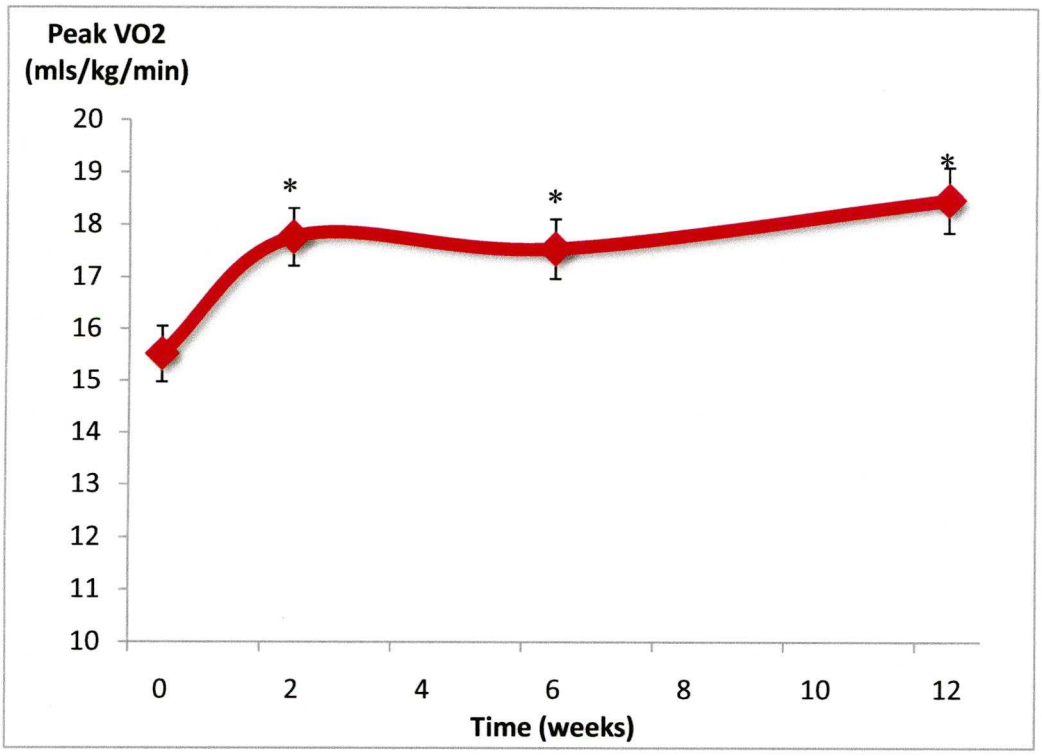

Figure 3.10: Longitudinal improvement in peak VO_2

3.1.2.4 Peak cardiac output and cardiac reserve

There was a signficant increase in peak cardiac power output and cardiac reserve at 2 weeks post CRT (peak CPO: baseline: 2.53 ± 0.10, 2 weeks: 2.96 ± 0.13 p=0.001, cardiac reserve: baseline: 1.89 ± 0.09, 2 weeks: 2.27 ± 0.11 p=0.004). There was no further increase between 2 and 6 weeks for either peak cardiac power output (2 weeks: 2.96 ± 0.13, 6 weeks: 3.07 ± 0.13 p=0.636) or cardiac reserve (2 weeks: 2.27 ± 0.11, 6 weeks: 2.41 ± 0.12 p=0.338). At 12 weeks post CRT there was no significant increase compared to the 6 week post stage in either peak cardiac power output (6 weeks: 3.07 ± 0.13, 12 weeks: 3.23 ± 0.15 p=0.492) or cardiac reserve (6 weeks: 2.41 ± 0.12, 12 weeks: 2.58 ± 0.14 p=0.438), however the 3 month results were signficantly improved compared to the 2 weeks post results (peak CPO: 2 week: 2.96 ± 0.13, 12 weeks: 3.23 ± 0.15 p=0.014, cardiac reserve: 2 weeks: 2.27 ± 0.11, 2 weeks: 2.58 ± 0.14 p=0.005) (see figure 3.11)

3.1.2.5 Peak RER and percentage of peak VO_2 at the anaerobic threshold.

There was no signficant change in either peak RER or the percentage of peak VO_2 at the anaerobic threshold between the baseline and 2 weeks tests (peak RER: baseline: 1.04 ± 0.02 2 weeks: 1.05 ± 0.02 p=1.0, peak VO_2 at the anaerobic threshold: baseline: 78.9 ± 11.7, 2 weeks: 69.1 ± 2.1 p=1.0). Between 2 and 6 weeks there was no change in peak RER (2 weeks: 1.05 ± 0.02, 6 weeks: 1.08 ± 0.02, p=1.0) and the percentage of peak VO_2 at the anaerobic threshold (2 weeks: 69.1 ± 2.1, 6 weeks: 70.1 ± 2.5, p=1.0).

Between the 6 and 12 week test there were also no significant changes in either RER (6 weeks: 1.08 ± 0.02, 12 weeks: 1.08 ± 0.01, p=1.0) or the percentage of peak VO_2

at the anaerobic threshold (6 weeks: 70.1 ± 2.5, 12 weeks: 68.9 ± 1.6, p=1.0) (see table 3.4)

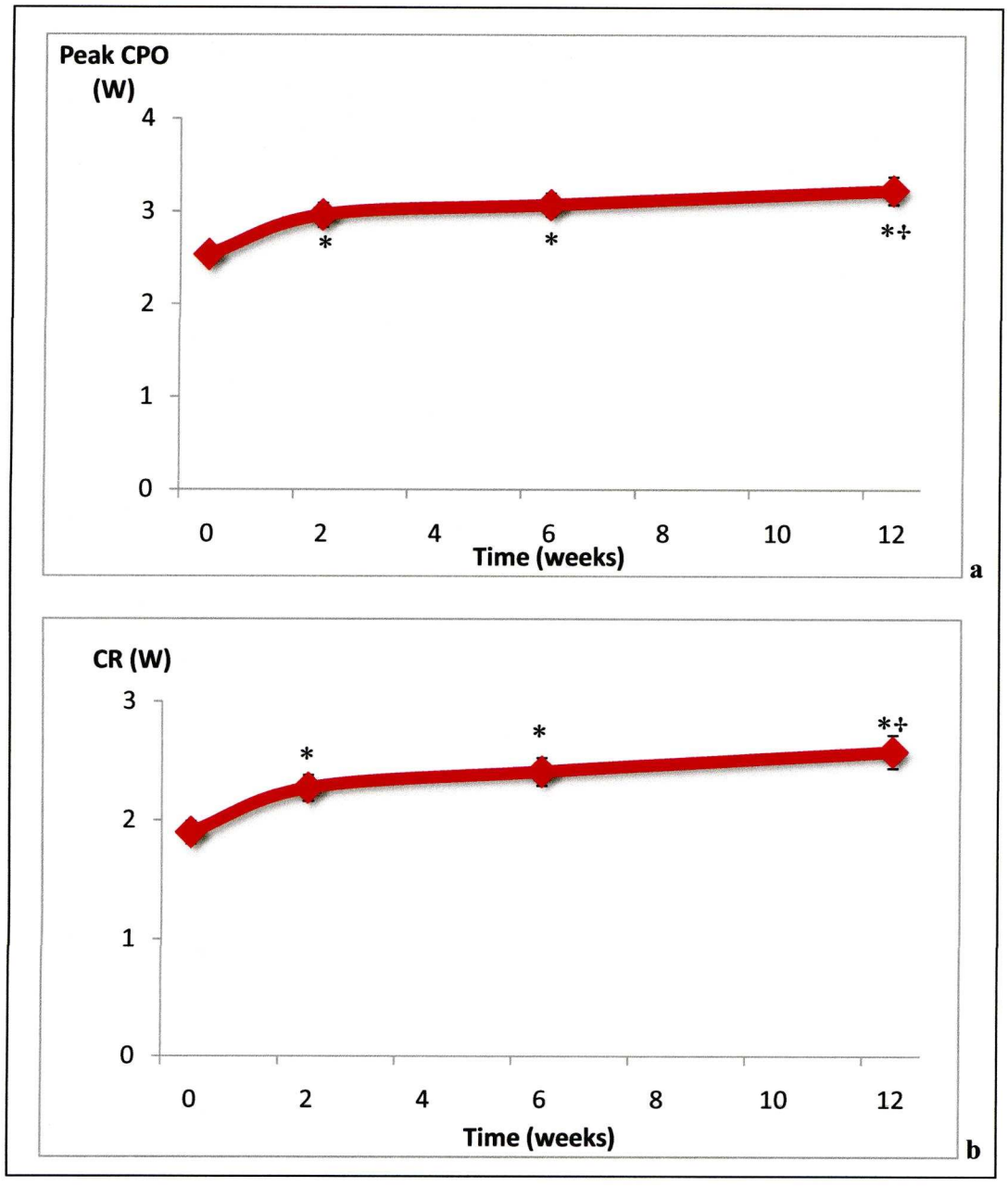

Figure 3.11 The longitudinal improvement in peak cardiac power output (CPO) (a) and cardiac reserve (CR) (b)

3.1.2.6 Echocardiographic parameters

Following cardiac resynchronisation therapy there was a trend towards an improvement in ejection fraction at 2 weeks however this failed to reach statistical significance (baseline: 21.71 ± 1.50, 2 weeks: 28.74 ± 1.97, p=0.068). There was however a significant change in ejection fraction at 6 weeks compared to baseline (baseline: 21.71 ± 1.50, 6 weeks: 30.72 ± 1.16 p=0.002). There was no signficant change between the 2 and 6 week tests (2 weeks: 28.74 ± 1.97, 6 weeks: 30.72 ± 1.16 p=1.0). Between 6 and 12 weeks the improvement in ejection fraction was maintained but not increased further (6 weeks: 30.72 ± 1.16, 12 weeks: 32.01 ± 1.43 p=1.0) (see figure 3.12a).

There was a small reduction in left ventricular end-diastolic dimension between baseline and 2 weeks however this just failed to reach statistical significance (baseline: 7.01 ± 0.15, 2 weeks: 6.60 ± 0.15 p=0.055). The change between baseline and 6 weeks also just failed to reach statistical signficance (6 weeks: 6.46 ± 0.15 p=0.052). There was no statistically signficant difference between baseline and 12 weeks (12 weeks: 6.67 ± 0.16 p=0.366). Between 2 and 6 weeks there was no signficant change in left ventricular end-diastolic dimension (2 weeks: 6.60 ± 0.15, 6 weeks: 6.46 ± 0.15 p=1.0). Between 6 and 12 weeks there was no change in left ventricular end-diastolic dimension (6 weeks: 6.46 ± 0.15, 12 weeks: 6.67 ± 0.16 p=1.0) (see figure 3.12b)

3.1.2.7 Skeletal muscle function

At 2 weeks post cardiac resynchronisation therapy there was no significant improvement in peak skeletal muscle torque in flexion or extension on the right (extension: baseline: 119.8 ± 9.0, 2 weeks: 128.8 ± 11.5 p=1.0, flexion: baseline: 63.5 ± 4.7, 2 weeks: 70.3 ± 4.5 p=0.292) or on the left (extension: baseline: 123.2 ± 9.8, 2 weeks: 130.5 ± 11.9 p=1.0, flexion: baseline: 64.2 ± 5.5, 2 weeks: 70.7 ± 4.5 p=0.708).

Between 2 and 6 week post cardiac resynchronisation therapy no significant change in peak muscle torque on the right (extension: 2 weeks: 128.8 ± 11.5, 6 weeks: 127.6 ± 10.7 p=1.0, flexion: 2 weeks: 70.3 ± 4.5, 6 weeks: 70.7 ± 5.3 p=1.0) or on the left (extension: 2 weeks: 130.5 ± 11. 9, 6 weeks: 131.3 ± 11.1 p=1.0, flexion: 2 weeks: 70.7 ± 4.5, 6 weeks: 72.3 ± 5.2 p=1.0).

There was also no significant improvement between 6 and 12 weeks post cardiac resynchronisation therapy on the right (extension: 6 weeks: 127.6 ± 10.5, 12 weeks: 123.5 ± 10.0 p=1.0, flexion: 6 weeks: 70.7 ± 5.3, 12 weeks: 71.1 ± 4.8 p=1.0) or on the left (extension: 6 weeks: 131.3 ± 11. 1, 12 weeks: 126.3 ± 9.9 p=0.882, flexion: 6 weeks: 72.3 ± 5.2, 12 weeks: 71.6 ± 4.3 p=1.0) (see table 3.4)

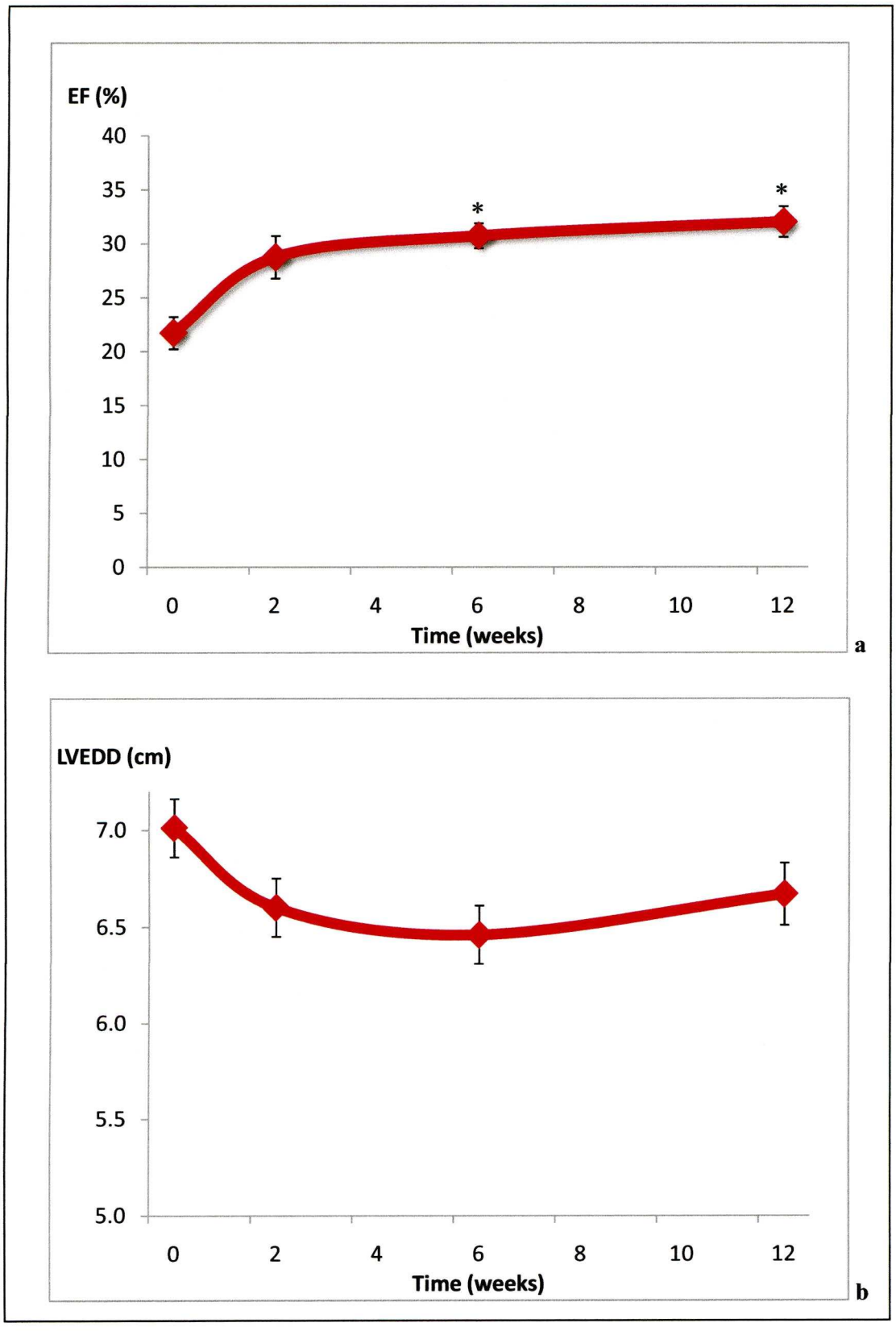

Figure 3.12: The longitudinal improvement in ejection fraction (a) and left ventricular end diastolic dimension (b)

Table 3.4: Longitudinal improvement following CRT

	Baseline	2 weeks	6 weeks	3 months
NYHA	3	2 *	2 *	2 *†‡
MLWHF	61.6 (3.7)	37.3 (4.0) *	33.1 (4.0) *	32.3 (3.6) *
Exercise Duration	322 (27)	478 (33) *	527 (33) *	558 (36) *
Peak VO_2	15.51 (0.54)	17.76 (0.55) *	17.54 (0.57) *	18.48 (0.62) *
RER	1.04 (0.02)	1.05 (0.02)	1.08 (0.02)	1.08 (0.01)
Percentage of peak VO_2 at AT	78.9 (11.7)	69.1 (2.1)	70.1 (2.5)	68.9 (1.6)
Peak CPO	2.53 (0.10)	2.96 (0.13) *	3.07 (0.13) *	3.23 (0.15) *†
CR	1.89 (0.09)	2.27 (0.11) *	2.41 (0.12) *	2.58 (0.14) *†
LVEDD	7.01 (0.15)	6.60 (0.15)	6.46 (0.15)	6.67 (0.16)
EF	21.71 (1.5)	28.74 (1.97)	30.72 (1.16) *	32.01 (1.43) *
Right Extension	119.8 (9.0)	128.8 (11.5)	127.6 (10.7)	123.5 (10.0)
Left Extension	123.2 (9.8)	130.5 (11.9)	131.3 (11.1)	126.3 (9.9)
Right Flexion	63.5 (4.7)	70.3 (4.5)	70.7 (5.3)	71.1 (4.8)
Left Flexion	64.2 (5.5)	70.7 (4.5)	72.3 (5.2)	71.6 (4.3)
Peak VE/VCO_2	41.6 (1.4)	39.4 (1.2)	39.2 (1.3)	38.3 (1.2)
Peak VE/VO_2	43.6 (2.1)	41.4 (1.6)	42.2 (1.6)	41.3 (1.4)
VE/VCO_2 slope	40.8 (1.6)	37.4 (1.2)	37.4 (1.3)	37.1 (1.3)
VE/VO_2 slope	45.9 (2.5)	41.8 (1.9)	43.0 (1.9)	42.5 (1.8)

*$p<0.05$ compared to baseline †$p<0.05$ compared to 2 weeks
‡$p<0.05$ compared to 6 weeks
All values expressed as mean ± SEM.

3.1.3 Predictors of response

At 3 months 27 (67.5%) out of the 40 patients were defined as responders. The baseline parameters showed that there was no signficant difference in patients age (responders: 66.4 ± 1.8 vs. non-responders: 63.0 ± 3.3 p=0.323) and baseline QRS duration (responders: 159.3 ± 3.7 vs. non-responders: 155.1 ± 4.5 p=0.48). There was a significant difference in the echocardiographic parameters at baseline between responders and non-responders with responders showing a less dilated LVEDD (responders: 6.76 ± 0.14 vs. non-responders: 7.30 ± 0.18 p=0.024) and a more impaired ejection fraction (responders: 21.61 ± 1.70 vs. non-responders: 29.13 ± 2.22 p=0.015). Peak skeletal muscle torque during extension at baseline was significantly different between the responders and non-responders (right: responders: 114.9 ± 8.6 vs. non-responders: 147.8 ± 12.9 p=0.032, left: responders: 113.9 ± 8.8 vs. non-responders: 144.6 ± 12.8 p=0.029) but there was no significant difference during flexion (right: responders: 61.3 ± 4.2 vs. non-responders: 75.2 ± 7.0 p=0.08, left: responders: 62.6 ± 5.0 vs. non-responders: 70.1 ± 6.0 p=0.15). There were also significant differences between the responders and non-responders in the baseline ventilatory equivalents for carbon dioxide production (peak VE/VCO_2: responders: 44.3 ± 1.6 vs. non-responders: 38.9 ± 2.4 p=0.04, left: responders: 43.7 ± 1.8 vs. non-responders: 38.0 ± 2.8 p=0.035). The baseline peak ventilatory equivalents for oxygen consumption (peak VE/VO_2) did just reach signficance (responder: 46.9 ± 2.3 vs. non-responders: 40.8 ± 3.4 p=0.049) whilst the ventilatory equivalent slope for oxygen consumption (VE/VO_2 slope) were not significantly different between the responders and non-responders (responder: 50.1 ± 3.5 vs. non-responders: 43.3 ± 4.0 p=0.15).

There was also no significant difference between the responders and non-responders in mean MLWHF scores (responders: 57.1 ± 3.5 vs. non-responders: 66.6 ± 5.3 p=0.16), exercise duration (responders: 344 ± 31.9 vs. non-responders: 349.1 ± 50.8 p=0.16), peak VO_2 (responders: 15.44 ± 0.63 vs. non-responders: 16.41 ± 1.00 p=0.39), RER (responders: 1.05 ± 0.02 vs. non-responders: 1.04 ± 0.02 p=0.83), percentage of peak VO_2 at AT (responders: 70.6 ± 3.6 vs. non-responders: 62.8 ± 4.3 p=0.09), peak CPO (responders: 2.42 ± 0.11 vs. non-responders: 2.79 ± 0.21 p=0.27) and cardiac reserve (responders: 1.80 ± 0.11 vs. non-responders: 2.09 ± 0.20 p=0.35). Full results are shown in table 3.5

Table 3.5: Baseline predictors of response

	Responders (n=27)	Non-Responders (n=13)	p-value
Age (years)	66.4 ± 1.8	63.0 ± 3.3	0.32
QRS duration (ms)	159.3 ± 3.7	155.1 ± 4.5	0.48
MLWHF scores	57.1 ± 3.5	66.6 ± 5.3	0.16
Exercise Duration (secs)	344 ± 31.9	349.1 ± 50.8	0.94
Peak VO_2 (mls/kg/min)	15.44 ± 0.63	16.41 ± 1.00	0.39
RER	1.05 ± 0.02	1.04 ± 0.02	0.83
Percentage of peak VO_2 at AT	70.6 ± 3.6	62.8 ± 4.3	0.09
Peak CPO	2.42 ± 0.11	2.79 ± 0.21	0.27
Cardiac Reserve	1.80 ± 0.10	2.09 ± 0.20	0.35
LVEDD	6.76 ± 0.14	7.30 ± 0.18	0.024
Ejection Fraction	21.61 ± 1.70	29.13 ± 2.22	0.015
Right Extension	114.9 ± 8.6	147.8 ± 12.9	0.032
Left Extension	113.9 ± 8.8	144.6 ± 12.8	0.029
Right Flexion	61.3 ± 4.2	75.2 ± 7.0	0.08
Left Flexion	62.6 ± 5.0	70.1 ± 6.0	0.15
Peak VE/VC02	44.3 ± 1.6	38.9 ± 2.4	0.04
Peak VE/V02	46.9 ± 2.3	40.8 ± 3.4	0.049
VE/VC02 Slope	43.7 ± 1.8	38.0 ± 2.8	0.035
VE/V02 Slope	50.1 ± 3.5	43.3 ± 4.0	0.15

All values expressed as mean ± SEM.

3.2 Study II. The effects of exercise rehabilitation in addition to cardiac resynchronisation therapy

3.2.1 Baseline Data

Baseline characteristics of the patients are shown in table 3.6. Mean age was 64.4 ± 1.5 (range: 38-80) years and 46 (92%) patients were male. The mean and mode NYHA class was 3 and there was evidence of a dilated cardiomypoathy with a left ventricular end diastolic dimension of 7.07cm ± 0.13 and a ejection fraction of 23.67 % ± 1.32. Thirty three (66%) of the patients were in sinus rhythm at baseline, the rest (17(34%)) were in atrial fibrillation. The primary cause of the dilated cardiomypathy was ischaemic in 37 (74%), valvular heart disease in 6 (12%) and idiopathic in 7 (14%).

3.2.2 Baseline cardiopulmonary data

The baseline cardiopulmonary haemodynamic data are shown in table 3.7. Resting heart rate was 76 ± 2/min and increased to 121 ± 4/min at peak exercise. This was associated with an increase in mean arterial pressure from 87.3 ± 1.2 mmHg to 104.8 ± 1.5 mmHg. Total exercise duration was 374 ± 27 seconds and patients did achieve a true maximal cardiopulmonary exercise test manifest by a peak RER of 1.0 ± 0.02. The subjects were significantly impaired in their cardiopulmonary exercise capacity with a peak VO_2 of 16.12 ± 0.49 mls/kg/min which was 67.1 ± 2.5 % of their predicted peak VO_2. Cardiac power output increased from a resting value of 0.63 ± 0.03 watts to a peak value of 2.48 ± 0.11 watts therefore giving a cardiac reserve of 1.85 ± 0.1 watts.

Table 3.6 Baseline characteristic of the study population

Male, n (%)	46 (92%)
Female, n (%)	4 (8%)
Age (yrs, range)	64.4 ± 1.5 (38-80)
NYHA class	3
Height (cm, range)	171.8 ± 1.1 (154-186)
Weight (kg, range)	84.4 ± 2.5 (55-139)
BMI (kg/m^2, range)	28.7 ± 0.7 (20-44)
QRS duration (msec, range)	160.4 ± 2.9 (124-198)
Sinus rhythm, n(%)	33 (66%)
Atrial Fibrillation, n(%)	17 (34%)
Aetiology	
Ischaemic	37 (74%)
Valvular	6 (12%)
Idiopathic	7 (14%)
Medication	
ACE inhibitors/ARB	49 (98%)
Diuretics	48 (96%)
Beta-blockers	30 (60%)
Digoxin	23 (46%)
Spironolactone	27 (54%)

All values expressed as mean ± SEM.

Table 3.7: Baseline cardiopulmonary data

Resting HR (min^{-1})	76± 2
Resting MBP (mm Hg)	88.3 ± 1.6
Resting VO_2 (mls/kg/min)	5.35 ± 0.18
Resting CO (L/min)	3.25 ± 0.13
Resting CPO (watts)	0.63 ± 0.03
Resting VE (L/min)	15.1 ± 0.7
Exercise duration (secs)	374 ± 27
AT (mls/kg/min)	11.63 ± 0.51
AT % peak VO_2 (%)	71.8 ± 2.4
Peak RER	1.00 ± 0.02
Peak HR (min^{-1})	121 ± 4
Peak MBP (mm Hg)	104.8 ± 1.5
Peak SBP (mm Hg)	152.7 ± 2.8
Peak VO_2 (mls/kg/min)	16.12 ± 0.49
% predicted peak VO_2 (%)	67.1 ± 2.5
Peak CO (L/min)	10.56 ± 0.41
Peak CPO (watts)	2.48 ± 0.11
Cardiac reserve (watts)	1.85 ± 0.1
Peak VE (L/min)	54.5 ± 2.0
Peak VE/VCO_2	44.36 ± 1.96
Peak VE/VO_2	43.46 ± 1.68
$VE/VCO_{2\ slope}$	43.94 ± 2.36
$VE/VO_{2\ slope}$	46.93 ± 2.44
Right extension (N-M)	128.4 ± 6.5
Right Flexion (N-M)	70.3 ± 3.9
Left Extension (N-M)	124.1 ± 6.5
Left Flexion (N-M)	72.8 ± 3.4

All values expressed as mean ± SEM.

3.2.3 Baseline to 3 months post CRT

Full results from baseline to 3 months post cardiac resynchronisation therapy are shown in table 3.8.

3.2.3.1 Functional measures and exercise duration

There was an improvement in NYHA classification from a mode of 3 to 2 (χ^2 $p<0.001$) (see figure 3.13), and in the Minnesota living with heart failure scores from 61.8 ± 2.5 to 31.8 ± 2.8 ($p<0.001$) (see figure 3.14). Exercise duration improved from a baseline of 374 ± 27 to 562 ± 31 ($p<0.001$) (see figure 3.15).

3.2.3.2 Peak VO_2 and the ventilatory equivalents for oxygen and carbon dioxide

Following cardiac resynchronisation therapy there was an increase in peak VO_2 (mls/min/kg) from 16.12 ± 0.49 to 18.41 ± 0.50 ($p<0.001$) (see figure 3.16). There was also an improvement in the ventilatory equivalents for carbon dioxide (peak VE/VCO_2: 44.36 ± 1.96 to 38.84 ± 0.98 $p<0.001$, VE/VCO_2 slope: 43.94 ± 2.36 to 37.49 ± 1.0 $p=0.001$) (see figure 3.17). There was no change in the ventilatory equivalents for oxygen (peak VE/VO_2: 43.46 ± 1.68 to 41.94 ± 1.10 $p=0.236$, VE/VO_2 slope: 46.93 ± 2.44 to 43.22 ± 1.42 $p=0.087$) (see figure 3.18).

3.2.3.3 Peak Cardiac output and Cardiac Reserve

At 3 months post there was an improvement in peak cardiac power output (W) from 2.48 ± 0.11 to 3.20 ± 0.11 ($p<0.001$) (see figure 3.19) and also in cardiac reserve (W) from 1.85 ± 0.10 to 2.54 ± 0.10 ($p<0.001$) (see figure 3.20).

3.2.3.4 Peak RER and percentage of peak VO_2 at the anaerobic threshold.

The peak respiratory exchange ratios (RER) achieved improved from 1.00 ± 0.02 to 1.08 ± 0.01 ($p<0.001$), however the percentage of peak VO_2 at the anaerobic threshold (%) remained unchanged at this point (71.8 ± 2.4 to 69.1 ± 1.3 ($p=0.319$)) (see figure 3.21).

3.2.3.5 Echocardiographic parameters

Following cardiac resynchronisation therapy there was a reduction in the left ventricular end-diastolic dimension from 7.07 ± 0.13 to 6.64 ± 0.11 ($p<0.001$). This was coupled with an improvement in the ejection fraction from 23.7 ± 1.32 to 32.4 ± 0.92 ($p<0.001$) (see figure 3.22).

3.2.3.6 Peak skeletal muscle torque

There was no improvement in peak skeletal muscle torque during extension (right: 128.3 ± 6.5 to 131.3 ± 6.9 $p=0.272$, left: 124.1 ± 6.5 to 127.2 ± 6.5 $p=0.149$) (see figure 3.23) or during flexion (right: 70.3 ± 3.9 to 72.8 ± 3.5 $p=0.101$, left: 72.8 ± 3.4 to 70.7 ± 3.2 $p=0.275$) (see figure 3.24).

Table 3.8: Longitudinal data baseline to 3 months

	Pre CRT	3 months Post CRT
NYHA class	3	2 *
MLWHF	61.8 ± 2.5	31.8 ± 2.8 *
Exercise Duration (seconds)	374 ± 27	562 ± 31*
Peak VO_2 (mls/kg/min)	16.12 ± 0.49	18.41 ± 0.50*
RER	1.00 ± 0.02	1.08 ± 0.01 *
Percentage of peak VO_2 at AT(%)	71.8 ± 2.4	69.1 ± 1.3
Peak CPO (W)	2.48 ± 0.11	3.20 ± 0.11*
CR (W)	1.85 ± 0.10	2.54 ± 0.10*
Left Ventricular End Diastolic Dimension (cm)	7.07 ± 0.13	6.64 ± 0.11*
Ejection Fraction (%)	23.7 ± 1.32	32.4 ± 0.92*
Right Extension (N-M)	128.3 ± 6.5	131.3 ± 6.9
Left Extension (N-M)	124.1 ± 6.5	127.2 ± 6.5
Right Flexion (N-M)	70.3 ± 3.9	72.8 ± 3.5
Left Flexion (N-M)	72.8 ± 3.4	70.7 ± 3.2
Peak VE/VCO_2	44.36 ± 1.96	38.84 ± 0.98 *
Peak VE/VO_2	43.46 ± 1.68	41.94 ± 1.10
VE/VCO_2 slope	43.94 ± 2.36	37.49 ± 1.00 *
VE/VO_2 slope	46.93 ± 2.44	43.22 ± 1.42

All values expressed as mean ± SEM.

3.2.4 Baseline data at randomisation

At 3 months the patients were randomised to either exercise training or control. The 2 groups were well matched at the point of randomisation (see table 3.9). There was similar rate of sinus rhythm in both the exercise group (16 patients (64%)) and the control group (17 patients (68%)).

3.2.4.1 Functional measures and exercise duration

There was no significant difference in either NYHA classification between the 2 groups at 3 months (exercise: 2 vs. control: 2 (χ^2 p=0.905)), or in the Minnesota living with heart failure scores from (exercise: 34.6 ± 4.5 vs. control: 29.0 ± 3.3 (p=0.325)). Exercise duration was also similar in both groups post randomisation (exercise: 581 ± 45 vs. control: 542 ± 43 (p=0.527)).

3.2.4.2 Peak VO_2 and the ventilatory equivalents for oxygen and carbon dioxide

Following randomisation there was no significant difference in peak VO_2 (mls/min/kg) between the 2 groups (exercise: 18.74 ± 0.68 vs. control: 18.08 ± 0.75 (p=0.521)). There were also no significant differences in the ventilatory equivalents for carbon dioxide (peak VE/VCO_2: exercise: 37.6 ± 1.1 vs. control: 40.1 ± 1.6 (p=0.195), VE/VCO_2 slope: exercise: 36.4 ± 1.1 vs. control: 38.6 ± 1.7 (p=0.290)). There was also no significant difference in the ventilatory equivalents for oxygen (peak VE/VO_2: exercise: 41.0 ± 1.2 vs. control: 42.8 ± 1.8 (p=0.420), VE/VO_2 slope: exercise: 42.7 ± 1.6 vs. control: 43.8 ± 2.4 (p=0.715)).

3.2.4.3 Peak cardiac output and cardiac reserve

At 3 months following cardiac resynchronisation therapy there was no signficant differences betweent the 2 groups in peak cardiac power output (w) (exercise: 3.27 ± 0.16 vs. control: 3.14 ± 0.15 (p=0.545)) and cardiac reserve (w) (exercise: 2.57 ± 0.14 vs. control: 2.51 ± 0.14 (p=0.772)).

3.2.4.4 Peak RER and percentage of peak VO_2 at the anaerobic threshold.

The peak respiratory exchange ratios (RER) achieved was similar in the 2 groups at 3 months (exercise: 1.10 ± 0.02 vs. control: 1.07 ± 0.01 (p=0.246)). The percentage of peak VO_2 at the anaerobic threshold (%) was also similar in both groups (exercise: 67.5 ± 1.7 vs. control: 70.8 ± 1.9 (p=0.200)).

3.2.4.5 Echocardiographic parameters

Following randomisation there was no signficant difference in the left ventricular end-diastolic dimension between the 2 groups (exercise: 6.64 ± 0.18 vs. control: 6.57 ± 0.11 (p=0.752)). There was also no significant difference in the ejection fraction between the 2 groups at this stage (exercise: 32.8 ± 1.2 vs. control: 32.6 ± 1.4 (p=0.895)).

3.2.4.6 Peak skeletal muscle torque

There was no significant difference between the 2 groups in peak skeletal muscle torque during extension (right: exercise: 135.0 ± 10.1 vs. control: 127.7 ± 9.6 (p=0.603), left: exercise: 135.0 ± 10.1 vs. control: 119.4 ± 8.0 (p=0.233)) or during flexion (right: exercise: 73.7 ± 5.1 vs. control: 71.9 ± 4.9 (p=0.805), left: exercise: 72.5 ± 4.5 vs. control: 68.8 ± 4.5 (p=0.567)).

3.2.5 Results at 6 months post cardiac resynchronisation therapy.

No patients in the exercise group had any complications from the exercise training and there were no problems with cardiac arrhythmias. Full results following randomisation are shown in table 3.9.

3.2.5.1 Functional measures and exercise duration

Following the period of exercise training the exercise group showed a further significant improvement in New York heart association class (2 vs. 1 (χ^2 $p<0.001$)) (see figure 3.13) and Minnesota living with heart failure score (34.6 ± 4.5 vs. 26.2 ± 4.1 ($p=0.013$)) (see figure 3.14). The exercise group also showed a significant increase in exercise duration (seconds) (581 ± 45 vs. 752 ± 36 ($p<0.001$)) (see figure 3.15). The control group showed a significant improvement in exercise duration (seconds) (542 ± 43 vs. 572 ± 44 ($p=0.028$)) but no improvements in NYHA class (2 vs. 2 (χ^2 $p=0.607$) and MLWHF score (29.0 ± 3.3 vs. 29.5 ± 3.6 ($p=0.949$).

Inter-group analyses confirmed that the improvements in NYHA class (mean change exercise: 1 vs. control: 0 ($p=0.001$)), exercise duration (seconds) (mean change exercise: 171 ± 35 vs. control: 30 ± 13 ($p<0.001$)), and MLWHF scores (mean change exercise: -8.4 ± 3.1 vs. control: 1.6 ± 3.1 ($p=0.026$)) were significantly better in the exercise group.

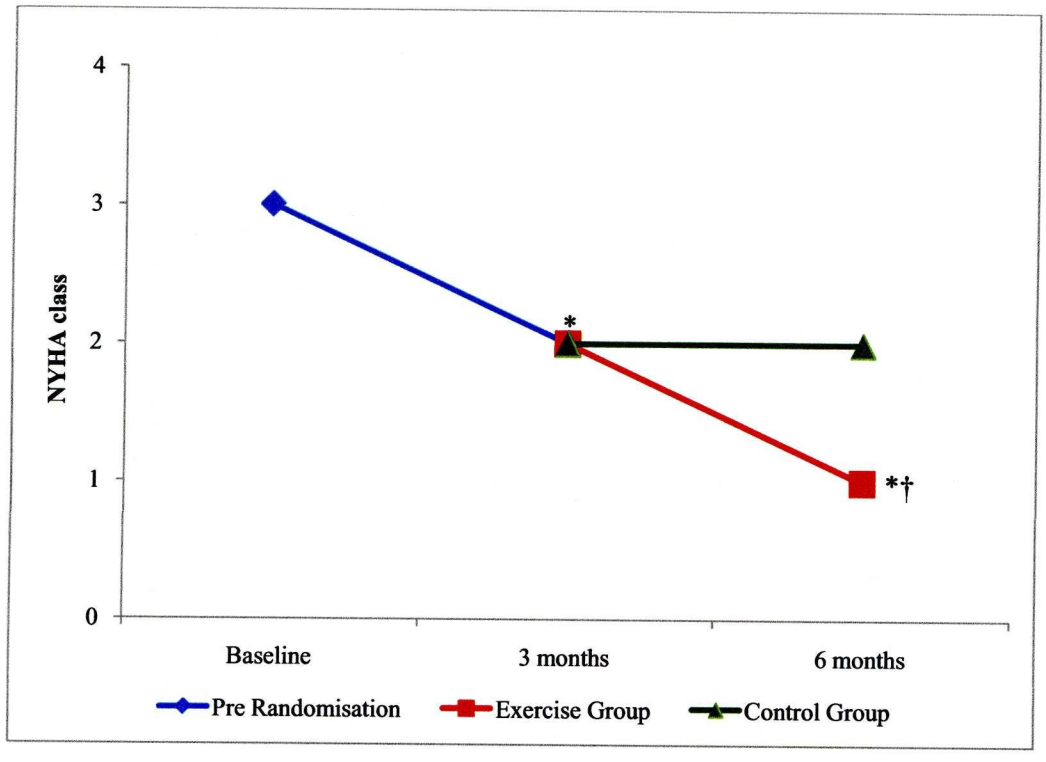

Figure 3.13: NYHA class

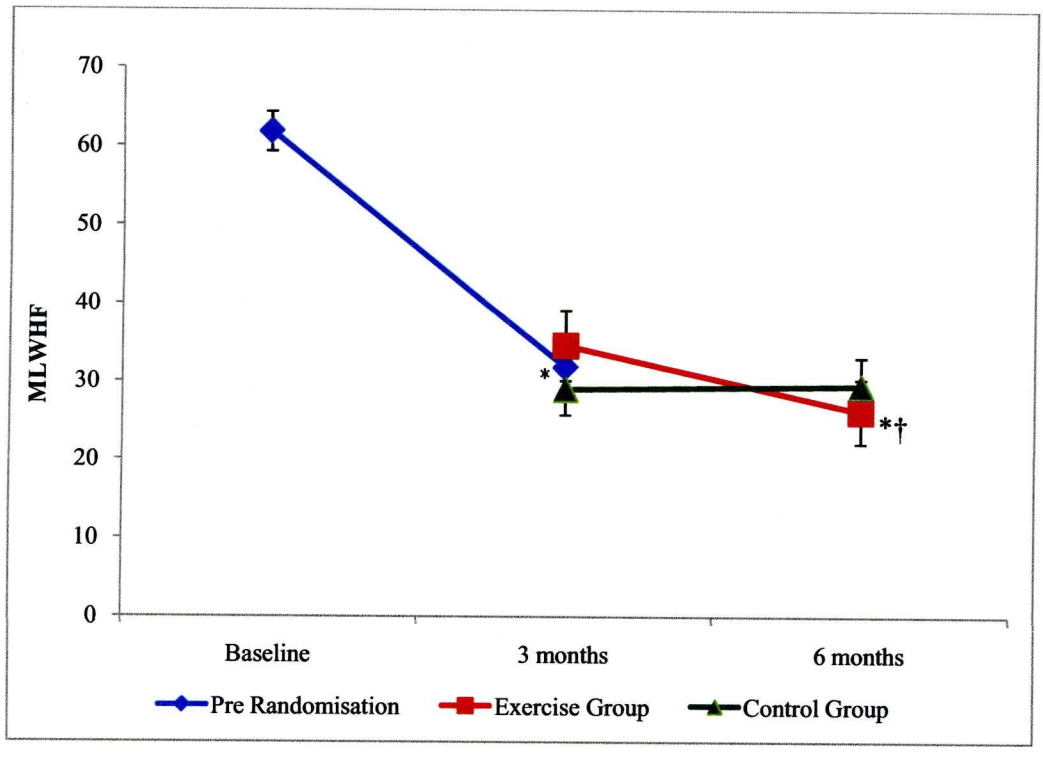

Figure 3.14: Minnesota living with heart failure scores

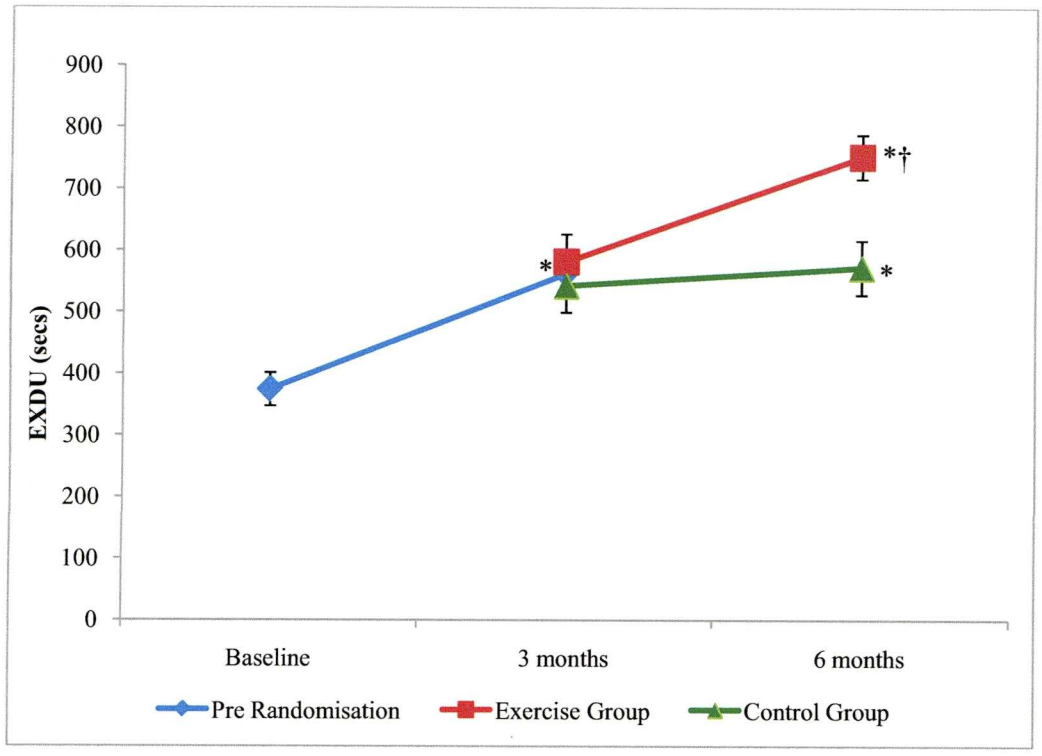

Figure 3.15: Exercise Duration

3.2.5.2 Peak VO_2 and the ventilatory equivalents for oxygen and carbon dioxide

There was a signficant increase in the peak VO_2 (mls/kg/min) following exercise training (18.74 ± 0.68 vs. 20.10 ± 0.77 (p=0.011)) (see figure 3.16). This improvement was not matched in the control group (18.08 ± 0.75 vs. 18.07 ± 0.78 (p=0.977)). There was no significant improvement in either group in the ventilatory equivalents for carbon dioxide production (peak VE/VCO_2: exercise: 37.6 ± 1.1 vs. 37.9 ± 1.3 (p=0.746) control: 40.1 ± 1.6 vs. 39.0 ± 1.6 (p=0.177), VE/VCO_2 slope: exercise: 36.4 ± 1.1 vs. 35.7 ± 1.2 (p=0.427) control: 38.6 ± 1.7 vs. 37.1 ± 1.8 (p=0.224)) (see figure 3.17) and for oxygen consumption (peak VE/VO_2: exercise: 41.0 ± 1.2 vs. 43.1 ± 1.6 (p=0.096) control: 42.8 ± 1.8 vs. 41.3 ± 2.0 (p=0.068), VE/VO_2 slope: exercise: 42.7 ± 1.6 vs. 43.4 ± 1.7 (p=0.610) control: 43.8 ± 2.4 vs. 41.9 ± 2.5 (p=0.285)) (see figure 3.18).

Inter-group analyses confirmed that the improvement in peak VO_2 (mls/kg/min) (mean change exercise: 1.37 ± 0.5 vs. control: -0.01 ± 0.30 (p=0.022)) was significantly better in the exercise group. There was also a difference between the 2 groups in the change in peak VE/VO_2 (mean change exercise: 2.1 ± 1.2 vs. control: -1.5 ± 0.8 (p=0.016)). The inter-group analyses showed no difference between the 2 groups in peak VE/VCO_2 (mean change exercise: 0.3 ± 1.0 vs. control: -1.1 ± 0.8 (p=0.266)), VE/VCO_2 slope (mean change exercise: -0.7 ± 0.8 vs. control: -1.5 ± 1.2 (p=0.585)) and VE/VO_2 slope (mean change exercise: 0.6 ± 1.3 vs. control: -1.8 ± 1.7 (p=0.241).

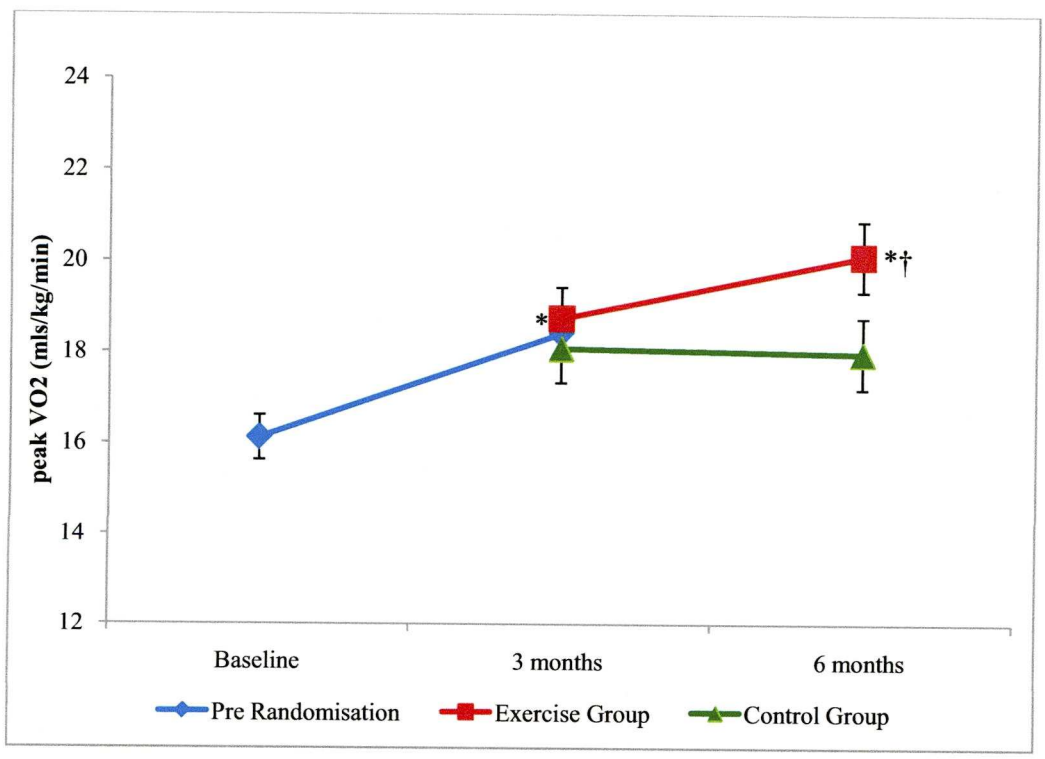

Figure 3.16: Peak VO_2

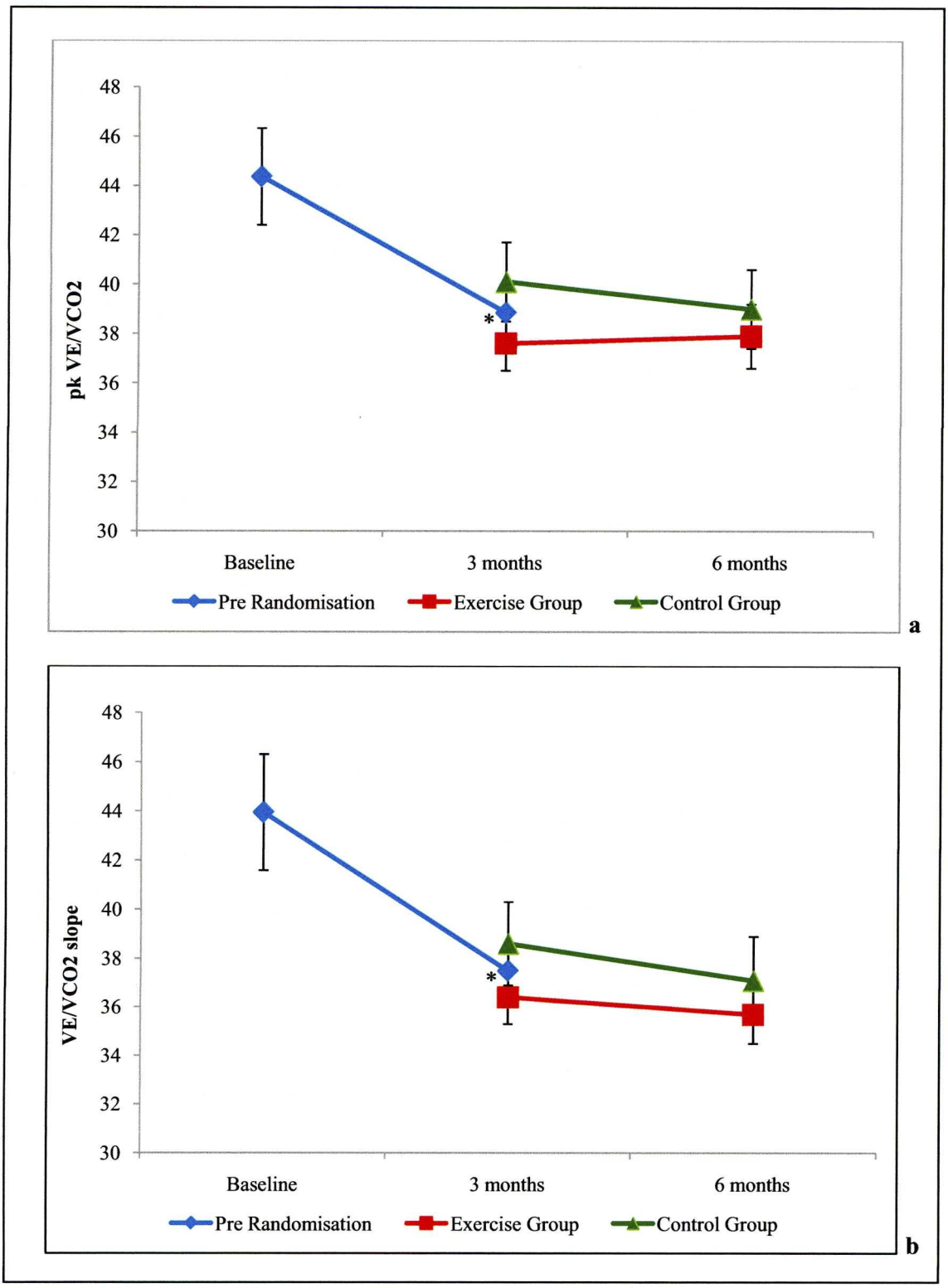

Figure 3.17: Ventilatory equivalents for carbon dioxide production; peak VE/VCO_2 (a), VE/VCO_2 slope (b)

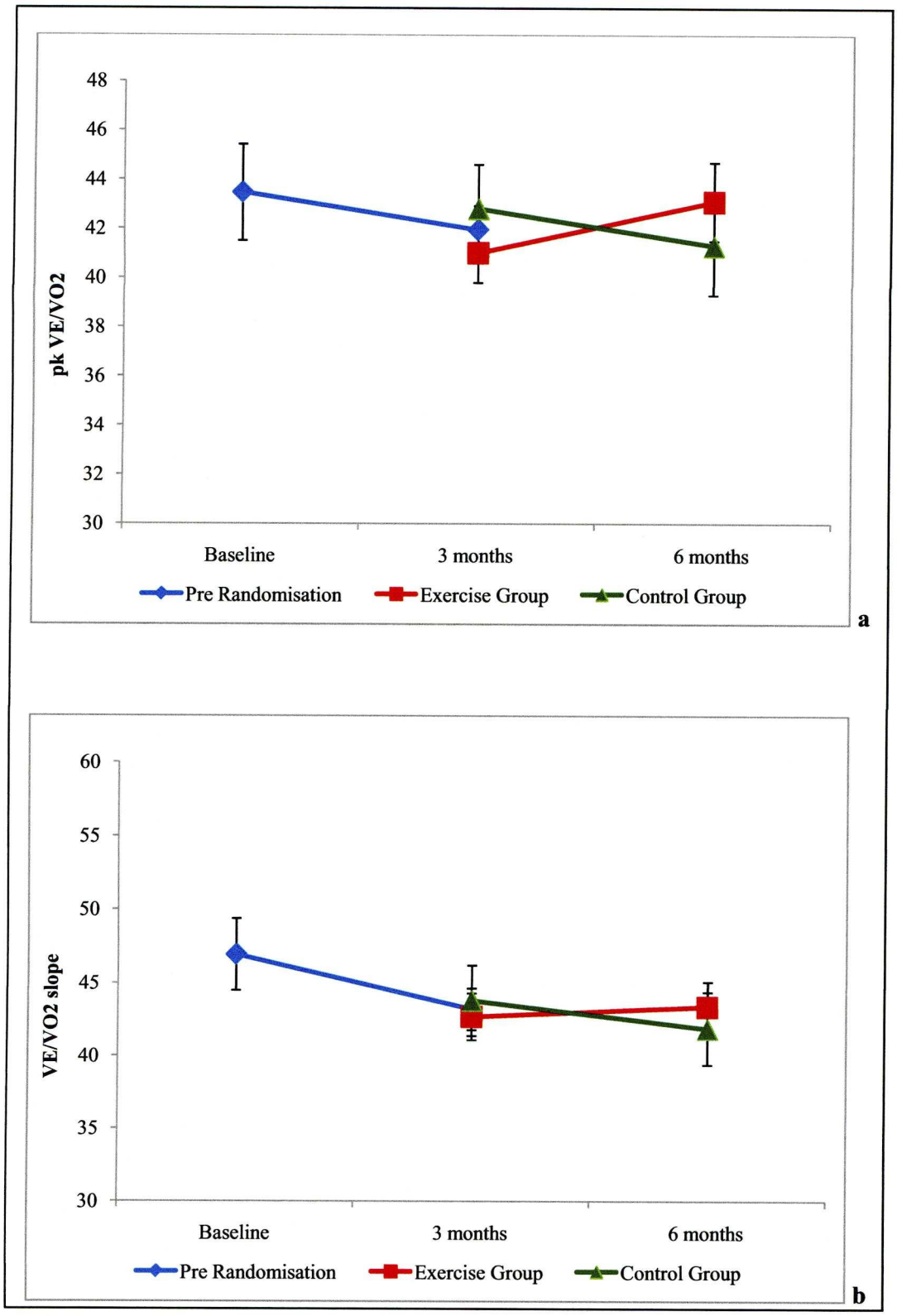

Figure 3.18: Ventilatory equivalents for oxygen production: peak VE/VO_2 (a), VE/VO_2 slope (b)

3.2.5.3 Peak cardiac output and cardiac reserve

The exercise group showed a further significant improvement in peak cardiac power output (w) (3.27 ± 0.16 vs. 3.76 ± 0.20 ($p<0.001$)) (see figure 3.19) and in cardiac reserve (w) (2.57 ± 0.14 vs. 3.05 ± 0.19 ($p<0.001$)) (see figure 3.20). This was not matched by the control group who showed no significant improvement in peak cardiac power output (w) (3.14 ± 0.15 vs. 3.20 ± 0.19 ($p=0.633$)) and in cardiac reserve (w) (2.51 ± 0.14 vs. 2.52 ± 0.18 ($p=0.968$)).

Inter-group analysis confirmed that the improvement in peak cardiac power output (w) (mean change exercise: 0.49 ± 0.12 vs. control: 0.06 ± 0.13 ($p=0.019$)) and cardiac reserve (w) (mean change exercise: 0.48 ± 0.11 vs. control: 0.01 ± 0.13 ($p=0.008$)).

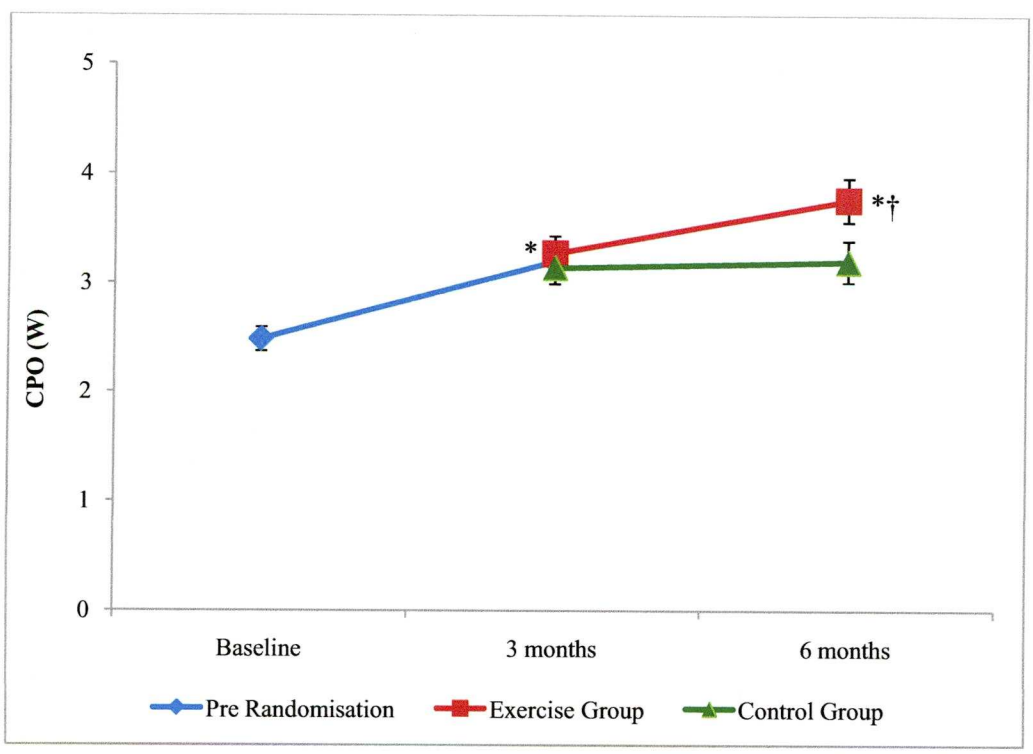

Figure 3.19: Peak cardiac power output

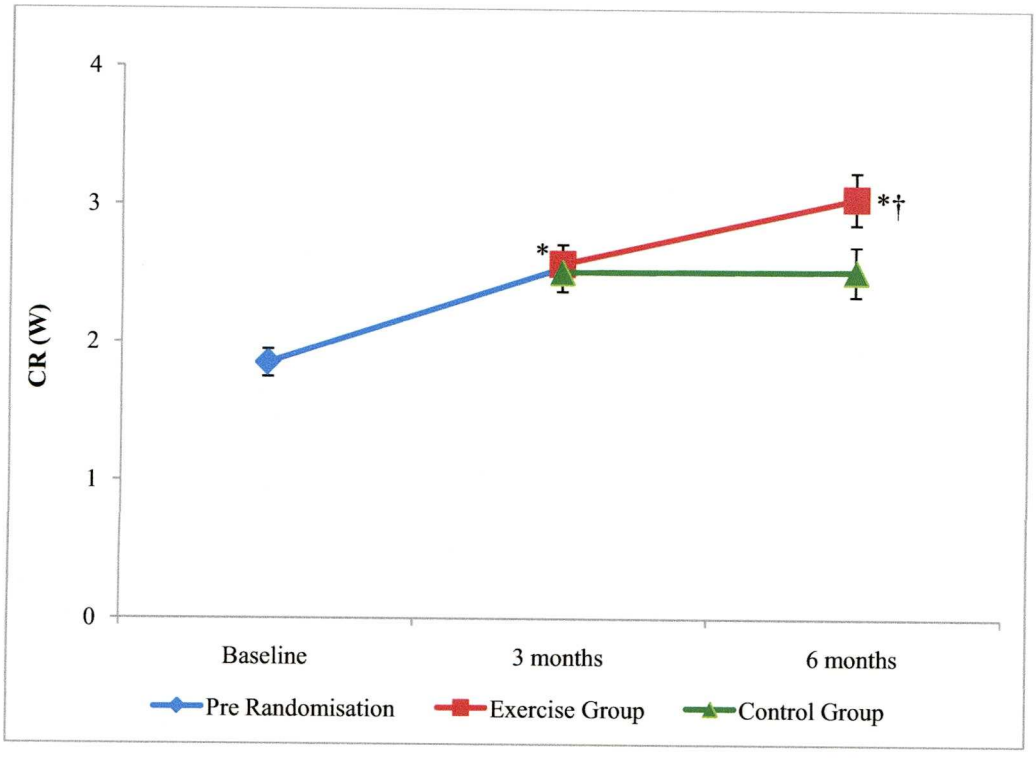

Figure 3.20: Cardiac Reserve

3.2.5.4 Peak respiratory exchange ratio and the percentage of peak VO_2 at the anaerobic threshold.

The maximum RER achievable was significantly increased in the exercise group (1.10 ± 0.02 vs. 1.14 ± 0.02 (p=0.001)) and there was a significant reduction in the percentage of peak VO_2 at the anaerobic threshold (%) (67.5 ± 1.7 vs. 62.1 ± 2.0 (p=0.010)) (see figure 3.21). The control group showed no significant change in the peak RER (1.07 ± 0.01 vs. 1.06 ± 0.02 (p=0.571)) and in the percentage of peak VO_2 at the anaerobic threshold (%) (70.8 ± 1.9 vs. 70.0 ± 2.3 (p=0.703)).

Inter-group analysis confirmed that the improvement in peak RER (mean change exercise: 0.04 ± 0.01 vs. control: -0.01 ± 0.01 (p=0.008)) was significantly greater in the exercise group. There was also a trend towards a difference between the two groups when assessing the change in the percentage of peak VO_2 at the anaerobic

threshold (%) but this did not reach significance (mean change exercise: -5.4 ± 1.9 vs. control: -0.8 ± 2.1 (p=0.109)).

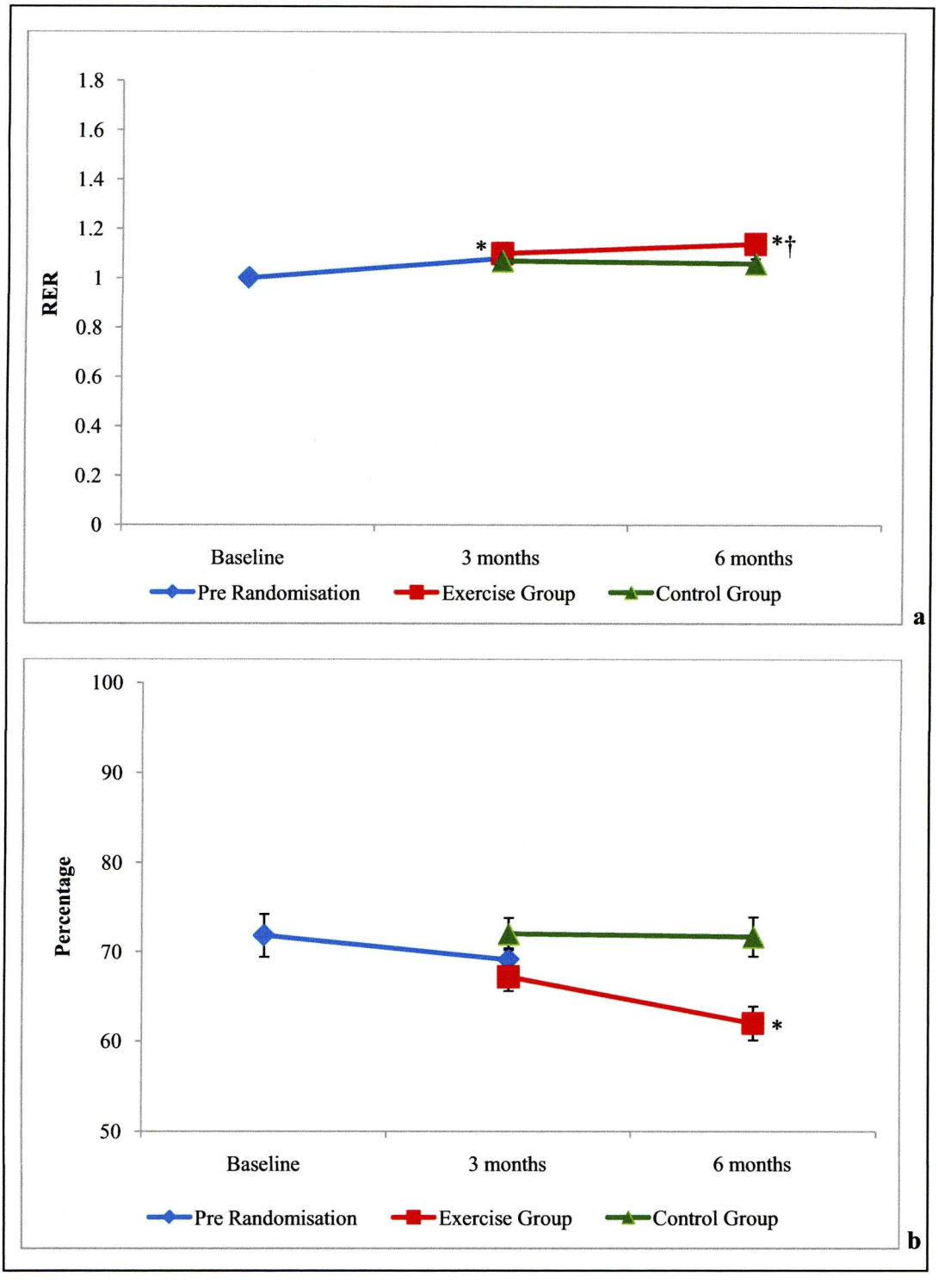

Figure 3.21: Peak respiratory exchange ratio (a) and the percentage of percentage of peak VO_2 at the anaerobic threshold (b)

3.2.5.5 Echocardiographic parameters

At 6 months the exercise group showed a trend towards an improvement in left ventricular end diastolic dimensions (cm) but this did not to reach statistical significance (6.64 ± 0.18 vs. 6.40 ± 0.11 (p=0.164)). The improvement in the control group did achieve significance (6.57 ± 0.11 vs. 6.34 ± 0.11 (p=0.006)). Conversely the ejection fraction (%) significantly improved in the exercise group (32.8 ± 1.2 vs. 37.4 ± 1.1 (p=0.010)) but not in the control group (32.6 ± 1.4 vs. 35.0 ± 1.4 (p=0.132)) (see figure 3.22).

Inter-group analyses of the changes showed no significant difference between the 2 groups in either left ventricular end diastolic dimensions (cm) (mean change exercise: -0.24 ± 0.17 vs. control: -0.23 ± 0.08 (p=0.963)) or ejection fraction (%) (mean change exercise: 4.5 ± 1.6 vs. control: 2.5 ± 1.6 (p=0.371)).

3.2.5.6 Peak skeletal muscle torque

After the period of exercise training the peak skeletal muscle torque during extension (N-M) was significantly improved in the exercise group (right: 135.0 ± 10.1 vs. 144.8 ± 11.5 (p=0.009)), left: 135.0 ± 10.1 vs. 143.6 ± 10.6 (p=0.004)) (see figure 3.23), during flexion there was an trend towards improvement but this did not reach significance (right: 73.7 ± 5.1 vs. 76.8 ± 5.6 (p=0.120), left: 72.5 ± 4.5 vs. 76.3 ± 5.4 (p=0.076)) (see figure 3.24). The control group showed a trend towards an improvement in the peak skeletal muscle torque during extension but this failed to reach significance (right: 127.7 ± 9.6 vs. 131.5 ± 9.9 (p=0.064), left: 119.4 ± 8.0 vs. 124.3 ± 8.2 (p=0.060)) and no significant change during flexion (right: 71.9 ± 4.9 vs. 71.0 ± 5.0 (p=0.680), left: 68.8 ± 4.5 vs. 71.2 ± 4.6 (p=0.334)).

Inter-group analyses showed no significant difference between the 2 groups in either extension (right: exercise: 9.8 ± 3.4 vs. control: 3.8 ± 2.0 (p=0.133)), left: exercise: 8.7 ± 2.8 vs. control: 5.0 ± 2.4 (p=0.309)) or flexion (right: exercise: 3.2 ± 2.0 vs. control: -0.9 ± 2.1 (p=0.168)), left: exercise: 3.9 ± 2.1 vs. control: 2.3 ± 2.4 (p=0.635)).

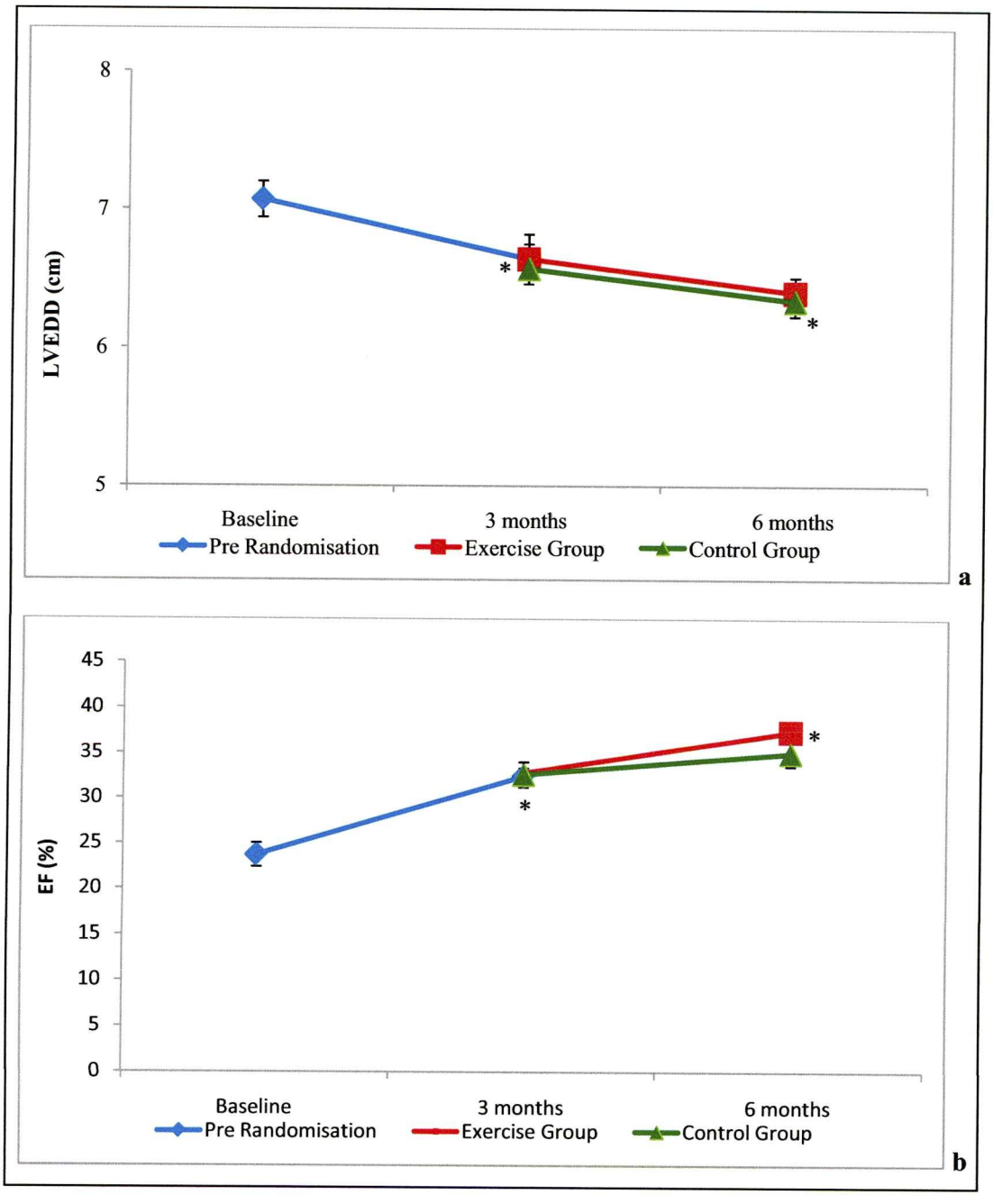

Figure 3.22: Left ventricular end diastolic dimensions (a) and ejection fraction (b)

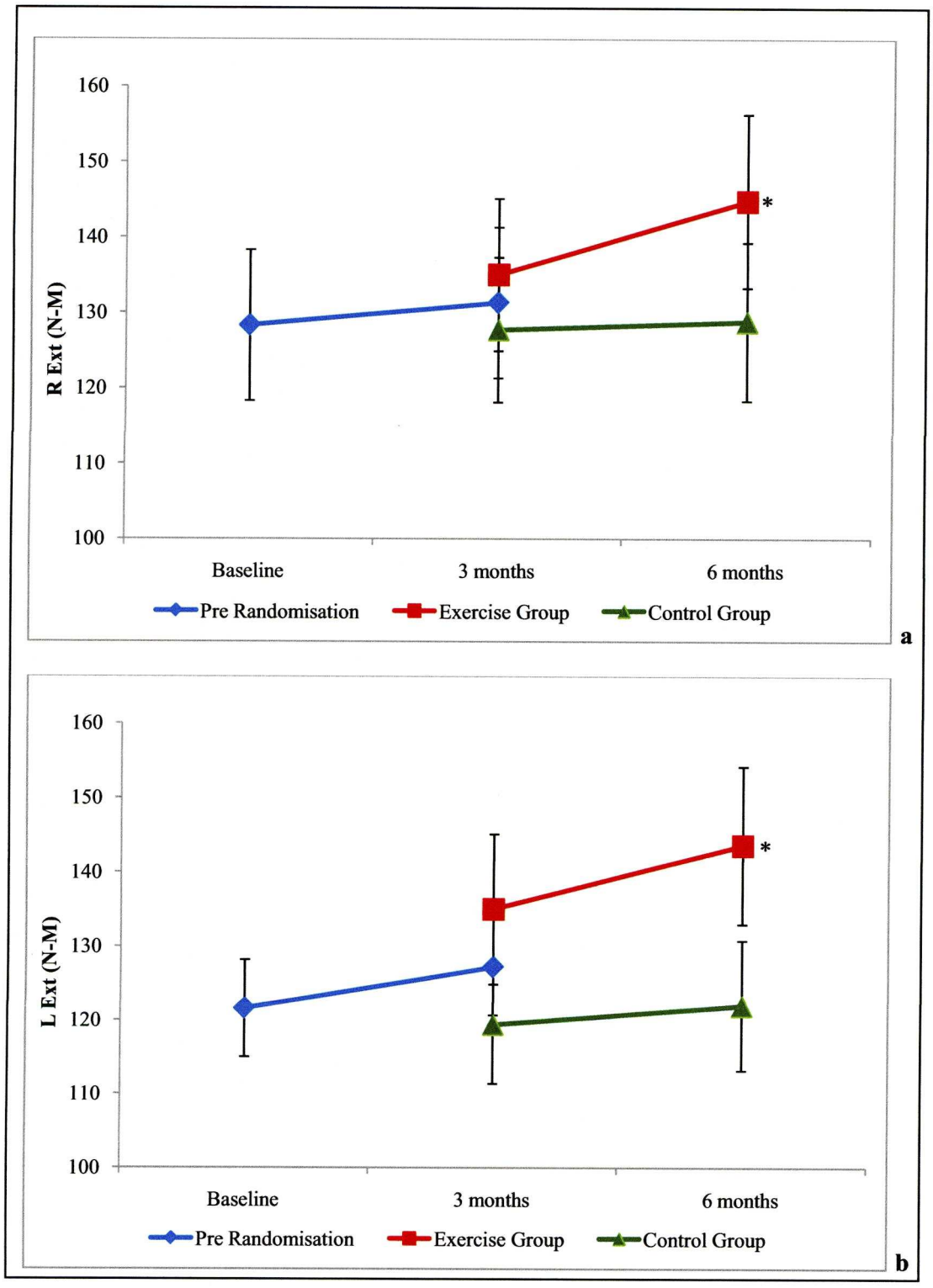

Figure 3.23: Peak skeletal muscle torque during extension on the right (a) and left (b) side.

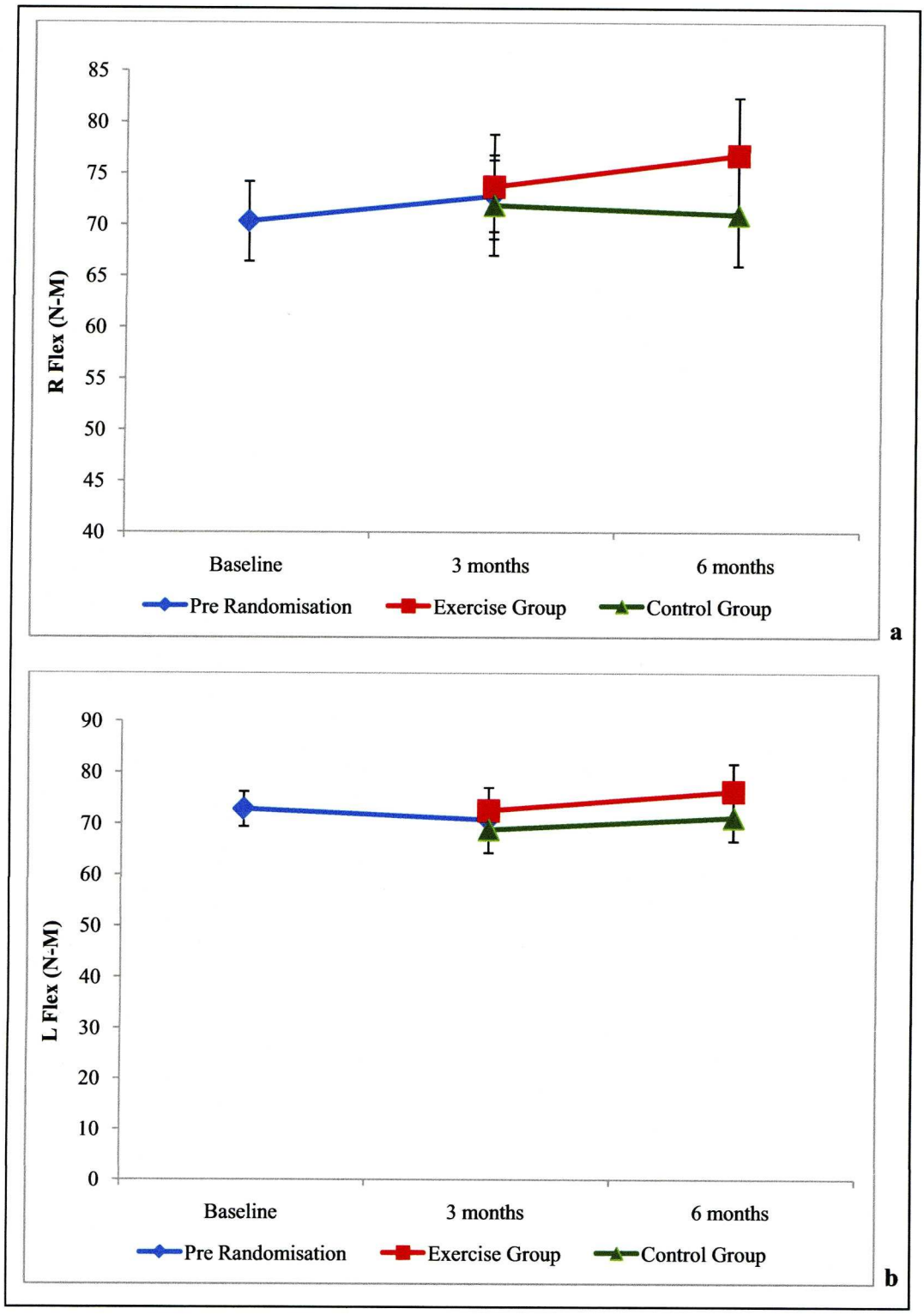

Figure 3.24: Peak skeletal muscle torque during flexion on the right (a) and left (b) side.

Table 3.9: Results from 3 to 6 months

	Exercise Group			Control Group		
	3 months	6 months	Δ change	3 months	6 months	Δ change
NYHA class	2	1 *	1 †	2	2	0
MLWHF	34.6 ± 4.5	26.2 ± 4.1 *	-8.4 ± 3.1†	29.0 ± 3.3	29.5 ± 3.6	1.6 ± 3.1
Exercise Duration (seconds)	581 ± 45	752 ± 36 *	171 ± 35†	542 ± 43	572 ± 44 *	30 ± 13
Peak VO_2 (mls/kg/min)	18.74 ± 0.68	20.10 ± 0.77*	1.37 ± 0.5†	18.08 ± 0.75	18.07 ± 0.78	-0.01 ± 0.30
RER	1.10 ± 0.02	1.14 ± 0.02 *	0.04 ± 0.01†	1.07 ± 0.01	1.06 ± 0.02	-0.01 ± 0.01
Percentage of peak VO_2 at the AT (%)	67.5 ± 1.7	62.1 ± 2.0 *	-5.4 ± 1.9	70.8 ± 1.9	70.0 ± 2.3	-0.8 ± 2.1
Peak CPO (W)	3.27 ± 0.16	3.76 ± 0.20 *	0.49 ± 0.12 †	3.14 ± 0.15	3.20 ± 0.19	0.06 ± 0.13
CR (W)	2.57 ± 0.14	3.05 ± 0.19 *	0.48 ± 0.11 †	2.51 ± 0.14	2.52 ± 0.18	0.01 ± 0.13
LVEDD (cm)	6.64 ± 0.18	6.40 ± 0.11	-0.24 ± 0.17	6.57 ± 0.11	6.34 ± 0.11 *	-0.23 ± 0.08
EF %)	32.8 ± 1.2	37.4 ± 1.1 *	4.5 ± 1.6	32.6 ± 1.4	35.0 ± 1.4	2.5 ± 1.6
Right Extension (N-M)	135.0 ± 10.1	144.8 ± 11.5*	9.8 ± 3.4	127.7 ± 9.6	131.5 ± 9.9	3.8 ± 2.0
Left Extension (N-M)	135.0 ± 10.1	143.6 ± 10.6*	8.7 ± 2.8	119.4 ± 8.0	124.3 ± 8.2	5.0 ± 2.4
Right Flexion (N-M)	73.7 ± 5.1	76.8 ± 5.6	3.2 ± 2.0	71.9 ± 4.9	71.0 ± 5.0	-0.9 ± 2.1
Left Flexion	72.5 ± 4.5	76.3 ± 5.4	3.9 ± 2.1	68.8 ± 4.5	71.2 ± 4.6	2.3 ± 2.4
Peak VE/VCO_2	37.6 ± 1.1	37.9 ± 1.3	0.3 ± 1.0	40.1 ± 1.6	39.0 ± 1.6	-1.1 ± 0.8
Peak VE/VO_2	41.0 ± 1.2	43.1 ± 1.6	2.1 ± 1.2	42.8 ± 1.8	41.3 ± 2.0	-1.5 ± 0.8
VE/VCO_2 slope	36.4 ± 1.1	35.7± 1.2	-0.7 ± 0.8	38.6 ± 1.7	37.1 ± 1.8	-1.5 ± 1.2
VE/VO_2 slope	42.7 ± 1.6	43.4 ± 1.7	0.6 ± 1.3	43.8 ± 2.4	41.9 ± 2.5	-1.8 ± 1.7

All values expressed as mean ± SEM.

* $p<0.05$ compared to 3 months, † $p<0.05$ compared to control group Δ change

3.2.6 Percentage change at 6 months

Full results for the percentage change between baseline and 6 months are shown in table 3.10 and figure 3.25.

3.2.6.1 Functional measures and exercise duration

The exercise group showed a 66.7% improvement in NYHA class and a 57.9% reduction in Minnesota living with heart failure scores. The improvement in the control group was 33.3% in NYHA class and 52.6% in Minnesota living with heart failure scores. There was a 101.3% improvement in exercise duration in the exercise group whilst the control group had a 53.0% improvement.

3.2.6.2 Peak VO_2 and the ventilatory equivalents for oxygen and carbon dioxide

There was a 24.7% improvement in peak VO_2 in the exercise group, the control group showed a 12.1% improvement. The exercise group showed a 14.6% reduction in the peak VE/VCO_2 and an 18.8% reduction in the VE/VCO_2 slope. The control group showed a 12.1% reduction in the peak VE/VCO_2 and a 15.6% reduction in the VE/VCO_2 slope.

There was a 0.8% overall reduction in the peak VE/VO_2 and a 7.5% reduction in the VE/VO_2 slope in the exercise group. The control group showed a 5.0% reduction in the peak VE/VO_2 and a 10.7% reduction in the VE/VO_2 slope.

3.2.6.3 Peak Cardiac output and Cardiac Reserve

The exercise group showed a 51.7% improvement in peak cardiac power output with a 64.8% improvement in cardiac reserve. The control group showed a 28.9%

improvement in peak cardiac power output and a 36% improvement in cardiac reserve.

3.2.6.4 Peak RER and percentage of peak VO_2 at the anaerobic threshold

The peak respiratory exhange ratio showed a 14.5% increase in the exercise group and a 6.6% increase in the control group. The exercise group showed a 13.4% reduction in the the percentange of peak VO_2 at the anaerobic threshold. The control group showed a 2.5% reduction at 6 months

3.2.6.5 Echocardiographic parameters

There was a 9.4% reduction in the left ventricular end diastolic dimensions in the exercise group, whilst the control group showed a 10.2% reduction. This was coupled with an increase in the ejection fraction of 57.8% in the exercise group and 48.1% increase in the control group.

3.2.6.6 Peak skeletal muscle torque

The exercise group showed a 12.8% increase in right sided extension and a 15.8% increase in left sided extension. The control group showed a 2.4% increase in right sided extension and 0.2% increase in left sided extension.

The exercise group showed a 9.2% increase in right sided flexion and a 4.8% increase in left sided flexion. The control group showed a 1.0% increase in right sided flexion and a 2.2% reduction in left sided flexion.

Table 3.10: Percentage change at 6 months

	Exercise group	Control group
NYHA class	66.7	33.3
MLWHF	57.9	52.6
Exercise Duration	101.3	53.0
Peak VO_2	24.7	12.1
Peak VE/VCO_2	14.6	12.1
VE/VCO_2 slope	18.8	15.6
Peak VE/VO_2	0.8	5.0
VE/VO_2 slope	7.5	10.7
Peak RER	14.5	6.6
Percentage of peak VO_2 at the anaerobic threshold	13.4	2.5
Peak cardiac power output	51.7	28.9
Cardiac Reserve	64.8	36.0
Left ventricular end diastolic dimensions	9.4	10.2
Ejection Fraction	57.8	48.1
Right Extension	12.8	2.4
Left Extension	15.8	0.2
Right Flexion	9.2	1.0
Left Flexion	4.8	2.2

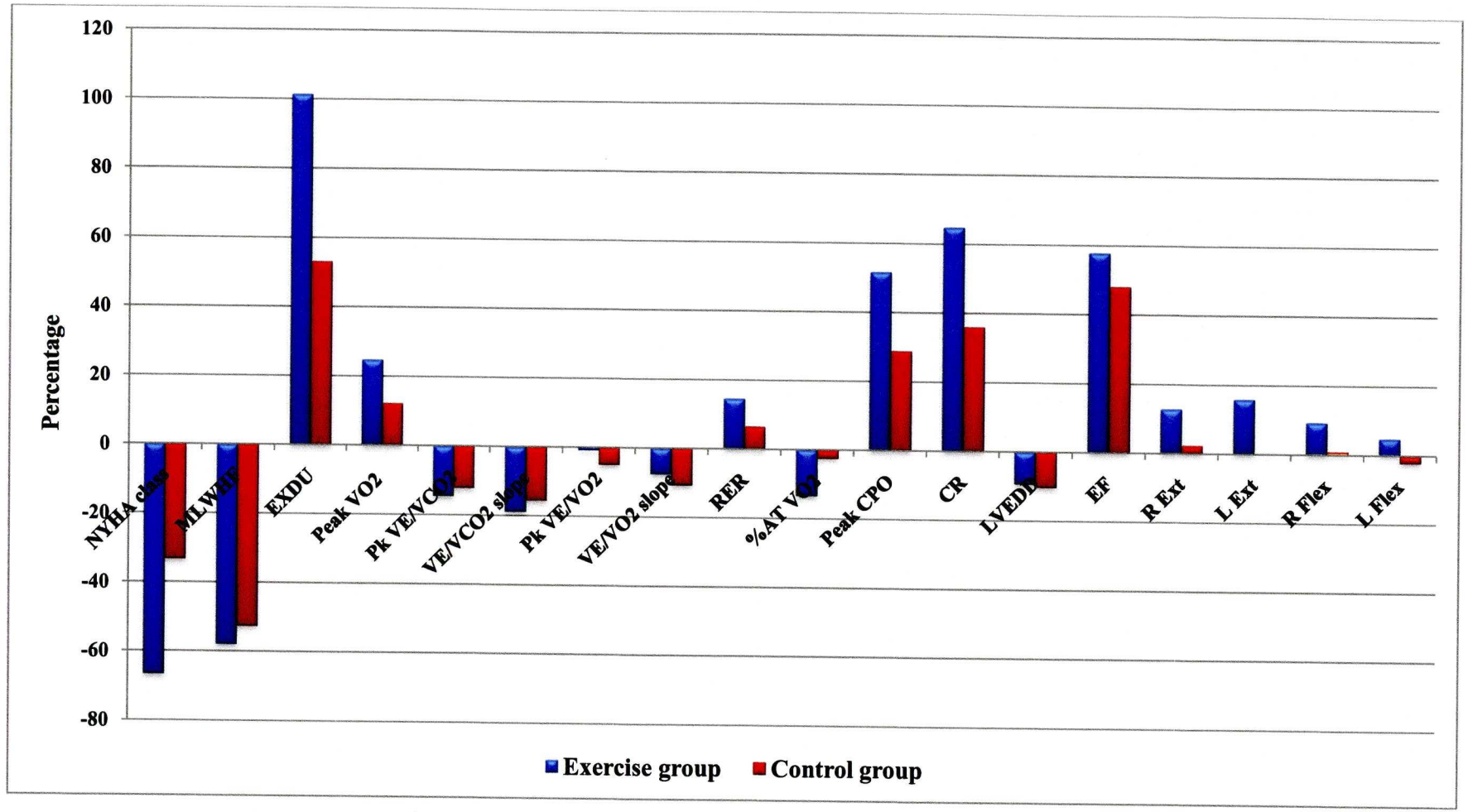

Figure 3.25: Percentage change at 6 months

3.2.7 Effect of exercise training in non responders

At 3 months post cardiac resynchronisation therapy there were 17 non responders (34%). After randomisation 9 of the non responders were randomised to the exercise group and 8 were randomised to the control group. At the 6 month test in the exercise group 6 (67%) of the 9 non responders at 3 months were now classified as responders. In the control group 2 (25%) of the 8 non responders at 3 months were now classified as responders. This difference was highly statistically significant (p=0.002).

3.3 Study III. The effectiveness of left ventricular lead placement via a mini thoracotomy to achieve cardiac resynchronisation therapy in patients with previously failed transvenous placement.

3.3.1 Baseline Data

Baseline characteristics for both groups are shown in Table 3.11. There was no significant difference in the mean age (mini thoracotomy: 66.4 ± 2.0 (range: 47-80 years) vs. transvenous: 64.5 ± 1.8 (range: 38-80 years) (p=0.48)) and gender distribution (mini thoracotomy: 86% male vs. transvenous: 78% male (p=0.053)) between the two groups at baseline. The mean and mode NYHA class was 3 in both groups and there was evidence of a similar cardiomypoathy in both groups with a dilated left ventricular end diastolic dimension (mini thoracotomy: 7.14 ± 0.94 vs. transvenous: 6.79±0.67 (p=0.14)) and an severely impaired ejection fraction (mini thoracotomy: 23.1 ± 7.8 vs. transvenous: 27.4 ± 8.1 (p=0.061)).

In the mini thoracotomy group 71% of the patients were in sinus rhythm at baseline whilst in the transevenous group 74% were in sinus rhythm (p=0.58). The cause of the dilated cardiomypathy was predominantly ischaemic in both groups (mini thoracotomy: 71% vs. transvenous: 74% (p=0.47)). Patients were well medicated in both groups with similar levels of usage of ACE inhibitors (mini thoracotomy: 100% vs. transvenous: 100% (p=1.0)), Beta blockers (mini thoracotomy: 57% vs. transvenous: 65% (p=0.093)), Digoxin (mini thoracotomy: 52% vs. transvenous: 44% (p=0.11)), Spironolactone (mini thoracotomy: 59% vs. transvenous: 59% (p=1.0)) and loop diuretics (mini thoracotomy: 94% vs. transvenous: 94% (p=1.0)).

Table 3.11: Baseline characteristics of the study population

	Mini thoracotomy Group (n-23)	Transvenous Group (n=35)	p value
Age (years)	66 .4 ± 2.0	64.5 ± 1.8	p=0.48
Sex (% male)	78	86	p=0.053
NYHA class	3	3	p=0.54
Peak VO_2 (mls/kg/min)	16.06 ± 0.79	15.59 ± 0.62	p=0.87
Ischaemic Aetiology of Cardiac Failure (%)	73.9	71.4	p=0.47
QRS width (ms)	159 ± 18	161 ± 21	p=0.74
Left Ventricular End Diastolic Diameter (cm)	6.79 ± 0.15	7.14 ± 0.17	p=0.14
Ejection Fraction (%)	27.4 ± 1.9	23.1 ± 1.3	p=0.061
Sinus Rhythm (%)	73.9	71.4	p=0.58
Atrial Fibrillation (%)	26.1	28.6	p=0.58
ACE Inhibitors or ARBs (%)	100	100	p=1.0
B-Blockers (%)	65	57	p=0.093
Digoxin (%)	44	52	p=0.11
Spironolactone (%)	59	59	p=1.0
Loop Diuretic (%)	94	94	p=1.0

All values expressed as mean ± SEM

3.3.2 Baseline cardiopulmonary data

The baseline cardiopulmonary haemodynamic data are shown in table 3.12. There was no significant difference between the two groups in any baseline cardiopulmonary measure. The mini thoracotomy group resting heart rate was 74 ± 3/min and increased to 119 ± 6/min at peak exercise. This was a coupled with a increase in mean arterial pressure from 87.5 ± 2.4 mmHg to 104.2 ± 2.3 mmHg. The transvenous group showed a simliar increase in heart rate from a resting value of 80± 3 to 116 ± 4 at peak exercise. This was again coupled to a increase in mean arterial pressure from 89.6 ± 1.8 to 105.4 ± 1.8.

Total exercise duration was similar in both groups (mini thoracotomy: 344 ± 42 vs. transvenous: 357 ± 33 seconds (p=0.797)) and patients did acheive a true maximal cardiopulmonary exercise test manifiest by a peak RER greater than 1 (mini thoracotomy: 1.02 ± 0.02 vs. transvenous: 1.01± 0.02 (p=0.703)). The subjects in both groups were significantly impaired in their cardiopulmonary exercise capacity with a reduced peak VO_2 (mini thoracotomy: 16.06 ± 0.79 vs. transvenous: 15.59 ± 0.62 mls/kg/min (p=0.638)). Both the groups showed a similar resting cardiac power output (mini thoracotomy: 0.61 ± 0.04 vs. transvenous: 0.64 ± 0.03 (p=0.521)) which increased at peak exercise (mini thoracotomy: 2.42 ± 0.19 vs. transvenous: 2.46 ± 0.13 p=0.852). Therefore the cardiac reserve for both groups was similar at baseline (mini thoracotomy: 1.80 ± 0.17 vs. transvenous: 1.81 ± 0.11 (p=0.969)).

Table 3.12: Baseline cardiopulmonary data

	Mini thoracotomy Group	Transvenous Group	p value
Resting HR (min^{-1})	74± 3	80± 3	p=0.181
Resting MBP (mm Hg)	87.5 ± 2.4	89.6 ± 1.8	p=0.478
Resting SBP (mmHg)	151.7 ± 4.1	153.2 ± 3.3	p=0.420
Resting VO_2 (mls/kg/min)	5.36 ± 0.37	5.43 ± 0.21	p=0.867
Resting CO (L/min)	3.20 ± 0.22	3.26 ± 0.14	p=0.806
Resting CPO (watts)	0.61 ± 0.04	0.64 ± 0.03	p=0.521
Resting VE (L/min)	14.5 ± 1.0	15.1 ± 0.8	p=0.683
Exercise duration (secs)	344 ± 42	357 ± 33	p=0.797
AT (mls/kg/min)	11.04 ± 0.82	11.22 ± 0.83	p=0.911
AT % peak VO_2 (%)	71.1 ± 4.4	70.6 ± 2.9	p=0.914
Peak RER	1.02 ± 0.02	1.01± 0.02	p=0.703
Peak HR (min^{-1})	119 ± 6	116 ± 4	p=0.734
Peak MBP (mm Hg)	104.2 ± 2.3	105.4 ± 1.8	p=0.673
Peak SBP (mm Hg)	151.7 ± 4.1	152.9 ± 3.4	p=0.773
Peak VO_2 (mls/kg/min)	16.06 ± 0.79	15.59 ± 0.62	p=0.638
Peak CO (L/min)	10.34 ± 0.72	10.40 ± 0.44	p=0.940
Peak CPO (watts)	2.42 ± 0.19	2.46 ± 0.13	p=0.852
Cardiac reserve (watts)	1.80 ± 0.17	1.81 ± 0.11	p=0.969
Peak VE (L/min)	54.6 ± 3.1	52.1 ± 2.5	p=0.542
Peak VE/VCO_2	45.37 ± 3.57	44.05 ± 1.72	p=0.713
Peak VE/VO_2	43.34 ± 2.84	44.25 ± 1.91	p=0.784
$VE/VCO_{2\ slope}$	45.77 ± 4.53	43.28 ± 1.80	p=0.563
$VE/VO_{2\ slope}$	48.70 ± 4.50	47.20 ± 2.30	p=0.746

All values expressed as mean ± SEM.

3.3.3 Post CRT exercise and haemodynamic measures

Full results from baseline to 6 months post cardiac resynchronisation therapy are shown in table 3.13

3.3.3.1 Functional measures and exercise duration

NYHA class was improved in both groups at 3 months (transvenous: 3 vs. 2 χ^2 $p<0.001$, mini thoracotomy: 3 vs. 2 χ^2 $p<0.001$). Between 3 and 6 months NYHA stayed at 2 in both groups, although there was a further significant improvement using the χ^2 test (transvenous: $p=0.003$, mini thoracotomy: $p<0.001$). Inter-group analysis of the change at 6 months showed no difference (transvenous: 1, mini thoracotomy: 1 $p=0.548$) (see figure 3.26).

Both groups showed an improvement in exercise duration (seconds) at 3 months (transvenous: 357 ± 33 vs. 571 ± 41 $p<0.001$, mini thoracotomy: 344 ± 41 vs. 439 ± 49 $p=0.007$). A further improvement occurred in both groups between 3 and 6 months (transvenous: 571 ± 41 vs. 666 ± 41 $p=0.014$, mini thoracotomy: 439 ± 49 vs. 576 ± 51 $p=0.001$). Inter-group analysis of the change at 6 months showed no difference (transvenous: 288 ± 35, mini thoracotomy: 218 ± 45 $p=0.215$) (see figure 3.27).

Minnesota living with heart failure (MLWHF) scores improved at 3 months in both groups (transvenous: 60.3 ± 3.0 vs. 29.7 ± 3.1 $p<0.001$, mini thoracotomy: 61.0 ± 3.7 vs. 36.8 ± 4.5 $p=0.001$). No further improvements were seen between 3 and 6 months in either group (transvenous: 29.7 ± 3.1 vs. 25.7 ± 3.2, mini thoracotomy: 36.8 ± 4.5 vs. 33.5 ± 4.5 $p=0.83$ $p=0.16$). Inter-group analysis of the change at 6

months showed no difference (transvenous:-34.8 ± 3.4, mini thoracotomy: -28.0 ± 5.2 p=0.252) (see figure 3.28).

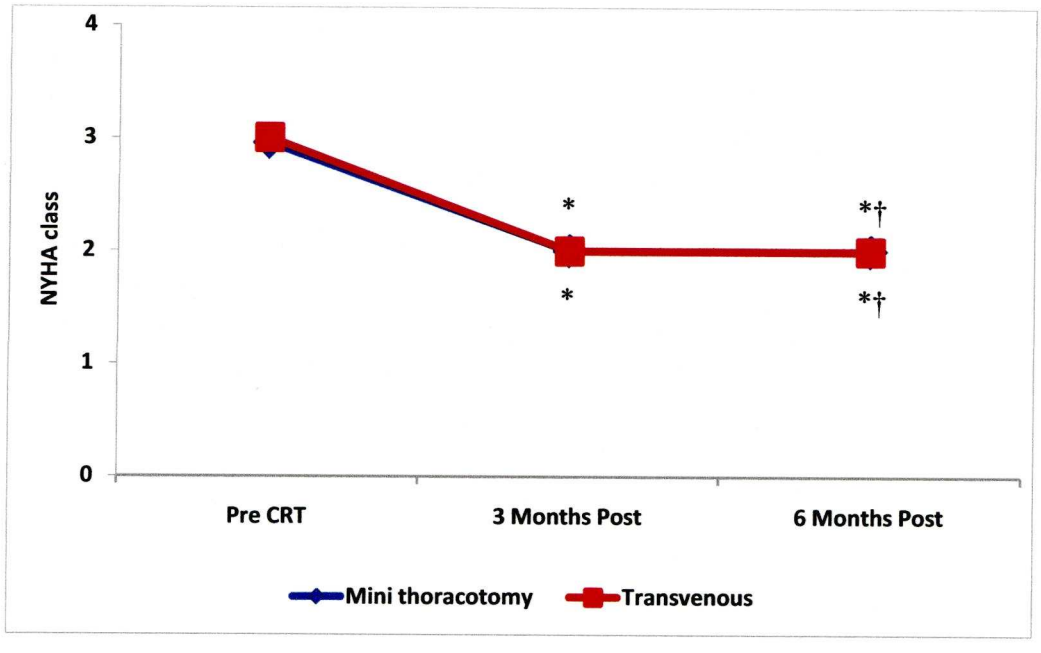

Figure 3.26: NYHA class

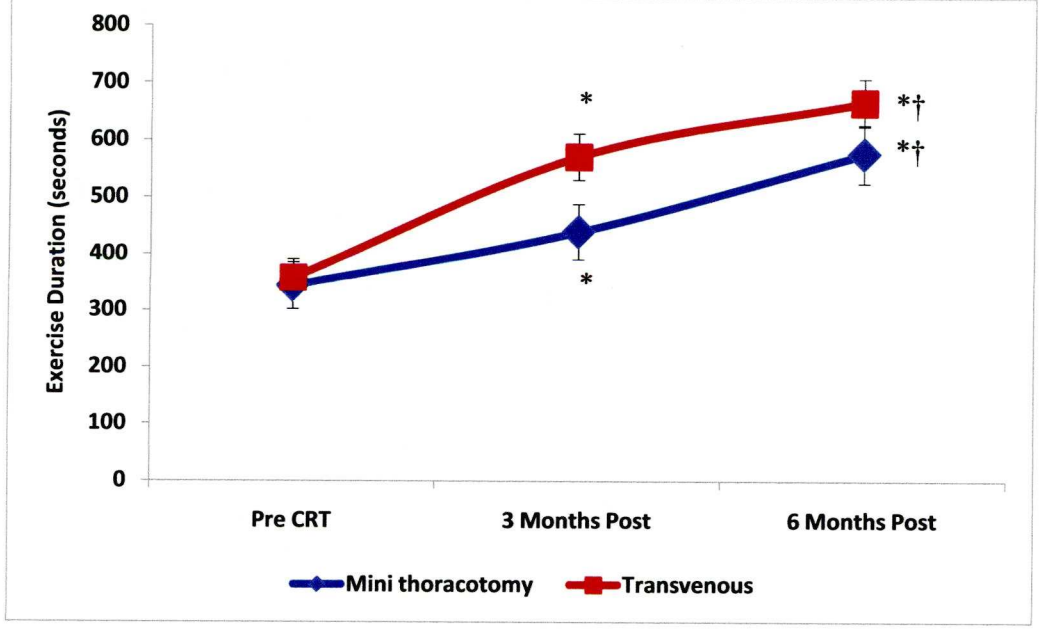

Figure 3.27: Exercise duration

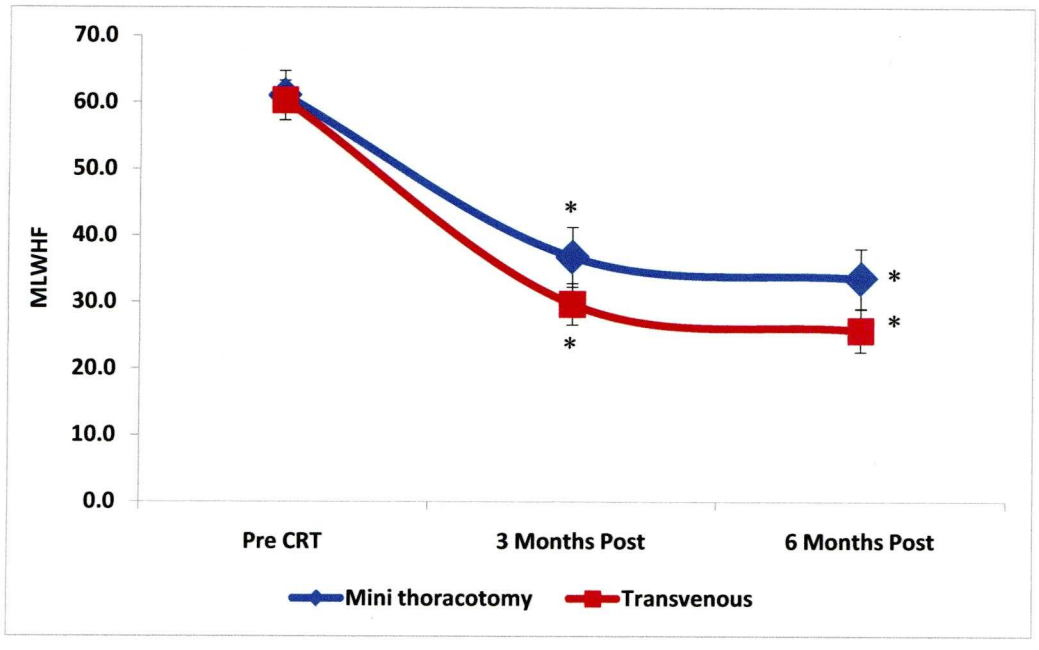

Figure 3.28: Minnesota living with heart failure

3.3.3.2 Peak VO_2 and peak respiratory exchange ratio

Both groups showed a significant improvement in peak VO_2 (mls/min/kg) at 3 months. The improvement seen in the mini thoracotomy group was of a smaller magnitude than that of the transvenous group at this stage (transvenous: 15.59 ± 0.62 vs. 18.42 ± 0.62 $p<0.001$, mini thoracotomy: 15.43 ± 0.79 vs. 16.91 ± 0.91 $p=0.015$). Between 3 and 6 months peak VO_2 was maintained in the transvenous group without further significant improvement (18.42 ± 0.62 vs. 18.98 ± 0.63 $p=1.0$). Whereas the mini thoracotomy group demonstrated a further significant improvement (16.91 ± 0.91 vs. 18.30 ± 1.05 $p=0.021$) to achieve a comparable overall level of peak VO_2 to the transvenous group at 6 months (see figure 3.29). Inter-group analysis of the change at 6 months showed no difference (transvenous: 3.04 ± 0.53, mini thoracotomy: 2.33 ± 0.73 $p=0.423$).

There were also significant improvements in the maximum respiratory exchange ratios (RER) achievable in the transvenous group at 3 months (1.01 ± 0.01 vs. 1.07 ± 0.01 p=0.045). No further change in RER occurred at the 6 months stage (1.07 ± 0.01 vs. 1.09 ± 0.02 p=0.569). In the mini thoracotomy group there was no significant improvement in the RER at 3 months (1.02 ± 0.02 vs. 1.07 ± 0.02 p=0.11) and between 3 and 6 months (1.07 ± 0.02 vs. 1.10 ± 0.02 p=0.34). However the overall improvement between baseline and 6 months was significant (1.02 ± 0.02 vs. 1.02 ± 0.10 p=0.020). Therefore inter-group analysis of the change at 6 months showed no difference (transvenous: 0.07 ± 0.02, mini thoracotomy: 0.08 ± 0.0 p=0.809) (see figure 3.30).

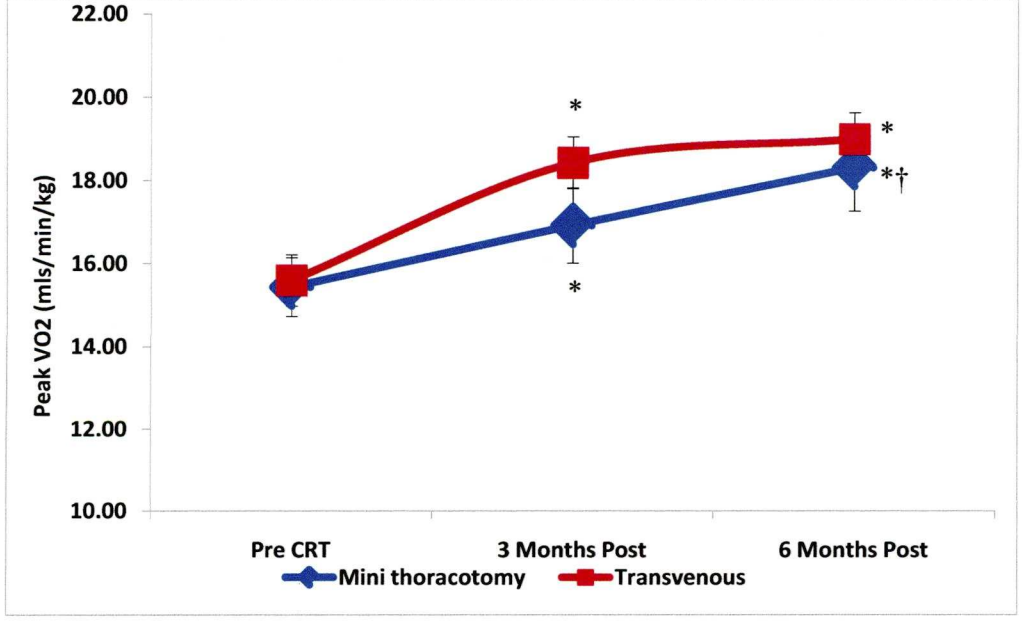

Figure 3.29: Peak VO_2

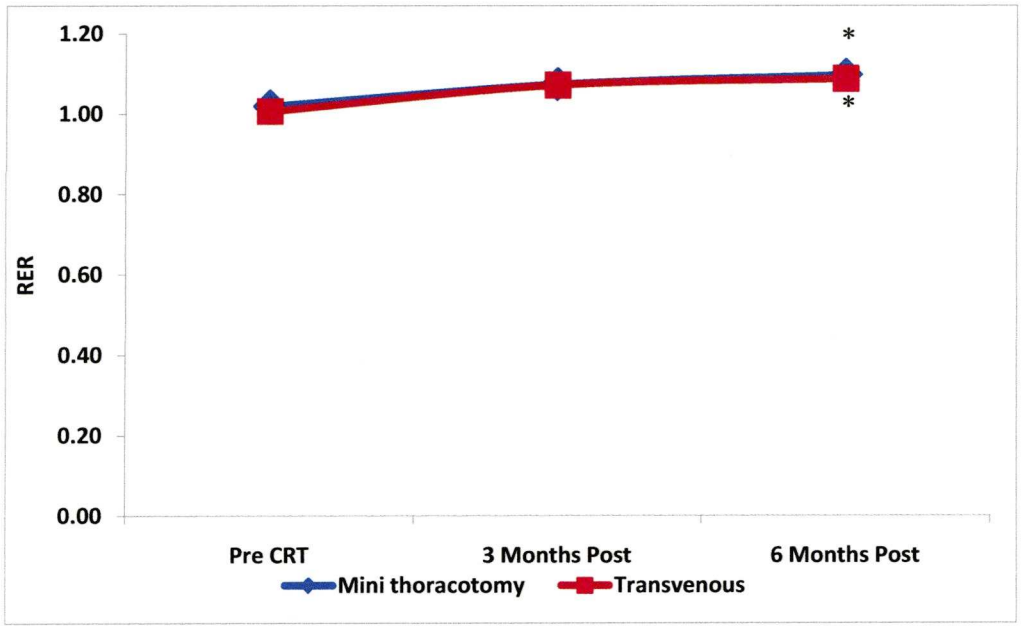

Figure 3.30: Peak RER

3.3.3.3 Peak cardiac power output and cardiac reserve

Haemodynamic assessment showed significant improvements at 3 months (peak CPO (watts) (transvenous: 2.46 ± 0.13 vs. 3.14 ± 0.15 $p<0.001$, mini thoracotomy: 2.42 ± 0.19 vs. 3.06 ± 0.18 $p<0.001$) and cardiac reserve (CR) (watts) (transvenous: 1.81 ± 0.11 vs. 2.49 ± 0.13 $p<0.001$, mini thoracotomy: 1.80 ± 0.17 vs. 2.41 ± 0.16 $p<0.001$)). Between the 3 and 6 months stage peak CPO and cardiac reserve showed further significant improvements in the transvenous group (peak CPO: 3.14 ± 0.15 vs. 3.39 ± 0.16 $p=0.007$, CR: 2.49 ± 0.13 vs. 2.75 ± 0.15 $p=0.005$) but not in the mini thoracotomy group (peak CPO: 3.06 ± 0.18 vs. 3.36 ± 0.28 $p=0.55$, CR: 2.41 ± 0.16 vs. 2.60 ± 0.25 $p=1.0$). Inter-group analysis of the change at 6 months showed no difference in peak CPO (transvenous: 0.90 ± 0.12, mini thoracotomy: 0.90 ± 0.19 $p=0.972$) and cardiac reserve (transvenous: 0.90 ± 0.11, mini thoracotomy: 0.76 ± 0.20 $p=0.503$) (see figure 3.31).

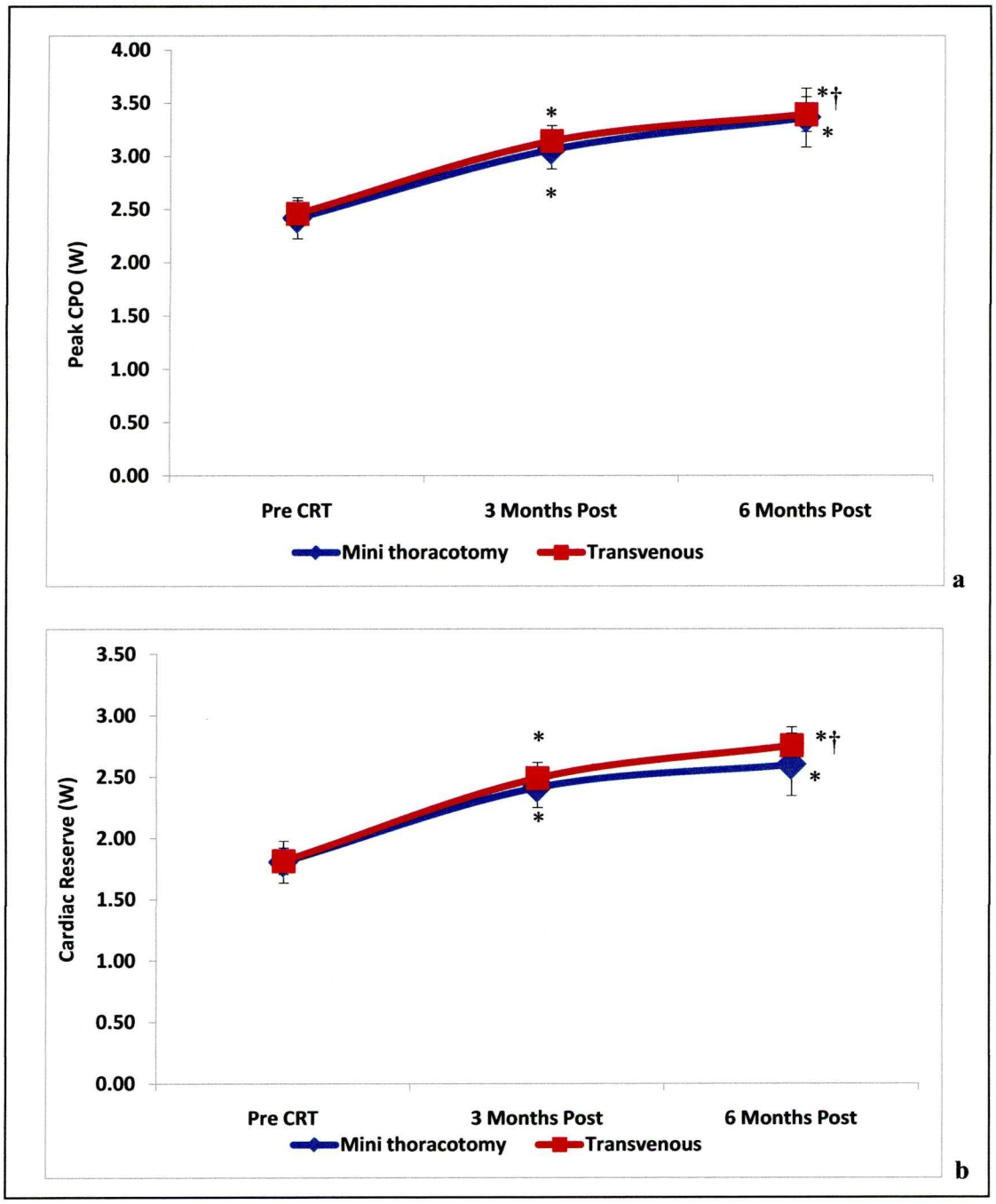

Figure 3.31: Peak cardiac power output (a) and cardiac reserve (b).

3.3.3.4 Echocardiographic parameters

At 3 months both groups showed a significant improvement in ejection fraction (%) (transvenous: 23.1 ± 1.3 vs. 32.3 ± 1.0 $p<0.001$, mini thoracotomy: 27.4 ± 1.9 vs. 34.5 ± 1.5 $p=0.006$). There were no further significant improvements at 6 months (transvenous: 32.3 ± 1.0 vs. 36.1 ± 1.2 $p=0.061$, mini thoracotomy: 34.5 ± 1.5 vs. 36.9 ± 1.3 $p=0.66$).

At 3 months the left ventricular end diastolic dimension (LVEDD) (cm) was significantly improved in the mini thoracotomy group (6.79 ± 0.15 vs. 6.38 ± 0.14 $p=0.003$) and a trend towards improvement in the transvenous group was seen (7.14 ± 0.17 vs. 6.72 ± 0.14 $p=0.09$). Between 3 and 6 months the transvenous group had a further trend towards improvement in LVEDD (6.72 ± 0.14 vs. 6.40 ± 0.09 $p=0.08$), and demonstrated a significant overall improvement at 6 months (pre: 7.14 ± 0.17 vs. 6 months: 6.40 ± 0.09 $p<0.001$). The mini thoracotomy group showed no further improvement in LVEDD between 3 and 6 months (6.38 ± 0.14 vs. 6.29 ± 0.13 $p=1.0$). Inter-group analysis of the change at 6 months showed no difference in ejection fraction (transvenous: 12.4 ± 1.5, mini thoracotomy: 8.4 ± 2.2 $p=0.118$) and LVEDD (transvenous: -0.56 ± 0.13, mini thoracotomy: -0.60 ± 0.14, $p=0.823$) (see figure 3.32).

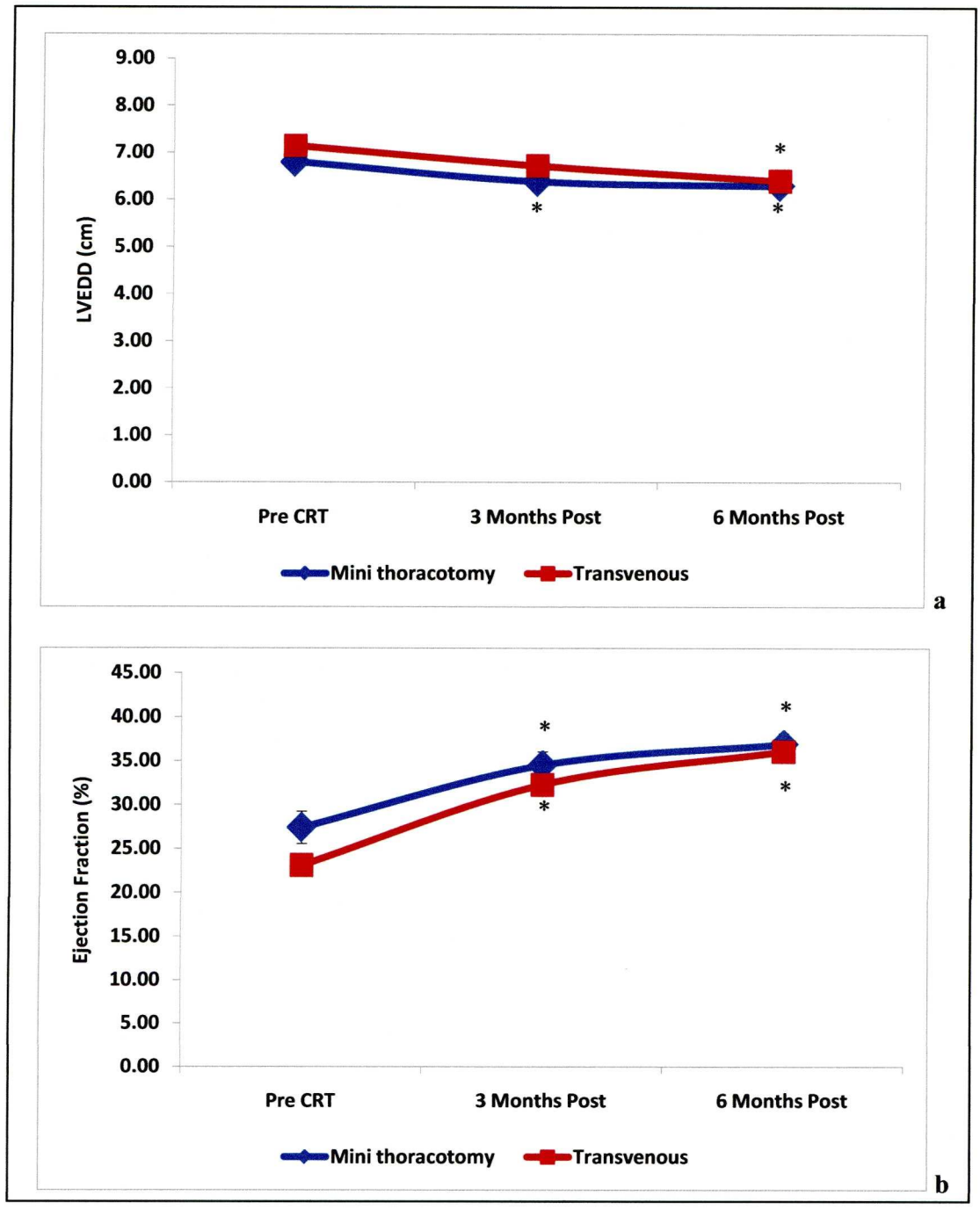

Figure 3.32: Left ventricular end diastolic dimensions (a) and Ejection fraction (b).

Table 3.13: Post cardiac resynchronisation therapy results

	Transvenous Group				Mini thoracotomy Group			
	Pre CRT	**3 months**	**6 months**	**Δ Change**	**Pre CRT**	**3 months**	**6 months**	**Δ Change**
NYHA class	3	2 *	2 *†	1	3	2 *	2 *†	1
Exercise Duration	357 (33)	571 (41) *	666 (41) *†	288 (35)	344 (41)	439 (49)*	576 (51)*†	218 (45)
Peak VO_2	15.59 (0.62)	18.42 (0.62) *	18.98 (0.63) *	3.04 (0.53)	15.43 (0.79)	16.91 (0.91) *	18.30 (1.05) *†	2.33 (0.73)
Peak CPO	2.46 (0.13)	3.14 (0.15) *	3.39 (0.16)*†	0.90 (0.12)	2.42 (0.19)	3.06 (0.18) *	3.36 (0.28) *	0.90 (0.19)
CR	1.81 (0.11)	2.49 (0.13) *	2.75 (0.15) *†	0.90 (0.11)	1.80 (0.17)	2.41 (0.16) *	2.60 (0.25) *	0.76 (0.20)
RER	1.01 (0.01)	1.07 (0.01) *	1.09 (0.02) *	0.07 (0.02)	1.02 (0.02)	1.07 (0.02)	1.10 (0.02) *	0.08 (0.03)
MLWHF	60.3 (3.0)	29.7 (3.1) *	25.7 (3.2) *	-34.8 (3.4)	61.0 (3.7)	36.8 (4.5) *	33.5 (4.5) *	-28.0 (5.2)
LV End Diastolic Dimension	7.14 (0.17)	6.72 (0.14)	6.40 (0.09) *	-0.56 (0.13)	6.79 (0.15)	6.38 (0.14) *	6.29 (0.13) *	-0.60 (0.14)
Ejection Fraction	23.1 (1.3)	32.3 (1.0) *	36.1 (1.2) *	12.4 (1.5)	27.4 (1.9)	34.5 (1.5) *	36.9 (1.3) *	8.4 (2.2)

Given as mean (SE) for continuous data and mode for discrete data (NYHA)
*$p<0.05$ compared to Pre, †$p<0.05$ compared to 3 months,

3.3.2 Percentage improvement at 6 months

At 6 months significant improvements were seen in all variables in both groups. Functional measures showed an overall 33.3% reduction in NYHA class in both groups and an increase in exercise duration (transvenous: 80.6%, mini thoracotomy: 63.5%). Peak VO_2 showed a 19.5% improvement in the transvenous group and a 14.5% improvement in the mini thoracotomy group. Haemodynamic measures during exercise showed an increase in peak CPO (transvenous: 36.6%, mini thoracotomy: 37.3%) and an increase in cardiac reserve (transvenous: 49.7%, mini thoracotomy: 42.1%). There was only a small improvement in RER (transvenous: 7.9%, mini thoracotomy: 6.9%). Echocardiographic measures showed a reduction in LVEDD (transvenous: 8.4%, mini thoracotomy: 8.2%) and an increase in ejection fraction (transvenous: 53.7%, mini thoracotomy: 30.7%). MLWHF scores showed a reduction of 57.7% in the transvenous group and 45.9% in the mini thoracotomy group (see figure 3.33).

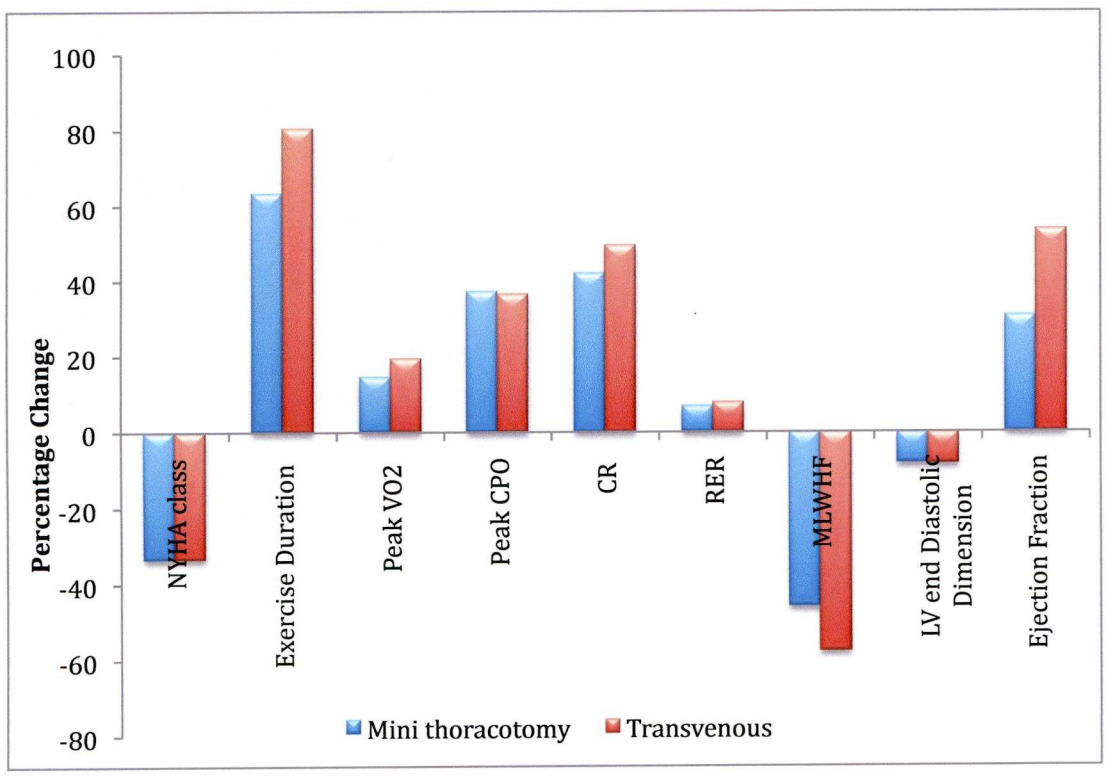

Figure 3.33: Percentage change at 6 months

3.3.5 Pacing parameters

In the transvenous group there was no significant increase in any pacing parameter (R wave sensed, LV lead impedance and threshold) at either 3 or 6 months. The mini thoracotomy group showed no change in either R wave or lead impedance but there was a significant increase in the threshold at 6 months (1.1 ± 0.2 vs. 2.3 ± 0.3, p=0.02). The percentage of ventricular pacing was >95% in both groups at each test. When comparing the transvenous and mini thoracotomy group measurements, the only significant difference was lower impedance in the mini thoracotomy group (implant: p=0.038, 3 months: p=0.02, 6 months: p=0.003). Full details of pacing parameters are given in table 3.14.

Table 3.14: Pacing parameters

	Transvenous			Mini thoracotomy		
	Pre	**3 months**	**6 months**	**Pre**	**3 months**	**6 months**
R wave (mv)	11.3 (1.4)	12.2 (1.5)	12.6 (1.7)	11.9 (1.9)	8.2 (1.3)	8.3 (1.1)
Impedance (Ω)	877.9 (93.9)	869.5 (80.0)	858.1 (91.6)	582.7 (87.0) †	446.0 (43.4) †	471.3 (52.1) †
Threshold (mv) at 0.4ms	1.1 (0.2)	1.5 (0.3)	2.9 (0.7)	1.1 (0.2)	1.7 (0.3)	2.3 (0.3) *
Ventricular pacing (%)	N/A	97 (1.0)	98 (0.7)	N/A	96 (0.9)	97 (0.9)

Values give as mean (SE), *p<0.05 compared to 3 months, † p<0.05 compared to transvenous group

3.3.6 Complication rate

Overall complications rates were low in both groups. During the peri-operative period the mini thoracotomy group had a statistically higher rate of renal impairment (mini thoracotomy: 13% vs. transvenous: 3% $p<0.001$), lower respiratory tract infection (mini thoracotomy: 9% vs. transvenous: 3% $p<0.001$) and pericardial effusions (mini thoracotomy: 4% vs. transvenous: 0% $p=0.003$). There were no complications due to the general anaesthetic or any evidence of cerebrovascular accidents, myocardial infarctions or unstable angina. The median length of stay was higher in the mini thoracotomy group (mini thoracotomy: 5.5 ± 0.6 days vs. transvenous: 3.0 ± 0.4 days, $p=0.001$).

During the 6 months of the study there was no significant difference in LV lead exit block (Mini thoracotomy: 4% vs. Transvenous: 3% $p=0.558$) or pocket haematoma (Mini thoracotomy: 9% vs. Transvenous: 6% $p=0.207$). There were no lead displacements or system infections and no patients required re-operation or system extractions during the study period.

Discussion

4.1 Study I: The longitudinal improvement in exercise haemodynamic measures following cardiac resynchronisation therapy.

This study explored the baseline characteristics of a group of patients being considered for cardiac resynchronisation therapy and the longitudinal improvement following CRT. Unlike the majority of trials looking at CRT which have traditionally used a pre and post design we were seeking to describe the rate of change that occurs following CRT. In addition to the standard functional class and quality of life assessments, I also assessed the effect of CRT on non-invasively measured cardiac ouput and skeletal muscle function. The effect of CRT on skeletal muscle has not previously been described.

From previous studies it has been shown that patients suitable for CRT are severly limited in terms of exercise capacity and functional status. It has been assumed that this limitation is due to dyssynchronous cardiac contraction leading to a reduced cardiac output. The majority of trials have not assessed the response of CRT to cardiac output and have instead used either peak VO_2 or exercise duration as surrogate marker of cardiac function. The disadvantage of this approach is that both peak VO_2 and exercise duration are measures that are affected by a variety of external factors including cardiac output. Therefore when we try to assess the difference in response in patients following CRT, a more detailed understanding of the changes following CRT would be needed to try to better predict the likelihood of response following CRT.

4.1.1 Baseline data

The baseline data shown in section 3.1.1 showed that the group was a typical group to be considered for cardiac resynchronisation therapy with a mean age of 65 years and a male preponderance. There was evidence of a severe dilated cardiomyopathy with signficant functional and quality of life impairment. All haemodynamic measures showed significant impairment and the results were very similar to data published in all the major trials (see table 4.1) (MIRACLE (Abraham et al., 2002), MIRACLE-ICD (Young et al., 2003), CARE-HF (Cleland et al., 2005a), COMPANION (Bristow et al., 2004)) and therefore could be considered a typical group prior to cardiac resynchronisation therapy.

Table 4.1: Baseline characteristics compared to other major trials

	Longitudinal study	**Miracle**	**Miracle-ICD**	**Companion**	**Care-HF**
Mean age (years)	**65**	64	67	67	65
Men (%)	**90**	90	77	67	73
Women (%)	**10**	10	23	33	27
NYHA III (%)	**100**	90	89	86	94
Peak VO_2 (mls/min/kg)	**15.5**	14.0	13.3	NA	NA
MLWHF scores	**62**	59	57	NA	45
LVEF (%)	**22**	22	24	22	26
LVEDD (cm)	**7.0**	7.0	7.6	6.7	7.2
QRS (ms)	**158**	166	164	160	165
Resting Heart rate (bpm)	**79**	74	71	72	70
Systolic BP (mm Hg)	**116**	115	114	111	117
Diuretics (%)	**100**	94	94	95	99
Digoxin (%)	**43**	79	NA	NA	43
ARB/ACEi (%)	**98**	92	91	89	95
Beta-blockers (%)	**82**	59	60	68	72
Spironolactone	**45**	NA	NA	54	56

4.1.2 Baseline relationships between cardiopulmonary variables

The correlations between baseline cardiopulmonary variable and skeletal muscle function were assessed using linear regressions. Whilst linear regression is a useful method of assessing relationship between 2 variables it should be noted that a significant correlation does not necessarily mean there is a significant realtionship between the variables. If linear regression is used haphazardly then there would be a risk of a chance relationship occurring between 2 variables with no real relationship. To use linear regression accurately it is important to assess 2 variables that have the possibility of a relationship rather than assessing any random variables. In this study we have assessed the exercise cardiopulmonary, the functioncal class, quality of life scores and skeletal muscle function. It is reasonable to expect these variables to have a possible linear relationship and therefore linear regression is valid. However this data is only being used as a means of exploring the baseline data and the limitations of linear regression mean that the results should be reviewed with caution.

The baseline exercise duration was closely related to the peak cardiac power output, cardiac reserve, peak VO_2 and the respiratory equivalents for oxygen and carbon dioxide. The baseline peak VO_2 was also closely related to peak cardiac power output, cardiac reserve and the respiratory equivalents for oxygen and carbon dioxide. Interestingly the variables that showed the most consistent correlations with other measures were peak cardiac power output and cardiac reserve. These two variables not only correlated with exercise duration, peak VO_2, the respiratory equivalents for oxygen and carbon dioxide but also with ejection fraction and peak skeletal muscle function in both legs. Therefore peak cardiac power output and

cardiac reserve provide a more comprehensive evaluation of a patient's overall physiology than either peak VO_2 or exercise duration. The majority of trials looking at cardiac resynchronisation therapy have solely focussed on peak VO_2 and exercise duration. However there is evidence from previous trials that peak cardiac power output is a superior predictor of mortality in patients with chronic heart failure (Williams et al., 2005) and this study confirms that peak cardiac power output correlates better than any other variable at baseline.

The fact that the baseline peak VO_2 does not correlate with peak skeletal muscle torque is suprising. When looking at different exercise protocols it has been shown that a treadmill based exercise protocol leads to a 10-15% higher peak VO_2 than a bicycle based protocol. The explantation given for this difference is that a treadmill based protocol uses more skeletal muscle compared to a bicycle explaning the higher peak VO_2. Hence one would expect peak VO_2 and peak skeletal muscle torque to be closely related. The lack of relationship between peak VO_2 and skeletal muscle function in this study may reflect that patients suitable for CRT are at the severe end of the spectrum of heart failure. They are likely to suffer from chronic skeletal muscle dysfunction and therefore by the time they are sympotmatic enough to be considered for CRT the skeletal muscle may well be so deconditioned that at this point it is no longer contributing in any meaningful way to the patients' peak VO_2, hence the lack of correlation. The reasons why a skeletal muscle myopathy occurs in chronic heart failure are not well described. It is hypothesised that in part it is a disuse myopathy due to a reduction in exercise capacity and also that the reduced cardiac output leads to a reduced skeletal muscle perfusion (Drexler et al., 1992). Therefore it is not suprising that there is a postive correlation between

skeletal muscle function and peak cardiac power output and cardiac reserve. This is further enforced by the fact that the only variables that correlated with skeletal muscle function were measures of cardiac output whether measured by rebreathing techniques (peak cardiac power output and cardiac reserve) or by echocardiographic methods (ejection fraction). These results provide some evidence for the muscle hypothesis of heart failure as described by Clark et al (see section 1.2.3.1) (Clark et al., 1996).

It is interesting to note that left ventricular end diastolic dimension did not correlate with any other measure. This can be explained by basic cardiac physiology. In vivo there are multiple mechanisms regulating cardiac output including cardiac contractility, heart rate, preload, after load, ventricular geometry and neurohormonal regulation. The force of contraction and stroke volume can be altered by the Frank-Starling mechanism (Starling, 1918;Frank, 1959). This states that the length and tension of the muscle at the time of stimulation determined the magnitude of its contractile response. Therefore increasing preload increasing the pre systolic tension and dilation of the left ventricle leading to an increase in sarcomere length would increase contractility. This mechanism is used as a compensatory mechanism for the heart, however whilst these mechanisms are very successful in the short term the long term effects of a chronically increased preload and left ventricular dilation lead to the clinical syndrome of heart failure (Braunwald and Ross, 1964). There is now good evidence that in patients with heart failure the Frank-Starling mechanism has been exhausted and therefore any further left ventricular dilation that occurs does not lead to any increase in cardiac function. Therefore when looking at a cross section of patients prior to CRT the left

ventricular end diastolic dimension of any one patient simply relates to the time spent with a chronically increased preload. As the Frank-Starling mechanism has been exhausted it is not surprising that the left ventricular end diastolic dimension does not correlate with any other haemodynamic measure.

There is no significant correlation between a person's quality of life, as measured by Minnesota living with heart failure, and almost any haemodynamic or functional measures. The only slight correlation was with the peak respiratory ventilatory equivalents for carbon dioxide which showed a small correlation which just reached signficance (R^2=0.10 p=0.045). This lack of correlation is interesting as it would seem reasonable to assume that a person with severe heart failure would be mainly impaired due to the cardiac disease and therefore there would be some correlation with measures of cardiac function. It should be remembered however that whilst heart failure starts as a one organ disease by the time a person has become symptomatic enough to be considered for CRT it is now a disease involving the whole body. Thus a person's MLWHF score will be dependent on more than simply their cardiac function and will include other organ dysfunction, psychological and social issues. Thereofore it is not suprising that a persons baseline MLWHF score does not correlate with other haeodynamic measure. Where MLWHF may be of more use is in the longitudinal response to CRT. In a longitudinal study the fact the quality of life scores are being assessed in the same indviduals and that the only signficant treatment done in that time is CRT. Therefore any changes seen are likely to be due to the CRT as the other organ dysfunction, psychological and social issue should not be altered. MLWHF scores were the most commonly used marker of quality of life at the time our studies were performed. The results from our study

have been recently corberated by Athanasopoulos et al who also showed that MLWHF showed poor correlation with cardiopulmonary variables and plasma NT-proBNP levels (Athanasopoulos et al., 2010). As mentioned in section 2.2.4 MLWHF incorporates physical, emotional, social and mental dimensions of quality of life. Whilst all these different dimensions are measured by MLWHF, it was never designed to measure any one dimension separately. Therefore when assessing the physical response to cardiac resynchronisation therapy it is not adequate to simply rely on quality of life scores as assessed by MLWHF. The only accurate objective measurement of physical response remains cardiopulmonary exercise testing.

4.1.3 Longitudinal response to cardiac resynchronisation therapy

Cardiac resynchronisation therapy is now a widely accepted treatment for suitable patients. The major trials to date have randomised almost 4000 patients and shown that by 6 months there are improvements in functional class, exercise duration and peak VO_2 (Bristow et al., 2004;Cleland et al., 2005b)). However these studies have only really focussed on a pre and post design. In this study we assessed how early it was possible to see signficant change following CRT. In our study at 3 months post CRT there were signficant improvements in NYHA class, Minnesota living with heart failure scores, exercise duration, peak VO_2, peak CPO, cardiac reserve, and ejection fraction. During the trial there was a gradual improvement in the ventilatory equivalents for oxygen consumption and carbon dioxide but these trends failed to reach statistical significance. The improvements in NYHA class, MLWHF, exercise duration, peak VO_2, and ejection fraction are in keeping with the data published in the major clinical trials (Bristow et al., 2004;Cleland et al., 2005b). There is very little data currently published on the effects of CRT on peak CPO and

CR. The only trial to date by Schlosshan et al showed that CRT led to a significant improvement in both peak CPO and cardiac reserve at 8 weeks post CRT (Schlosshan et al., 2006). In this study there was a similar significant improvement in NYHA class and peak VO_2 when compared to our study. Both studies also showed no significant change in RER. Interestingly whilst both confirmed a significant improvement in exercise duration, peak CPO and cardiac reserve the magnitude observed in our study does appear to be smaller than that reported by Schlosshan et al. This may be explained by the fact the patient population in the Schlosshan et al study appears to be more impaired than in our study. This is evident by the patients in our study having a higher baseline peak VO_2, peak CPO, CR and a lower VE/VCO_2 slope and VE/VO_2 slope (see table 4.2). When comparing studies it is important to remember that different exercise protocols and different cardiopulmonary analysis systems may well give slightly different results. The difference between the 2 studies can also be explained by the relatively small numbers in both groups especially the study by Schlosshan et al. When working with small numbers the possibility of some outliers affecting the overall data set increase and therefore it is possible that in the Schlosshan study the larger percentage increases in some measures is related to a small number of people showing above normal improvements. With a signficantly larger population in our study and longer follow up (12 versus 8 weeks) this effect should have been reduced to give a more accurate data set.

Table 4.2: Comparisons to study by Schlosshan et al.

	Longitudinal study			Schlosshan et al		
	Pre CRT	**Post CRT**	**% change**	**Pre CRT**	**Post CRT**	**% change**
NYHA	3	2*	-33.3	3	2 *	-33.3
Exercise duration	322	558 *	73.3	374	531 *	42
Peak VO2	15.51	18.48 *	19.1	13.9	16.81 *	20.9
RER	1.04	1.08	3.8	1.09	1.09	0
VE/VCO2 slope	40.8	37.1	-9.1	46.9	37.5 *	-20
VE/VO2 slope	45.9	42.5	-7.4	57.7	42.6 *	-26.2
Peak CPO	2.53	3.23*	27.7	1.92	2.63 *	37
CR	1.89	2.58 *	36.5	1.18	1.83 *	55.1

In our study there was no significant improvement in either peak RER or the percentage of peak VO_2 at the anaerobic threshold. This suggests that the overall improvement seen at maximum exercise is made up of a combination of an improved aerobic and anaerobic capacity. The fact that the peak RER is not different pre and post provides reassurance that the exercise tests were truly maximal and similar levels of exertion were achieved at all tests.

Echocardiographic parameters showed a significant improvement in ejection fraction that became significant at 6 weeks post CRT. The 2 week test did show a trend towards an improvement in ejection fraction from 21.7% to 28.7% but this just failed to reach statistical significance (p=0.068). Cardiac resynchronisation therapy provides a more co-ordinated ventricular contractions and therefore it

would be expected that there would be a significant improvement seen immediately. In keeping with our results none of the major trials to date have reported on an acute response in ejection fraction. The earliest reported improvement was at 1 month (Gras et al., 2002) . In the current study the improvement at 2 weeks was very close to being statistically signficant and we feel that the fact it failed to reach signficance is most likely to be related to the relatively small numbers involved in this study. Left ventricular end diastolic dimension showed a trend towards improvements throughout the study but this just failed to reach signficance at both 2 weeks and 6 weeks post CRT. This can be explained by the fact that reverse remodelling will take some time and therefore it would not be too suprising that improvements are delayed. However it is also possible that the lack of significance may in part be due to the relatively small sample size.

It has already been appreciated that patients with cardiac failure have signficant skeletal muscle dysfunction which is responsible for at least part of the symptoms that patients suffer (Clark et al., 1996). However the effect of cardiac resynchronisation therapy on skeletal muscle function has not previously been described. In this study despite improvements in functioncal class, exercise capacity and haemodynamic measures there were no significant improvement in peak skeletal muscle torque in either leg. Therefore cardiac resynchronisation therapy by itself does not improve skeletal muscle function at 3 months, and thus a major cause of symptoms is left untreated despite CRT. Patients suitable for CRT have been gradually deconditioning over a long period of time and CRT by itself doesn't resolve this deconditioning. The cardiopulmonary data show that the patients have had a significant improvement in the ability to exercise. However this does not

necessarily equate to an increased amount of regular exercise in day to day life. By the time patients have reached a level of symptoms severe enough to make them suitable for CRT their confidence in performing unsupervised exercise is likely to have been significantly reduced. Therefore to improve a patients confidence to perform regular exercise a structured supervised exercise programme may well be required to achieve a higher level of exercise in the long term and start to reverse the skeletal muscle deconditioning.

4.1.4 Predictors of response

Cardiac resynchronisation therapy has been shown to improve both morbidity and mortality in suitable patients. However each of the major trials have shown around a 30% non responder rate. Implantation of a CRT device does carry some risk of complication and in a health care system with a limited budget it is obviously important to try and target the patients who are most likely to benefit to minimise cost and complications. Currently QRS duration is the most commonly used marker for ventricular dyssynchrony (Bristow et al., 2004;Cleland et al., 2005b). However as these trials have shown a 30% non responder rate there has been a large amount of interest recently into finding more accurate predictors of response.

Alternative predictors of response have ranged from basic echocardiographic parameters (Cleland et al., 2005b) to complex tissue Doppler echocardiography and nuclear imaging (Ascione et al., 2008;Trimble et al., 2008). In the published literature to date no single measure has been shown to be a good reproducible predictor of response. In the largest trial to date looking at predictors of response (the PROSPECT trial) a multitude of echocardiographic parameters were assessed

in an international multi centre trial. No single measure showed a reliable degree of accuracy in predicting response (Chung et al., 2008).

In our study we assessed the variables that were significantly different between responders and non responders. As shown in previous studies QRS duration, baseline exercise duration and peak VO_2 were not good predictors of response. The strongest predictors of response were the baseline ejection fraction and the left ventricular end diastolic dimensions. Responders had a significantly lower ejection fraction and a less dilated left ventricular end diastolic dimension. Non responders had a significantly higher peak skeletal muscle torque during extension in both sides and significantly better ventilatory equivalents for oxygen consumption (peak VE/VO_2) and carbon dioxide production (VE/VCO_2 slope and peak VE/VCO_2). The overall picture therefore is that a responder was generally in a more impaired state than a non responder. This is shown by a worse ejection fraction more impaired skeletal muscle function and worse ventilatory equivalents in the responder group. In the REVERSE trial it was shown that CRT is of benefit in patients with mild heart failure, however due to the patients only having mild impairment the differences did not achieve significance until 12 months post CRT. This does raise the possibility that the non responder group is simply less impaired and therefore longer term follow up would be needed to see if they achieve a delayed response.

4.1.5 Limitations of this study

This study is a non randomised prospective study without a control group. Whilst having a control group would have shown the benefits of CRT in more detail it was felt that the large scale multi centre trials have already described this adequately. The main reason for this study was to assess the relationships in variables at baseline in patients suitable for CRT and assess the effects of CRT on peak CPO, CR and skeletal muscle torque. As the numbers in this trial are fairly small it is important to take account of this when reviewing the results. We have shown statistically significant improvements in some variables which are in keeping with previously published data, however a longer term follow up and a larger cohort may have provided some more information.

4.1.6 Conclusions

This study shows that CRT leads to signficant improvement in functional class and exercise haemodynamics as early as 2 weeks following CRT. This is significantly earlier than has previously been reported. At baseline peak CPO was the single best variable when looking at correlation with the patients other variables. QRS duration was a poor predictor of response and it is shown in this study that the more severe the heart failure the better the chance of response within 3 months of CRT. CRT by itself does not improve skeletal muscle function and therefore a structured exercise programme may help to improve the benefit.

4.2 Study II. The effects of exercise rehabilitation in addition to cardiac resynchronisation therapy

In this study the baseline characteristics and haemodynamic measurements were very similar to those of the longitudinal study and in keeping with previously published data (Schlosshan et al., 2006). The initial stage of the study was a three month longitudinal follow up with simple CRT. This allowed us to again see the longitudinal response of CRT. Similar to study I at three months after CRT we demonstrated significant improvements in all functional and haemodynamic measures. These improvements were of a similar magnitude and over a similar time scale to those seen in other multicentre trials (Cleland et al., 2005b;Abraham, 2006) . At 3 months there was a 14% improvement in the peak VO_2 and approximately a 30% improvement in the peak cardiac power output and cardiac reserve. Ejection fraction also showed a 37% improvement. In addition to these improvements the MLWHF score improved by almost 50%. The baseline peak VO_2 was 16.12mls/kg/min which is slightly higher than has previously been reported in CRT trials (Abraham et al., 2002;Schlosshan et al., 2006). However, the correlation between peak VO_2 and NYHA class is known to be poor (Genth et al., 1996) and it is important to remember that the measured peak VO_2 can vary depending on the testing method and protocol utilised.

Peak VO_2 showed significant improvement at 3 months without a significant change in the percentage of VO_2 at the anaerobic threshold. This suggests that the improvement in peak VO_2 was due to an equal improvement in the capacity to

perform aerobic and anaerobic exercise. Following CRT the increased RER reflects an ability to exercise to a greater level of physiological stress. In the longitudinal study described in study I there was a trend towards an increased peak RER at 3 months but this was not statistically significant. The most likely reason that this reached significance in this study but not study I is the larger study population in this study. The increase in peak RER was not a familiarisation response as a separate exercise test had been performed prior to the study and the results discarded. The results at 3 months support the theory that CRT improves function due to enhanced central cardiac function alone. This study again confirms the absence of any peripheral skeletal muscle changes 3 months after CRT alone.

At the point of randomisation there were no significant differences between the 2 groups. Randomisation was delayed until the 3 month stage in order to limit bias. Had patients been aware at an earlier stage that they were going to be in the exercise group there would have been the potential for them to self-train. This would have influenced the 3 month results and made any comparison between the 2 groups less reliable. The exercise training group underwent a graduated intensity exercise programme over 3 months whilst the control group were given no specific advice relating to exercise. We recognise that this exercise training programme was more intensive, frequent and prolonged than the usual cardiac rehabilitation offered to patients following myocardial infarction or coronary revascularisation. The provision of cardiac rehabilitation post revascularisation is very varied throughout the UK. Wright et al showed that the average programme of once a week sessions for 6 weeks led to no significant improvement in objective cardiopulmonary measurements (Wright et al., 2002). Previous trials looking at exercise in CHF have

had varying intensity and frequency. In the Extra Match meta analyses the trials varied from 2 to 7 times a week and 50% to 80% of the peak heart rate (Piepoli et al., 2004) and in HF-Action the exercise programme was 30 minutes 3 times a week for 3 months at 60-70% of heart rate reserve in the supervised stage. This was then followed by home unsupervised exercise programme of 40 minutes 5 times a week for a minimum of 1 year again at 60-70% heart rate reserve (O'Connor et al., 2009). However, by the end of the trial the average duration of exercise was only 50 minutes per week (O'Connor et al., 2008). As our trial was based over a 3 month training period but did not have an extended home unsupervised programme like HF-Action, we felt it appropriate to have a higher intensity of exercise. Hence we started at 80% and went up to 90% of peak heart rate. Despite the high intensity it was well tolerated and no patients in the exercise group had any complications from the exercise training. Attendance at the exercise programme was extremely high with the average being 98.5% attendance for the study. This is likely to have been influenced by the fact that the visits were physician supervised and it is debateable whether this level of attendance would occur in a non-trial setting. However this high level of attendance is similar to that in other supervised programmes such as HF-Action and we hypothesise that if patients and clinical staff were made fully aware of the extent of improvements possible with a structured exercise programme then attendance figures may well be close to those achieved in this study.

At six months, those patients undertaking exercise training demonstrated further significant improvements in NYHA class, exercise time, peak VO_2, peak CPO, CR, RER and MLWHF score which were not mirrored in the control group. Although in-group analysis showed a significant improvement in skeletal muscle function

with exercise training this was not supported by significant inter-group changes compared to the control group. This may reflect the relatively small number of patients in each group. Equally it may be due to the frequency or duration of the training programme. Had the patients exercised more frequently or for a longer period the differences in improvement in peak skeletal muscle function may have achieved significance. Nevertheless the overall changes at the end of the study were greater in the exercise group for most variables. The overall improvement in exercise duration seen in the control group (53%) was comparable to previously published data (Schlosshan et al., 2006). However, the introduction of exercise training increased the improvement to 101%. This level of improvement has never been described following CRT alone. Peak VO_2, known as a powerful predictor of prognosis (Mancini et al., 1991), was improved by 12% in the control group compared with 25% in the exercise group. Again this level of improvement has never previously been reported. In all haemodynamic measures the addition of exercise training doubled the percentage improvement at 6 months when compared to the control group. The exercise group also showed more substantial improvements in both right (13%) and left sided (16%) peak skeletal muscle function. The control group showed only a 2.4% improvement in right sided and a 0.2% improvement in left sided extension during the same period. The likely explanation behind these overall changes is that CRT alone improves functional capacity and QOL by enhancing cardiac function and exercise training improves functional capacity further by enhancing skeletal muscle and cardiac function.

After 3 months of cardiac resynchronisation therapy 17 out of the 50 (34%) patients were classified as non-responders. This rate is comparable with the major clinical

trials which have shown a non responder rate of approximately 30% (Abraham et al., 2002;Young et al., 2003). Recently there has been increasing focus in trying to predict responders to cardiac resynchronisation therapy. In this study there were similar numbers of non responders in both groups with 9 in the exercise group and 8 in the control group at 3 months, however the addition of exercise duration lead to a dramatic reduction in the number of patients being classified as non responders from 9 to 3, an improvement of 67%. This improvement in responder rate at 6 months cannot be simply explained by a delayed response to cardiac resynchronisation therapy as the changes were not matched in the control group where the reduction was only from 8 non responders at 3 months to 6 at 6 months, an improvement 25%. The difference between the reduction in non responders in the exercise and control group was highly significant. Therefore the addition of exercise training not only doubles the improvement seen following CRT it can also help to transform non responders to responders. It has been previously described that exercise training is useful in patients with heart failure and it is therefore not surprising that there is an improvement in responder's rates with exercise training. However the major trials have focussed on patients with mild cardiac failure (NYHA class 1-2). Patients with more advanced heart failure are usually less physically and psychological able to perform an exercise programme. The mechanism behind the improvements seen in this study may be that CRT improves the patient from severe to mild heart failure. Exercise training then builds on the newly improved physically and psychological level to lead to even further improvements.

4.2.1 Limitations of this study

This study used a randomised controlled protocol. A further control group who were suitable for CRT but who were randomised to exercise training alone would have improved the methodology. However in view of the CARE-HF study (Cleland et al., 2005b) which showed a mortality benefit from CRT it was considered unethical to withhold CRT even temporarily. Overall the data set was relatively small and therefore some caution should be exerted when interpreting the results. However, all the principal measures achieved highly significant improvements. In view of the relatively small number of patients involved in this study it was not appropriate to look for benefits in mortality or CHF hospitalisation. These endpoints could only accurately be assessed by larger scale trials.

By the very nature of exercise training it is impossible to blind the patient to whether they are in the exercise or control group. We attempted to limit any potential impact by delaying randomisation until the 3 month stage. We also tried to minimise bias from actual training visits in the exercise training group by performing the exercise training in a non clinical setting and by utilising a physician not involved in the pacemaker implant or follow up.

4.2.2 Clinical implications of this study

In view of the significantly improved outcomes in the exercise group it would be reasonable to suggest that exercise training should be offered to all patients following CRT. This would ensure the best possible outcome from CRT. The

exercise programme used in this study was a practical regime which could be used in clinical practice.

4.2.3 Conclusions

Cardiac resynchronisation therapy is an effective treatment for suitable patients. The addition of exercise training significantly enhances the benefits seen by improving both the central cardiac function and the peripheral skeletal muscle function. Exercise training would provide only a small additional cost to the overall cost of CRT, and we therefore feel that it would be justified to offer this to all patients following CRT.

4.3 Study III. The effectiveness of left ventricular lead placement via a mini thoracotomy to achieve cardiac resynchronisation therapy in patients with previously failed transvenous placement.

This study is the first to directly compare functional and clinical improvements following lead placement via a mini thoracotomy with transvenous placement of CRT. Surgical placement of the LV lead is well recognised and was used in the initial evaluation of CRT (Auricchio et al., 1999b;Auricchio et al., 2002). These studies placed the LV epicardial lead via a full thoracotomy. This did carry some risk in the peri-operative period with a prolonged recovery time and high complication rate (2.4% wound complications and 9.8% atrial fibrillation) (Auricchio et al., 2002). In the longer term 7.3% developed lead exit block at 12 months (Auricchio et al., 2002) which led to the development of transvenous placement via the coronary sinus (Linde et al., 2002). Transvenous placement is now the standard method of implantation (Bristow et al., 2004;Cleland et al., 2005b) although there are limitations. Firstly the implantation success rate is approximately 90% with a significant operator learning curve (Abraham et al., 2002;Bristow et al., 2004;Cleland et al., 2005b). Also the final site of LV lead can be compromised due to inadequate venous anatomy, stimulation of adjacent structures or high thresholds. These problems may in part be responsible for the 30% non-responder rate seen in trials (Bristow et al., 2004;Cleland et al., 2005b).

Improvements in surgical epicardial lead technology, new implanting tools and new surgical techniques including mini-thoracotomy (Mair et al., 2005;Shah et al.,

2006;Doll et al., 2008) and robotic/thoracosopic implantation (Jansens et al., 2003) reflect a resurgence of interest in the option of surgical epicardial LV lead positioning. Such advances mean it is now possible to place an epicardial lead in any position on the LV (Mair et al., 2005;Shah et al., 2006;Doll et al., 2008). These methods of implantation have been proposed as potential alternatives for patients with failed transvenous lead implantation. Initial case studies and small case series have shown successful delivery of CRT. To date there has been 3 trials directly comparing surgical epicardial LV lead placement via a mini thoracotomy versus transvenous lead placement. In the first trial to report Mair et al compared 70 patients who received transvenous LV lead placement to 16 patients who had their LV lead placed mini thoracotomy. In this study they purely assessed pacing parameters at follow up of 16 months. There was no significant increase in surgical epicardial lead threshold during this study, which suggests that long term surgical epicardial lead performance is reasonable. Interestingly the transvenous group in this study had an exceptionally high complication rate with 25 (36%) LV lead related complications (failed implantation, CS-dissection, loss of pacing capture, diaphragm stimulation or lead dislodgment). This rate of complications would be considered excessively high and may reflect a lack of experience in transvenous LV lead placement. The study also did not assess any objective exercise or functional measures to see if similar improvements were achieved between mini thoracotomy and transvenous LV lead placement (Mair et al., 2005). Shah et al reported data on 11 patients receiving surgical epicardial LV lead placement and in keeping with our study showed a higher peri-operative morbidity but significant improvements in functional class following surgical epicardial LV lead placement. However there was no assessment of exercise capacity or cardiopulmonary measures in this study

to compare surgical epicardial and transvenous lead placement. (Shah et al., 2006). Both the trials by Mair et al and Shah et al were prospective and non-randomised. The only randomised trial to data was reported by Doll et al. In this study they randomised 80 patients in a 1 to 1 basis to either surgical epicardial or transvenous LV lead placement. The transvenous group had a shorter inpatient stay but a higher exposure to radiation. At 6 months there was no significant difference in LV lead pacing parameters (Doll et al., 2008). These three studies therefore confirmed that surgical epicardial lead placement was a technically viable procedure. However none of these studies had actually assessed any functional or cardiopulmonary improvement following surgical epicardial lead placement. Therefore concerns persisted regarding peri-operative morbidity, long recovery times and improvements in cardiopulmonary measures following surgical placements of the left ventricular lead. In our study there were no major adverse events (death, myocardial infarction or stroke) in either group. There were however significantly higher rates of post operative respiratory tract infections, transient renal dysfunction and pericardial effusions in the mini thoracotomy group. This higher complication rate combined with the recovery from a general anaesthetic, led to an increased length of stay when compared to the transvenous group. Pacing complications such as exit block and pocket haematoma were similar in both groups for the study duration and were comparable with other studies (Shah et al., 2006;Doll et al., 2008). However, our period of follow up was limited to six months and exit block has been reported as a late occurring phenomenon after mini thoracotomy pacing. In this study there was a sub acute rise in LV lead threshold of the mini thoracotomy group. This does raise the possibility of long term exit block and longer term analysis is planned in due course.

The benefits of CRT have been extensively described with significant improvements in functional class, haemodynamic measures and mortality (Abraham et al., 2002;Bristow et al., 2004;Cleland et al., 2005b). In this study peak VO_2, exercise time and NYHA class all improved significantly in both groups at three months, but to a lesser extent in the mini thoracotomy group. Thereafter peak VO_2 only increased significantly in the mini thoracotomy group between 3 and 6 months, although there were further improvements in both groups in exercise time and NYHA classification. Regarding peak VO_2 alone, as the most reliable objective marker of functional capacity and considering its use as a selection criteria for cardiac transplantation (Mancini et al., 1991), it is possible to conclude that the significant improvement in functional capacity with transvenous CRT was seen over a shorter time scale. The improvement in the mini thoracotomy group was made over two stages whilst the transvenous group managed a similar improvement in one. It is likely that the longer hospital stay and higher complication rate delayed the improvements in patients receiving mini thoracotomy placement of the LV lead. This has an important impact on deciding the ideal time to assess responder status following CRT when achieved using transvenous or mini thoracotomy approaches. Interestingly both groups demonstrated highly comparable values for RER at all stages of the study with all significant increases only seen between the baseline and 3 month assessments. This confirms comparable levels of physiologic exertion throughout the study and excludes any possibility of motivational bias.

Evaluation of left ventricular function showed significant increases in EF in both groups at 3 months, which was maintained at 6 months. These overall

improvements were comparable to previous studies (Auricchio et al., 1999b;Bristow et al., 2004;Cleland et al., 2005b). Reduction in LVEDD was only significant at 3 months in the mini thoracotomy group but had reached statistical significance in both groups at 6 months. We are unable to explain this delayed remodelling in the transvenous group. It may possibly be due to the fact that ventricular size was non-statistically greater and EF lower at baseline in this group indicating a greater degree of disease. Supporting this theory is the fact that dynamic left ventricular function in the form of CPO and CR also increased significantly in a two stage process in the transvenous group. There were no significant improvements in the mini thoracotomy group between the 3 and 6 month assessments.

When comparing the overall improvements between the groups at 6 months there was no significant difference in any variable. This therefore shows that similar improvements can be attained using mini thoracotomy implantation compared to the transvenous. Despite the improvements in lead technology and implantation tools mini thoracotomy lead placement is more invasive than transvenous. The longer recovery time and increased peri-operative complications in conjunction with the associated cost increases mean that transvenous lead placement should remain the first choice for patients requiring CRT.

This study has focussed on mini thoracotomy placement of the LV lead as an alternative for patients with failed transvenous leads. Another possible indication for mini thoracotomy placement of the LV lead would be for non-responders to CRT. One major limitation of transvenous leads is that placement is dictated by

venous anatomy and does not necessarily correlate with the ideal site of LV pacing. Surgical epicardial leads have the advantage that they can be placed anywhere on the left ventricular wall. It is therefore potentially possible to map the LV and pace the most appropriate site for maximum synchrony. This indication was outside the remit for this study and would need further trials.

4.3.1 Conclusions

This is the first prospective controlled study to show that epicardial lead placement via a mini lateral thoracotomy is a safe and viable procedure compared to transvenous placement. We confirm a longer in patient stay, increased complication rate and a sub acute threshold rise in the mini thoracotomy group. This leads to a delay in the rate of improvement in peak VO_2 in the mini thoracotomy group. However despite this there are comparable improvements in all measures following mini thoracotomy achieved CRT albeit over a longer timescale. Hence mini thoracotomy placement of the LV lead is an acceptable alternative approach but should remain a second-line procedure.

4.3.2 Limitations

This study is a prospective controlled trial rather than a randomised controlled one. In view of the wide clinical evidence for transvenous lead placement we felt it was not possible to have a randomised protocol. The results have to be viewed with this in mind. The trial has relatively small patient numbers and follow up is 6 months. Whilst this group has been large enough to show statistically significance it is possible that longer follow up might have highlighted some differences between the two groups not seen in this study. As exercise tests were performed prior to CRT

implantation it was only possible to enrol patients in NYHA III. Patients with more severe heart failure may potentially have more risk from a surgical placement of an epicardial lead than the group studied in this trial.

Conclusions

5.1 General Conclusions

Cardiac resynchronisation therapy is a widely accepted treatment for patients with symptomatic heart failure and evidence of electromechanical dyssynchrony. There is now a wide body of clinical experience with CRT which shows that in selected cases there are significant improvements. However there is consistently a small but significant non responder rate which implies that our understanding of patient selection is still limited. Detailed study of the changes following CRT is important to understand the mechanism of action of CRT which may assist in better patient selection. In the first longitudinal study we showed that patients suitable for CRT were significantly limited. At baseline the patients' clinical condition correlated best with peak cardiac power output and cardiac reserve suggesting that the main impairment is in cardiac performance. The patients' perceived quality of life scores, as assessed by the Minnesota living with heart failure, showed surprisingly poor correlation with any cardiopulmonary or skeletal muscle parameters. This highlights the importance in obtaining objective functional exercise testing in patients as a patient's own perceived symptom level could be misleading.

Following cardiac resynchronisation therapy there were significant improvements seen within two weeks, which were maintained for the rest of the study. This rapid improvement suggests that the main improvement is due to a more co-ordinated efficient ventricular contraction leading to improvements in exercise cardiopulmonary variables and quality of life scores. However CRT by itself had no impact on skeletal muscle function which has become deconditioned due to

impaired perfusion and disuse. Skeletal muscle deconditioning is an important cause of impaired exercise capacity in patients with heart failure. Therefore we conclude that CRT has no effect on a major cause of symptoms in heart failure.

In the second study we confirmed that even at 6 months CRT by itself has no effect on skeletal muscle function and did not provide further improvement in functional or exercise cardiopulmonary measure after the initial improvements. The addition of exercise training 3 months after CRT lead to an improvement in peak skeletal muscle function which was associated with further increases in functional class, exercise duration, quality of life scores and exercise cardiopulmonary haemodynamics. The addition of exercise training led to a near doubling of the improvement seen in exercise duration and haemodynamic measures at 6 months compared to CRT alone. Never before have such improvements been reported following cardiac resynchronisation therapy.

Exercise training in addition to CRT also helped to transform patients who had been classified as non responders at 3 months to responders by 6 months. Thus we can not only enhance the improvements seen following CRT but also improve the number of patients who benefit. In the exercise group only 3 out of 25 (12%) patients were still non responders following CRT and exercise training. This level of non responders is significantly lower then has previously been described in any major CRT trials.

In the third study we showed that in patients in whom transvenous left ventricular lead placement had been unsuccessful surgical epicardial placement of the left

ventricular lead placement was a viable alternative. Surgical epicardial placement led to similar improvements to transvenous placement but in some variables the improvement was delayed compared to the transvenous approach. The mini thoracotomy group also had a higher peri-operative complication rate. Therefore form this study it has to be concluded that CRT via the transvenous route is still is the gold standard and that the mini thoracotomy route is an alternative in patients where the coronary sinus anatomy is unsuitable.

These three studies have improved our knowledge of the mechanism behind the improvements seen following cardiac resynchronisation therapy and how to maximise the improvements. They have provided valuable insight in to method to approach difficult patient groups such as non responders and patients with inappropriate coronary sinus anatomy. This information will enable physicians to individualise therapy for patients requiring cardiac resynchronisation therapy and therefore ensure we achieve the maximum benefit.

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Appendix 1

Methodology behind the forumale for Cardiac Power Output.

In systems with fluid flow, power is related to pressure and the flow rate. In the cardiovascular system the pressure is measured using the mean arterial pressure (measured in mmHg), and the flow rate by the cardiac output (measured in L/min). Hence when considering the cardiac system the formulae would be

Cardiac Power Output = Mean Arterial Pressure x Cardiac Output x K

Where K is the conversion factor to convert the product of mean arterial pressure and cardiac output to watts. The calculation of the conversion factor is as follows:

CPO = 1 mmHg x 1 L/min
Power: 1 W = 1 J/s = 1 N.m/s
BP: 1 mmHg = 133 N/m^2
Volume: 1 L = 10^{-3} m^3

Therefore
CPO = 1 mmHg x 1 L/min
= 133 N/m^2 x 10^{-3} m^3/min
= 133 x10^{-3} N.m/min
= 0.133 N.m/min
= 0.133 N.m / 60 s
= 0.133/60 N.m/s
= 0.00222 N.m/s
= 0.00222 J/s
= 2.22x10^{-3} W

Hence the conversion factor to convert CPO from (BP mmHg x CO L/min) to CPO in watts is

CPO W = MAP mm Hg x CO L/min x K, where K = 2.22x10^{-3}.

Appendix 2

The Cardiothoracic Centre - Liverpool NHS
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Thomas Drive
Liverpool
L14 3PE

CONSENT FORM (Version 2, Jan 5th 2004)

RESEARCH INTO BIVENTRICULAR PACING AT THE CARDIOTHORACIC CENTRE

Please initial box

1. I consent to the use of my "blood" for the purpose of this research. ☐
2. I confirm that I have read and understand the information sheet dated for the above study and have had the opportunity to ask questions. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time,without giving any reason, without my medical or legal rights being affected. ☐
4. I understand that sections of any medical notes may be looked at by responsible Individuals from the Cardiothoracic Centre or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
5. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of person taking consent (if different from researcher)	Date	Signature

1 for patient; 1 to be kept in hospital notes; 1 copy to the research labs

Appendix 3

Minnesota Living with Heart Failure Questionnaire.

Visit Date:
Patient Name:
Baseline test [ ], 1 week post test [ ], 6week post test [ ], 3months post test [ ], 6months post test [ ].

These questions concern how your heart failure (heart condition) has prevented you from living as you wanted during the last month. The items listed below describe different ways some people are affected. If you are sure an item does not apply to you or is not related to your heart failure, then circle 0 (No) and go on to the next item. If an item does apply to you, circle the number rating how much it prevented you from living as you wanted. Remember to think about ONLY THE LAST MONTH. *Did your heart failure prevent you from living as you wanted during the last month by:*

		No	**Very Little**				**Very Much**
1	Causing swelling in your ankles, legs, etc.?	0	1	2	3	4	5
2	Making the work around your house or yard difficult?	0	1	2	3	4	5
3	Making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
4	Making you sit or lie down to rest during the day?	0	1	2	3	4	5
5	Making you tired, fatigued, or low on energy?	0	1	2	3	4	5
6	Making your working to earn a living difficult?	0	1	2	3	4	5
7	Making your walking about or climbing stairs difficult?	0	1	2	3	4	5
8	Making you short of breath?	0	1	2	3	4	5
9	Making your sleeping well at night difficult?	0	1	2	3	4	5
10	Making you eat less of the foods you like?	0	1	2	3	4	5
11	Making your going places away from home difficult?	0	1	2	3	4	5
12	Making your sexual activities difficult?	0	1	2	3	4	5
13	Making your recreational pastimes, sports, or hobbies difficult?	0	1	2	3	4	5
14	Making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
15	Giving you side effects from medications?	0	1	2	3	4	5
16	Making you worry?	0	1	2	3	4	5
17	Making you feel depressed?	0	1	2	3	4	5
18	Costing you money on medical care?	0	1	2	3	4	5
19	Making you feel a loss of self-control in your life?	0	1	2	3	4	5
20	Making you stay in a hospital?	0	1	2	3	4	5
21	Making you feel you are a burden to your family or friends?	0	1	2	3	4	5