The effect of cardiac rehabilitation exercise training on left ventricular remodelling in patients with recent myocardial infarction

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Abstract

The present thesis examined the effect of cardiac rehabilitation (CR) exercise training on reverse left ventricular (LV) remodelling in a cohort of post-myocardial infarction (MI) patients with mildly abnormal LV ejection fraction (LVEF). Specifically, the thesis aimed to evaluate the effect of 10 weeks of exercise training on (1) the N-terminal fragment of the counter regulatory neurohormone brain natriuretic peptide (NT-pro-BNP), (2) LV structural and functional parameters through the use of conventional echocardiography, and (3) LV mechanics via the application of speckle tracking echocardiography (STE). Accordingly, a large cohort of patients completed a single longitudinal protocol to provide data for three separate experimental studies.

A number of cardiovascular adaptations were observed following completion of 10 weeks of CR exercise training. Firstly, an improvement in exercise capacity was evident. Secondly, study one demonstrated that resting NT-pro-BNP was reduced and that the acute increase in NT-pro-BNP observed following bouts of maximal and submaximal exercise may be attenuated. Thirdly, in study two, LV volumetric adaptation was evidenced by reduced LV end diastolic volume (EDV) and end systolic volume (ESV). Furthermore, a positive correlation between reduced resting NT-pro-BNP and reduced EDV provided an indication of the relationship between NT-pro-BNP and reverse LV volumetric remodelling. Finally, the main finding of study three was related to LV functional adaptation, indicated by a reduction in LV twist and twist velocity.

Collectively, findings from the three experimental studies presented in this thesis provide evidence of volumetric and functional reverse LV remodelling, further to 10 weeks of CR exercise training in post-MI patients. It is likely that these cardiac adaptations may contribute to the improved cardiovascular exercise capacity and reduced mortality commonly witnessed following CR exercise training in the post-MI population.
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Definition of terms

Afterload: the ‘load’ against which the LV must eject blood during systole

Brain natriuretic peptide (BNP): counter regulatory neurohormone cleaved from proBNP and released in response to cardiac myocyte ‘stretch’

Cardiac myocyte: myocardial muscle cell

Cardiac rehabilitation (CR): a multidisciplinary approach to restoration and improvement of physical, psychological and social function

Cardiopulmonary exercise test (CPEX): maximal cycle exercise test with ventilatory gas analysis

Chronic heart failure (CHF): diagnosis with underlying physiology of insufficient cardiac output to meet metabolic demand

Collagen: predominant protein in connective tissue

Coronary heart disease (CHD): reduced coronary artery blood flow due to atherosclerotic stenosis

Diastole: relaxation phase of the cardiac cycle between aortic valve closure and mitral valve closure

Endocardium: inner layer of LV myocardium

Epicardium: outer layer of the LV myocardium

Fibrosis: abnormal formation of fibrous tissue

Immunoassay: laboratory technique that makes use of the binding between an antigen and antibody to identify and quantify the specific antigen or antibody in a sample

Left ventricle (LV): myocardial chamber responsible for systemic circulation

LV apex: the tip of the LV, distal to the papillary muscles

LV base: superior portion of the LV between the papillary muscles and the mitral annulus

LV ejection fraction (LVEF, %): percentage of end diastolic volume ejected during systole

LV end diastolic volume (LVEDV, ml): volume of blood in the LV at end-diastole

LV end systolic volume (LVESV, ml): volume of blood in the LV at end-systole
LV hypertrophy: enlargement of the LV myocardium

LV mechanics: terminology describing the deformation of the LV during systole and diastole

LV remodelling: LV morphological change in health and disease

LV systolic dysfunction (LVSD): impairment of LV systolic function

LV twist (°): rotational deformation of the LV calculated by subtracting LV basal rotation from LV apical rotation

LV wall stress: LV wall stress = (pressure x radius)/wall thickness (La Place’s Law)

Myocardial extracellular matrix: non-cellular component of the myocardium consisting primarily of collagen

Myocardial infarction (MI): cardiac myocyte necrosis following ischemic insult

Myocardium: muscular tissue of the heart

Necrosis: cell death

N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP): biologically inactive N-terminal fragment of proBNP

Peak oxygen uptake (VO$_{2\text{peak}}$ ml.kg$^{-1}$.min$^{-1}$): highest O$_2$ uptake attained during exercise. Preferred to maximal oxygen uptake (VO$_{2\text{max}}$) in patient populations as a true VO$_{2\text{max}}$ is rarely achieved

Preload: cardiac myocyte stretch at end-diastole

Renin-angiotensin-aldosterone system (RAAS): neurohormonal system essential for the maintenance of fluid and sodium balance and cardiovascular hemodynamics

Reverse LV remodelling: any reversal of pathological alterations to LV mass, size, geometry and/or function, either spontaneously or in response to therapy

Speckle tracking echocardiography (STE): echocardiographic technique allowing the quantification of LV deformation by tracking myocardial ‘speckles’ through space and time

Stain rate (SR): the rate at which myocardial deformation occurs

Strain (%): normalised, dimensionless measure of myocardial deformation defined as the percentage change in length of a particular myocardial segment, relative to its end diastolic length
**Sympathetic nervous system:** branch of the autonomic nervous system responsible for vasoconstriction, increased heart rate and increased LV contractility and relaxation

**Systole:** contraction phase of the cardiac cycle between mitral valve closure and aortic valve closure

**Titin:** giant ‘spring like’ sarcomeric protein which acts as a store for systolic potential energy which is subsequently released as an aid to diastolic untwist

**Transthoracic echocardiography:** ultrasonic cardiac imaging technique by which the structure and function of the heart and great vessels can by noninvasively visualised
CHAPTER 1
General introduction
1.1 Study context

Cardiovascular diseases (CVD), including cardiac, cerebrovascular and peripheral arterial pathologies account for a global mortality of 17.3 million (World Health Organisation, 2012). Of these, coronary heart disease (CHD) is the leading single cause of death, with most recent figures indicating 7.25 million deaths per annum, accounting for 12.8% of all deaths (World Health Organisation, 2012). As a whole, in 2009, CHD cost the UK economy £6.7 billion, a quarter of which was due to direct health care costs (British Heart Foundation, 2012).

Myocardial infarction (MI) and angina are the most common presentations of CHD for which the development of atheroma in the coronary arteries is the predeterminate feature (British Heart Foundation, 2012). Acutely, treatment strategies for MI focus on myocardial reperfusion through the use of pharmacological fibrinolysis and primary percutaneous coronary intervention (PPCI) (O’Gara et al., 2013). Chronically, prevention of atherosclerotic disease progression and attenuation of adverse left ventricular (LV) structural and functional maladaptation, otherwise known as pathological LV remodelling, are the ultimate targets of a well established regime of cardiovascular medication and rehabilitation (Fihn et al., 2012).

A comprehensive post-MI cardiac rehabilitation (CR) programme constitutes a multidisciplinary approach to restoration and improvement of physical, psychological and social function. Patient education emphasises long-term disease self-management and secondary prevention (Buckley et al., 2013). As an integral component, appropriately prescribed exercise training has been shown to improve functional capacity (Lee et al., 2008, Giallauria et al., 2008, Zheng et al., 2008, Valkeinen et al., 2010) and reduce cardiovascular and all cause mortality in patients with MI (Lawler et al., 2011). A multifactorial mode of action is likely responsible, but the precise physiological mechanisms, and their relative contribution, remain to be confirmed. In addition to attenuated autonomic and neurohormonal activation, improvements in ventilatory efficiency, skeletal muscle metabolism and vascular endothelial function clearly improve functional capacity in this patient group, (Gielen et al., 2010). Furthermore, in combination with the direct myocardial effects demonstrated in a number of animal models (Kemi and...
exercise may favourably impact upon pathological LV maladaptation by reducing disease
specific systemic dysfunction (Haykowsky et al., 2011). Evidence of this clinically beneficial
LV adaptation, known as reverse remodelling, following CR exercise training in post-MI
patients is, however, inconclusive (Haykowsky et al., 2011). Moreover, the advent of timely and
effective treatment for acute MI has led to an increasingly prevalent population of MI survivors
with relatively preserved LV function (Furman et al., 2001, Kim et al., 2011b). The impact of
CR exercise training on LV remodelling has not been studied in this group.

The assessment of patient symptoms in an acute and chronic medical condition, such as post-MI
LV remodelling, provides useful, but subjective, information for the clinician. The ability to
quantify and monitor the effect of the disease objectively, however, is vital to successful
therapeutic management. Subsequently, the measurement of blood borne biomarkers and the
application of cardiovascular imaging, especially transthoracic echocardiography, are
considered important tools in the assessment of post-MI patients. Clinically, biomarkers and
echocardiography are integral to the process of differential diagnosis and are further utilised in
the ongoing evaluation of cardiac structure and function, to quantify the response to medical
intervention. Likewise, in clinical research, the assessment of outcome following therapeutic
intervention can be evaluated through the use of these techniques. Therefore, to establish the
effect of CR exercise training on LV remodelling, both biochemical and echocardiographic
assessment may prove useful. B-type natriuretic peptide (BNP), a counter regulatory
neurohormone released in response to LV dysfunction, is indicative of hemodynamic
compromise and LV remodelling (Lee and Tkacs, 2008). Measurement of this biomarker before
and after a CR exercise training programme may provide insight into neurohormonal status, and
thus a surrogate indication of reverse LV remodelling. Further, the use of conventional
echocardiography provides the opportunity to directly assess aspects of LV structural and
functional remodelling. Finally, the use of speckle tracking echocardiography (STE) to measure
LV mechanics may provide the medium through which components of functional LV
remodelling, which would be otherwise undefined with conventional echocardiographic methods, may be characterised.

1.2 Thesis Overview
Positive physiological adaptation following post-MI CR exercise training is well documented. The effect of this intervention specifically on LV structure and function, however, has not been unequivocally confirmed. Consequently, through the measurement of NT-pro-BNP, conventional echocardiographic indices and STE derived LV mechanics, the focus of the present thesis is to examine the ability of CR exercise training to facilitate reverse LV remodelling. Data was collected between September 2009 and December 2011 from a large cohort of post-MI patients, all of whom were eligible for the University Hospital, Coventry CR exercise programme. The collected data allowed completion of three separate investigations, each examining a different aspect of the reverse LV remodelling process.

Initially, in chapter two of this thesis, a full literature review explores the key concepts and existing evidence relating to the progression and reversal of post-MI LV remodelling. In particular, the influence of CR exercise training on this clinical condition is discussed. Further to an overview of the general methods employed in the collection of data for this thesis (chapter three), three experimental chapters are subsequently presented (chapters four to six), followed, in chapter seven, by an overall, integrated discussion of the findings. Limitations for all three experimental chapters are collectively addressed in chapter seven.
CHAPTER 2

Review of Literature
2.1 Introduction

The beneficial effects of CR exercise training in post-MI patients are relatively well documented including compelling evidence of improved functional capacity and ultimately reduced mortality (Lee et al., 2008, Giallauria et al., 2008, Zheng et al., 2008, Valkeinen et al., 2010, Lawler et al., 2011). Multiple physiological mechanisms likely contribute to these well established outcomes but it is evident from the literature that much remains to be understood, particularly in relation to cardiac adaptation. Whilst ventilatory, skeletal muscle and vascular endothelial adaptation have been consistently demonstrated (Gielen et al., 2010), the effect of CR exercise training on cardiac structure and function remains poorly characterised. The following literature review will first provide an overview of the pathophysiology of MI and the subsequent development and reversal of LV structural and functional remodelling. Secondly, the role of the cardiac biomarker B-type natriuretic peptide (BNP) in the evaluation and management of post-MI LV remodelling will be discussed, with an emphasis on the chronic utility of this indicator of myocardial dysfunction. Thirdly, echocardiographic parameters, both conventional and novel, will be examined in relation to the characterisation of post-MI structural and functional LV remodelling. Finally, prior to the introduction of the aims of this thesis, a full review of the literature pertaining to the effects of CR exercise training on BNP and LV remodelling will be presented.

2.2 Pathophysiology and treatment of myocardial infarction

The formation, evolution and rupture of an atherosclerotic lesion in the human coronary artery involves complex biomolecular and cellular processes (Standring, 2008). A detailed explanation of this phenomenon is out with the scope of this thesis, but a brief overview of the underpinning concepts is required as a background to MI and LV remodelling. Briefly, the development of coronary artery atherosclerosis is preceded by the consumption of an atherogenic diet, rich in cholesterol and saturated fat (Fuster, 2008). Glycation and oxidation of lipoprotein molecules contributes to increased inflammatory cytokine production, subsequent proliferation and
migration of smooth muscle cells and the growth of a lipid rich, potentially unstable
atherosclerotic plaque (Crawford et al., 2010). In the event of plaque rupture or erosion,
development of superimposed thrombosis and distal embolisation invariably results in
insufficient myocardial perfusion with subsequent anginal pain and myocyte necrosis (Hamm et
al., 2011). Plaque rupture and erosion is governed collectively by a multitude of structural,
physiological and biomolecular factors and is the predominant cause of MI (Yla-Herttuala et al.,
2011).

Ischemic heart disease (IHD) with the underlying pathophysiological mechanism of plaque
instability is initially classified with a working diagnosis of acute coronary syndromes (ACS).
Further clinical evaluation aims to establish a diagnosis of unstable angina, non-ST elevation
myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI). On admission
with acute chest pain and persistent ST-segment elevation of >20 min duration, patients are
likely to develop STEMI, with elevated cardiac troponin indicating irreversible cardiac myocyte
necrosis due to complete occlusion of an epicardial coronary artery (Steg et al., 2012). Rapid,
complete and sustained reperfusion by PPCI or fibrinolytic therapy is the primary objective in
these patients. Those without persistent ST-segment elevation may have more indeterminate
ECG changes as a result of a partially occlusive thrombus. In these patients, pharmacological
treatment initially aims to relieve ischemia. Subsequent determination of cardiac troponin will
confirm the diagnosis of NSTEMI in the presence of myocardial necrosis, or unstable angina in
its absence (Hamm et al., 2011).

Following cessation of the acute phase, MI can be characterised on the basis of the
transmurality of the infarction (figure 2.1). ST-elevation MI commonly results in a ‘full
thickness’, or transmural infarction, which extends through the myocardium from
subendocardium to subepicardium. Infarctions resulting in necrotic subendocardium and/or
intramural myocardium, without fully extending to the epicardium, are primarily a result of
subtotal coronary artery occlusion i.e. NSTEMI (Bonow et al., 2012). The extent of
transmurality, as a contributory factor to the overall size of the infarction, has significant bearing on LV systolic and diastolic performance and ultimately on myocardial recovery and LV remodelling in the chronic phase of MI (Fuster, 2008).

**Figure 2.1** Classification of myocardial infarction by transmurality. Dependant on the severity and duration of coronary artery occlusion, myocardial infarction may develop subendocardially, subepicardially, intramurally or transmurally. From (Study Blue Inc, 2012)

**2.3 Left ventricular remodelling**

With specific relation to MI, the following section will discuss the process of LV remodelling and the prognostic implications of this progressively detrimental maladaptation. In addition, section 2.3.4 will summarise the role of neurohormonal activation in chronic LV remodelling, prior to a full discussion of the counter regulatory neurohormone, BNP, in section 2.4. To conclude this section, the concept of reverse LV remodelling will be introduced.

**2.3.1 Introduction to the concept of left ventricular remodelling**

Pfeffer and colleagues (1985) first proposed the term ‘LV remodelling’ in the 1980’s to describe progressive LV dilation and impairment of cardiac function following chronic coronary artery occlusion. The term has since been applied to all aspects of LV morphological change in both health and disease (Hellawell and Margulies, 2012). Remodelling results from chronic alterations in hemodynamic loading conditions and is characterised by geometric and structural
changes. This results in altered myocardial architecture and LV chamber configuration with a subsequent impact upon function (Konstam et al., 2011, Sutton and Sharpe, 2000). It is now clear that the overarching pathological or physiological environment determines the nature in which the LV remodels and there is general acceptance for a system of classification (figure 2.2). With very few exceptions, development of concentric geometry/hypertrophy can be attributed to increased cardiomyocyte thickness in response to systolic pressure overload, whereas eccentric geometry/hypertrophy is caused by myocyte lengthening as an adaptation to volume overload (Gaasch and Zile, 2011, Carabello, 2012, Frohlich and Susic, 2012).

Simplistically, cardiomyocyte shape and sarcomere organisation is different in eccentric versus concentric hypertrophy; ‘long and thin’ with a ‘parallel arrangement’ in the former as opposed to ‘short and fat’ with a ‘series arrangement’ in the latter (Koitabashi and Kass, 2012).

Classification of LV remodelling is dependent on the measurement of a number of parameters, namely LV mass, LV volume and the relative wall thickness (RWT), as calculated by the ratio of LV wall thickness to chamber radius. Figure 2.2 depicts the interplay between these parameters and the resultant classification (Gaasch and Zile, 2011). The development of LV hypertrophy (i.e. increased LV mass) has important implications in the evolution of pathological LV remodelling.

**Figure 2.2** Classification of left ventricular remodelling. Progression to physiological or pathological remodelling/hypertrophy is determined by the interrelationship between end diastolic volume, left ventricular (LV) mass and relative wall thickness (RWT). LVH; left ventricular hypertrophy (From Gaasch and Zile, 2011).
2.3.2 Left ventricular hypertrophy in response to pathologic stimulus

In accordance with Grossman’s original theory of LV wall stress and hypertrophy (Grossman et al., 1975), increased intraventricular pressure is related to thickening of cardiac myocytes and thus the LV wall. Subsequently, when considering the relationship between wall stress, pressure, radius and wall thickness based on La Place’s Law (wall stress = (pressure x radius)/wall thickness), an increase in wall thickness has the compensatory effect of a reduction in LV systolic wall stress and thus mechanical normalisation (Levick, 2003). In recent years, however the hypothesis of adaptive/physiological hypertrophy in response to pathologic stimulus has been questioned (Opie et al., 2006). Animal and human studies examining the complex signalling pathways responsible for the hypertrophic response to a variety of pathological conditions have determined not only adaptive, but maladaptive molecular cascades (Sugden 2001; Baines and Molkentin 2005). Adaptive hypertrophy is characterised by myocyte survival whilst maladaptive hypertrophy features detrimental apoptosis, myocyte degeneration and fibrosis (Mann et al., 2012). In support of this hypothesis, Golia and colleagues (2011) showed that the LV hypertrophy associated with aortic stenosis, was in part related to apoptosis and subsequent myocardial fibrosis. Therefore, despite an increase in LV mass, which would hypothetically offset the imbalance in La Place’s law, the proportion of this which could be considered functionally beneficial was, in fact, inadequate to normalise wall stress and maintain LV function. The ‘quality’ of the hypertrophy i.e. physiologic versus fibrotic is therefore key to the maintenance or degeneration of LV function as opposed to hypertrophy per se. This molecular dichotomy has important implications in the development of LV remodelling following MI.

2.3.3 Left ventricular remodelling following acute myocardial infarction

The combined effects of increased volumes due to stretched and dilated infarcted tissue, and the volume and pressure overload in non-infarcted territories leads to the complex entity of post-MI remodelling (Opie et al., 2006). Following the initial insult of an acute MI, there ensues a cascade of molecular, cellular and interstitial perturbations which result in characteristic post-
MI structural remodelling and a subsequent progressive decline in function (Konstam et al., 2011). Initially, myocardial fibrosis occurs during repair of necrotic tissue with resultant non-contractile scar formation and an elongation and thinning in the infarct zone. An initially adaptive increase in LV blood volumes (and subsequently pressures) follows in an attempt to augment stroke volume and maintain appropriate cardiac output via the Starling Mechanism (Cohen et al., 2000). A gradual progression from an elliptical to a spherical configuration then becomes apparent as hypertrophic myocyte elongation in the noninfarcted zone, known as infarct expansion, leads to an increase in LV mass and an enlargement of the LV cavity (Mitchell et al., 1992, Mann et al., 2010). As a result of these changes, the performance of the LV is progressively impaired, exaggerated by loss of function in the pathologically hypertrophied myocytes and interstitial fibrosis with collagen deposition in the extracellular matrix of the noninfarcted zone (figure 2.3) (Konstam et al., 2011, Mann et al., 2012). Essentially, progression to a more spherical geometry reduces contractile efficiency as cardiomyocytes are required to shorten more to achieve the same ejected net volume (Koitabashi and Kass, 2012).

Both the extent of structural LV remodelling and the subsequent reduction in LVEF are directly proportional to the infarct size (McKay et al., 1986), underlining the imperative for rapid coronary artery revascularisation and myocardial reperfusion. Ultimately, continuation of the LV remodelling process will result in the progressive accumulation of pulmonary and peripheral oedema due to the inability of the decompensated heart to maintain appropriate cardiovascular hemodynamics. The subsequent presentation of breathlessness, lethargy and impaired functional capacity, define the progression from asymptomatic post-MI LV dysfunction to a diagnosis of chronic heart failure (CHF). With appropriate medical management, CHF can to an extent be stabilised, albeit it a temporary reprieve from the ‘vicious circle’ of clinical heart failure mediated by persistent neurohormonal overexpression. With this progressive decline in LV function, LVEF provides a global measure of the degree of dysfunction. With the intricate relationship between gross LV structure and function, however, it is likely that the subtlety of
the alteration to LV mechanical function may not be ‘captured’ by this measure. Therefore, in addition to the assessment of LV structure and LVEF in the management of LV remodelling, alternative imaging modalities may complement conventional echocardiography.

**Figure 2.3** Evolution of pathological left ventricular remodelling following myocardial infarction. Following acute myocardial infarction (A), thinning and elongation of fibrotic scar occurs in the infarct zone (B). Subsequently, myocyte hypertrophy and increased interstitial collagen (C) drive the progression of left ventricular dilation and the transition from an elliptical to spherical configuration (D). (Adapted from Konstam, Kramer et al., 2011)

### 2.3.4 Left ventricular remodelling and neurohormonal activation

Further to the specific infarct related geometrical changes, the progression of LV remodelling is mediated by the overexpression of compensatory neurohormonal mechanisms (Mann and Bristow, 2005). Sympathetic outflow is increased both by attenuated inhibition (baroreceptors and mechanoreceptors) and increased excitation (peripheral chemoreceptors and metaboreceptors) of the adrenergic nervous system, such that cardiovascular hemodynamics may be maintained and functional capacity preserved (Standring, 2008, Floras, 2003). The renin angiotensin aldosterone system (RAAS) is also activated which, in tandem with the increased adrenergic response, facilitates maintenance of cardiac output through sodium and water retention, peripheral arterial vasoconstriction, increased contractility and inflammatory cytokine activation (responsible for cardiac repair) (Fuster, 2008). Ultimately, however, persistent over
expression of these and other biologically active compensatory molecules contributes to the progression of LV remodelling by virtue of the detrimental effect they have on cardiac myocytes and the extracellular matrix (Bonow 2012). To counteract these deleterious effects, counterregulatory neurohormones such as the natriuretic peptides (e.g. B-type natriuretic peptide (BNP), atrial natriuretic peptide (ANP)) are excreted in an effort to maintain sodium and water homeostasis (Lee and Tkacs, 2008). A full discussion of BNP will be provided in section 2.4.

2.3.5 Prognostic implications of left ventricular remodelling
The development of structural and functional LV remodelling is strongly linked to adverse outcome. Death and hospitalisation from chronic heart failure (CHF) is closely related to decreasing LVEF and increasing ESV, EDV and infarct length (Solomon et al., 2005) (figure 2.4). The specific geometry of LV remodelling is further predictive. For example, it has been reported that those with hypertensive concentric hypertrophy have the highest incidence of cardiac events and premature mortality (Koren et al., 1991). This, it has been proposed, may be related to prolongation of action potentials, increased dispersion of refractoriness, and lowering of the ventricular fibrillation threshold (Kahan and Bergfeldt, 2005). Furthermore, independently, and irrespective of aetiology, both LV mass and LV hypertrophy are predictors of cardiovascular morbidity and mortality (Verma et al., 2008, Foppa et al., 2005). This observation extends to a number of pathological contexts. For example, a two to four fold increase in risk of death or nonfatal complications has been observed where LV hypertrophy exists in conjunction with a diagnosis of hypertension, CAD or uncomplicated MI (Vakili et al., 2001). More specifically, in high risk post-MI patients (LVEF <35%), Verma and colleagues (2008) reported that the risk of death or the composite end point of death from cardiovascular causes, reinfarction, heart failure, stroke or resuscitation after cardiac arrest was lowest for patients with normal geometry and increased progressively with concentric remodelling, eccentric hypertrophy and concentric hypertrophy. With such profound association with
prognosis, the reversal of LV remodelling is an attractive target for medical intervention and other potentially successful therapeutic strategies such as CR exercise training (Haykowsky et al., 2011) which will be discussed in this review in due course.

Figure 2.4 Prognostic implications of ejection fraction, end diastolic volume and infarct segment length. Following myocardial infarction, the combined end point of death and hospitalisation from heart failure (HF) incrementally increases with declining ejection fraction, increasing end diastolic volume and increasing infarct segment length. (From Solomon, Skali et al. 2005 reprinted with permission in Konstam, Kramer et al., 2011).

2.3.6 Reverse left ventricular remodelling: an introduction

Reverse remodelling was first documented in a cardiac myoplasty study (Kass et al., 1995) where latissimus dorsi muscle was wrapped around the hearts of dilated cardiomyopathy patients and chronically paced in synchrony with ventricular systole. Favourable adaptation to end systolic and end diastolic pressure volume relationships were witnessed with a corresponding improvement in ejection fraction. Of particular interest was the persistence of these changes following cessation of pacing, indicating a chronic adaptation associated with reduced chamber dimensions i.e. ‘reverse remodelling’. Subsequently, reverse LV remodelling has been defined in a variety of ways, most commonly in terms of reductions in LV volumes, dimensions and mass i.e. structural reverse remodelling (Shah and Solomon, 2010, Mann et al.,
Generally, any reversal of pathological alterations to LV mass, size, geometry and/or function, either spontaneously or in response to medical therapies, is classed as reverse remodelling (Hellawell and Margulies, 2012). Whilst there is no standardised convention as to what constitutes clinically significant reverse LV remodelling, it is clear from the literature that structural rather than functional changes provide superior correlation with clinical outcomes and are, accordingly, more commensurate with the term (Konstam et al., 2011, Verma et al., 2008, Cheng and Vasan, 2011, Gaasch and Zile, 2011). The assessment of reverse remodelling with structural parameters, therefore, has obvious clinical rationale. However, the relative paucity of data in relation to reverse functional remodelling may also represent the lack of sensitivity and reliability of conventional functional echocardiographic parameters i.e. LVEF (Feigenbaum et al., 2012). Consequently, there may be the opportunity to classify functional reverse remodelling using alternative echocardiographic techniques such as speckle tracking echocardiography (STE). This emerging technique, which will subsequently be addressed in section 2.5, allows the detailed quantification of three dimensional LV deformation and may provide more accurate characterisation of global and regional LV function.

**2.3.7 Reverse left ventricular remodelling – medical strategies**

Mechanical, electrophysiological and pharmacological therapies have proven effective in attenuating and reversing LV remodelling in post MI and CHF patients (Mann et al., 2012, Koitabashi and Kass, 2012). By mechanically ‘unloading’ the left ventricle through the use of ventricular assist devices (LVAD) in heart transplant candidates, the reversal of a myriad of biomolecular maladaptations can result in improved LV dimensions, LV function and neurohormonal status (Delgado et al., 1998, Zafeiridis et al., 1998, Ambardekar and Buttrick, 2011). Interestingly, studies have shown that right ventricular myocyte size is unaffected by LVAD therapy which has led authors to conclude that reverse remodelling with LVAD relates directly to ventricular unloading rather than the concurrently observed improvement in neurohormonal control (Barbone et al., 2001, Koitabashi and Kass, 2012).
A second invasive option in severe HF addresses the electromechanical dyssynchrony present in 30-60% (dependant on diagnostic criteria) of heart failure patients (Hawkins et al., 2006). Independent of coexisting risk factors, this dyssynchrony can have a significant impact on LV remodelling, morbidity and mortality (Cho et al., 2012, Kashani and Barold, 2005, Chalil et al., 2007). Biventricular pacing, otherwise known as cardiac resynchronisation therapy (CRT), can augment LV contractile performance via the acute and chronic restoration of normal synchronous contraction (Cho et al., 2012). This approach can lead to reverse structural and functional LV remodelling (Sutton and Keane, 2007, St John Sutton et al., 2009) and ultimately improvements in long term survival by influencing the electrophysiological, molecular and cellular properties of the LV (Moss et al., 2009, Daubert et al., 2009).

Pharmacotherapy provides a less invasive and more widely applicable strategy for the manipulation of LV remodelling. Both β-adrenergic receptors (β-ARs) and the renin-angiotensin-aldosterone system (RASS) are activated in response to the hemodynamic stress associated with MI. Whilst acutely beneficial, the detrimental chronic adaptations from activation of these systems directly contributes to adverse LV remodelling through β-AR induced pathologic myocellular toxicity and RASS induced cardiac fibrosis, cellular necrosis and cardiomyocyte hypertrophy (Gray et al., 1998, Solomon et al., 2011). β-blockade has clearly been shown to reverse remodel the LV as evidenced by significant reductions in indexed LVEDV and LVESV and improvements in LVEF (MERIT-HF Study Group, 1999, McKelvie et al., 1999). The mechanisms responsible are still poorly understood but may include improvements in β-AR function, energy utilisation and calcium handling (Lowes et al., 2002). Likewise, angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB) can prevent the progression of LV hypertrophy and dilation, primarily by blocking relevant signalling pathways and additionally by enhancing nitric oxide (NO) production, attenuating β-adrenergic signalling and reducing myocardial collagen content (Koitabashi and Kass, 2012, St John Sutton et al., 2003). Up-regulated aldosterone receptors on cardiac myocytes can also be blocked with the potassium-sparing diuretics Spironolactone and...
Eplerenone, thus reducing fibrosis, improving cardiac function and augmenting the effects of ACE inhibitors in animal models (Fraccarollo et al., 2003). Not only has reverse remodelling been reported with these agents, but clear correlation between their anti-remodelling effects and all cause mortality and HF hospitalisation has been demonstrated (Konstam et al., 2011).

In relation to patients with mildly abnormal LVEF following MI, pharmacological therapy is the most utilised medical strategy. Whilst impressive reverse remodelling results have been demonstrated with cardiovascular medication, these therapies are not without risk and/or adverse side effects (Messerli et al., 2008). Furthermore, intolerance and contraindication to cardiovascular medication are both well documented and up to 47% of patients are non-compliant with their prescribed medication regime (Naderi et al., 2012, Messerli et al., 2008). The potential, therefore, for complementary, or indeed replacement therapies in the treatment of LV remodelling is of significant clinical interest. In particular, any intervention that has the potential to contribute to normalisation of autonomic and neurohormonal overexpression may contribute to a reverse LV remodelling effect, independent of pharmacology. One such intervention is exercise training (Gielen et al., 2010)

2.4 Neurohormonal activation and left ventricular remodelling – B-type natriuretic peptide

Throughout the continuum of post-MI LV remodelling, the natriuretic peptides, in particular BNP, have a pivotal role, both physiologically as a counterregulatory mechanism (Lee and Tkacs, 2008) and medically as a diagnostic and prognostic tool (McMurray et al., 2012). It is the intention of the following section to provide an overview of the pathophysiology of BNP, an insight into its general clinical utility and specifically a perspective on its relationship with LV remodelling.
2.4.1 The biochemistry and physiological role of B-type natriuretic peptide

The natriuretic peptide family comprises three peptides: atrial natriuretic peptide, B-type natriuretic peptide and C-type natriuretic peptide. All are tissue specific, uniquely regulated and contribute to plasma volume homeostasis through potent natriuretic, diuretic and vasodilating actions (Levin et al., 1998). Atrial and B-type natriuretic peptides are secreted from atrial and ventricular myocytes as biologically active amino acid hormones whereas C-type natriuretic peptide is synthesised as an amino acid precursor protein, and secreted predominantly by vascular endothelial cells (Lee and Tkacs, 2008). The human BNP gene is located on chromosome 1 and encodes the 108 amino acid prohormone proBNP (Hall, 2004). Through the action of the proteolytic enzyme furin, proBNP is intracellularly cleaved to form the biologically active 32-amino acid hormone BNP and the inactive 76-amino acid N-terminal fragment NT-pro-BNP. For the remainder of this thesis, the abbreviations BNP and NT-pro-BNP will be used independently when referring to the results of individual studies or for the biological action of the neurohormone. However, for simplicity, the term NT-pro-BNP will be adopted for the collective description of data from a number of trials and for the general discussion of the biomarker. This simplification is justified on the basis of research increasingly favouring the measurement of NT-pro-BNP over BNP. Both have been shown to provide similar diagnostic accuracy for HF (Richards et al., 2006) with NT-pro-BNP offering the advantage of superior sample stability (Yeo et al., 2003, Downie et al., 1999).

Initially isolated in the porcine brain, BNP is also found in the human brain but is present to a much greater extent in cardiac myocytes (Hall, 2004). In a healthy heart, there is greater storage of BNP in atrial tissue than ventricular, although ventricular BNP expression is significantly upregulated, more so than atrial, in response to myocardial stress (Luchner et al., 1998). Acute and chronic myocyte ‘stretch’ is the predominant stimulus for activation of the proBNP gene and subsequent BNP secretion, most commonly in response to high intra-ventricular filling pressures and volume overload (Ruskoaho, 2003, McGrath et al., 2005, Suttner and Boldt, 2004). In addition, myocardial hypoxia is now known to promote BNP secretion, independent
of myocyte stretch (Hopkins et al., 2004). Secretion of BNP is constitutive and increased demand is satisfied by rapid release from limited atrial and ventricular storage which is ultimately replenished through transcriptional synthesis (McGrath and de Bold, 2005). Chronically, in the context of cardiovascular pathology, de novo synthesis is enhanced to sustain increased secretion with the cardiac ventricles becoming the predominant source (Hall, 2005, Lee and Tkacs, 2008). In response to the increased LV wall stress associated with myocardial dysfunction (i.e. MI), the function of increased natriuretic peptide secretion is to combat the progressively deleterious effects of neurohormonal and autonomic over-activation. The mechanisms by which this is achieved can be broadly grouped into cardiovascular, renal and central nervous system (figure 2.5) (Levin et al., 1998). In combination, these act to reduce total systemic vascular resistance and plasma volume in an attempt to restore normal myocardial loading conditions. Whilst all the biological processes indicated in figure 2.5 are not fully discussed in the body of this review, the schematic provides a comprehensive overview from which key concepts are identified, and subsequently described in full.

**Figure 2.5** The physiological effects of B-type natriuretic peptide. Increased natriuretic peptide secretion reduces blood pressure and plasma volume through coordinated actions in the brain, adrenal gland, kidney, and vasculature. The minus sign indicates that a decrease in plasma volume leads to a decrease in venous return, which in turn decreases the secretion of the natriuretic peptides. URO, urodilatin; NEP, neutral endopeptidase; CNP, C-type natriuretic peptide; NPR-A, NPR-B, and NPR-C, natriuretic peptide receptors A, B, and C, respectively; AVP, arginine vasopressin; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; \( U_{Na}\), urinary sodium excretion; UV, urinary volume; BP, blood pressure. The receptors that mediate the functions of the natriuretic peptides are indicated in brackets. (From Levin and Gardner, 1998).
Through a complex sequence of biochemical mechanisms, natriuretic peptides have a profound effect on intracellular calcium handling (Suttner and Boldt, 2004). This results in a multitude of cardioprotective responses including improved myocardial relaxation, vasodilation of vascular smooth muscle and suppression of sympathetic nervous system activity (Lee and Tkacs, 2008). Altered calcium handling also reduces the influence of other intrinsically linked regulatory systems such as the renin-angiotensin-aldosterone system (RAAS), reducing vasoconstriction and sodium and water retention. Furthermore, natriuresis and diuresis are promoted through the direct action of natriuretic peptides on the kidneys. Glomerular filtration rate is known to increase in response to natriuretic peptide mediated dilation of afferent renal arterioles and a corresponding constriction of the efferent arterioles (Marin-Grez et al., 1986). Finally, the diuretic and natriuretic effects of the peptides on the kidneys appear to be augmented by the central inhibition of salt and water appetite (Blackburn et al., 1995, Burrell et al., 1991). The intrinsic physiological role of BNP and its association with hemodynamic health has established this natriuretic peptide as a widely clinically utilised cardiac biomarker.

2.4.2 Clinical Utility and prognostic implications B-type natriuretic peptide

The measurement of NT-pro-BNP has utility in a variety of clinical settings and across the spectrum of cardiac diseases although its potential use as a therapeutic measure in CR exercise training programmes remains to be established. The greatest utility is currently in the diagnosis and management of CHF patients, an understanding of which provides relevant background to underpin the discussion of its application in patients with recent MI.

The diagnostic utility of resting NT-pro-BNP measurement in acutely dyspnoeic patients has been confirmed in several landmark studies, particularly in the presence of diagnostic uncertainty (Maisel et al., 2002, Januzzi et al., 2005). When compared to clinical judgement alone, the measurement of NT-pro-BNP demonstrates greater accuracy in the diagnosis or exclusion of acute HF in emergency departments. As such, international guidelines advocate
NT-pro-BNP measurement in this setting (Hunt et al., 2009, McMurray et al., 2012, Great Britain. NICE, 2010). Raised NT-pro-BNP has also been shown to be incrementally associated with poor prognosis and adverse outcomes in CHF, and as a predictor of mortality consistently outperforms other more conventional measures such as LVEF and NYHA class (Maisel et al., 2004, Kirk et al., 2004, Bettencourt et al., 2004, Masson et al., 2008). Finally, for the prediction of mortality or need for urgent transplantation in advanced HF, the measurement of NT-pro-BNP has also been proven to be more robust in comparison to the accepted measures of \( \text{VO}_2 \text{peak} \), blood urea nitrogen, pulmonary capillary wedge pressure and systolic blood pressure, (Sachdeva et al., 2010).

Serial measurement of NT-pro-BNP also has an emerging role in guiding effective medical therapy for CHF. Several studies have demonstrated favourable outcomes with aggressive titration of pharmacological therapy, in conjunction with standard care, where the explicit intention of treatment has been a targeted reduction in NT-pro-BNP (Januzzi et al., 2011). Meta-analyses have suggested potential reductions in mortality when adopting this approach and a reduction in NT-pro-BNP is thus considered an important therapeutic target (Felker et al., 2009, Porapakkham et al., 2010). It is likely that this relates to the level of NT-pro-BNP expression being representative of general hemodynamic status, and the emerging data has begun to establish a link between reduced NT-pro-BNP and improvements in parameters of structural and functional reverse LV remodelling (Weiner et al., 2013, Januzzi, 2012). This serial approach to measurement could potentially be adopted in CR exercise programmes as an additive measure of clinical and therapeutic outcome in CHF and IHD. The addition of this measure to the standard, sub-maximal CR exercise assessment may provide valuable evidence of the true clinical worth of CR.

The utility of resting NT-pro-BNP measurement in the management of ischemic heart disease (IHD) has also been extensively studied. When measured on presentation, NT-pro-BNP does not appear to be sufficiently discriminatory to diagnose MI (Bhardwaj et al., 2011, Haaf et al.,
2011), but values at this time point or immediately following MI, are strongly predictive of long
term cardiovascular outcome and mortality (de Lemos et al., 2001, James et al., 2003, Kim et
al., 2011b). Furthermore, in patients referred for assessment of IHD symptoms, and in
populations of stable CHD patients with previous MI, angiographically documented CHD or
exercise induced ischemia, raised NT-pro-BNP is similarly predictive, independent of systolic
or diastolic dysfunction on echocardiography (Bibbins-Domingo et al., 2007, Kragelund et al.,
2005). Independent of the predominant NT-pro-BNP stimulus of LV stretch, myocardial
hypoxia also mediates NT-pro-BNP secretion. In the context of acute MI, therefore, it is likely
that both mechanisms contribute to raised NT-pro-BNP (Hall, 2005). It is less clear in chronic
stable, asymptomatic CHD what the mechanisms for continued elevation may be, but
subclinical, undetectable hypoxia and/or LV dysfunction may be responsible (Bibbins-Domingo
et al., 2003). Irrespective of the mechanism, raised NT-pro-BNP through the spectrum of acute
and chronic MI is highly prognostically significant (Kragelund et al., 2005, Kim et al., 2011b),
further indicating the potential of a role for serial measurement in CR exercise programmes.
This approach could provide CR professionals with an objective means of assessing progress
over the course of CR and could even identify those who are in need of further medical
intervention.

2.4.3 Summary of post-MI left ventricular remodelling and B-type natriuretic peptide
Myocardial infarction can lead to progressive alteration in LV geometry with subsequent loss of
systolic and diastolic function. This process, known as LV remodelling, is chronically driven by
neurohormonal overexpression and is an attractive target for medical intervention by virtue of
its prognostic significance. As NT-pro-BNP provides an insight into the hemodynamic status of
the LV, it may indirectly reflect LV remodelling, or indeed reverse remodelling. Reverse LV
remodelling has been successfully attributed to several medical therapies, with the resultant
structural changes being relatively well defined. In contrast, however, functional reverse
remodelling is poorly characterised, potentially as a result of the historical lack of a sufficiently
sensitive and non-invasive means of measurement. It is interesting to note that independently or collectively, cardiac biomarkers and echocardiography are not routinely utilised to evaluate the clinical outcome of CR exercise training programmes despite the existence of significant potential in this area.

2.5 Left ventricular mechanics

The concept of LV mechanics, whilst not new, has more recently come to prominence with advancing imaging technology (Mor-Avi et al., 2011). As alluded to in previous sections, whilst the assessment of gross structure with conventional echocardiography provides valuable clinical information, the sensitivity of these measurements may be insufficient to characterise the subtleties of LV systolic and diastolic function. The following review sections provide an understanding of the architectural and deformational characteristics of the LV and their collective classification as components of LV mechanics. In line with the theme of this literature review, the pathological effects of heart disease on LV mechanics will be reviewed prior to a discussion of the significance of LV mechanics in the study of pathological remodelling and therapeutic reverse remodelling in the patient with recent MI.

2.5.1 Myocardial architecture and deformation

The myocardium has a transmural laminar structure created by the adhesion of adjacent cardiac myocytes with collagen. These structures are typically four cells thick and are separated by cleavage planes (Sengupta et al., 2006b). In a transmural continuum, obliquely wound fibres progress from a left handed helix, with an angle of approx. -60°, in the subepicardium, to a right handed helix, with an angle of approx +60°, in the subendocardium (figure. 2.6). Consequently, mid wall fibres are circumferentially aligned. Geometric configuration resembles two oppositely wound and overlapping coiled springs with clockwise descending and anticlockwise ascending loops of myofibres (Sengupta et al., 2007).
Figure 2.6 Schematic of the transmural and helical fibre arrangement of the myocardium. Myocytes are arranged in cleavage planes and progress transmurally from a -60° left handed helix in the subepicardium, to a 90° horizontal alignment in the mid myocardium and a +60° right handed helix in the subendocardium (left panel) (from Sengupta, Krishnamoorthy et al., 2007). The subsequent arrangement of myofibres resembles two oppositely wound and overlapping coiled springs resulting in counter clockwise rotation at the apex and clockwise rotation at the base during systole (right panel) (from Nakatani, 2011).

The complex multidirectional deformation of the LV during systole can, in part, be explained by this intricate fibre arrangement and the accompanying sequence of electrical activation.

Depolarisation begins subendocardially in the right handed helix near the apical septum and graduates in a clockwise direction along the orientation of the muscle fibres from apex to base and from the subendocardium to the subepicardium (Scher, 1995). Subsequently, repolarisation occurs in reverse i.e. base to apex (Opthof, 2006). The anisotropic nature of the myocardium dictates that the propagation velocity of the electrical impulse is faster along fibres (apex to base), rather than across fibres (endocardium-epicardium) (Punske et al., 2005), hence the following sequence of mechanical activation. Mechanical activation of the LV follows the apico-basal trajectory of electrical depolarisation, in the direction of the alignment of myocytes which are limited to contraction along their long axis (Spotnitz, 2000).

During the isovolumic period of systole, shortening of the subendocardial fibres occurs simultaneously with a corresponding stretching of the subepicardial fibres. This results in
ventricular narrowing and elongation and a brief apical clockwise and basal counter-clockwise rotation around the longitudinal LV axis when viewed from the apex (Buckberg et al., 2011) (figure 2.7). Epicardial stretching is a vital component of the intrinsic determination of systolic ejection force, by way of the stretch activation mechanism (Campbell and Chandra, 2006). Thereafter, the onset of systolic ejection coincides with the initiation of subepicardial and continuation of subendocardial contraction which results in a global reduction in ventricular cavity dimensions, in particular longitudinal shortening (Sengupta et al., 2007). The greater and dominant torque produced by the larger radius of the epicardial helix results in a rapid counter-clockwise rotation at the apex and the reciprocal at the base (Buckberg et al., 2011) (figure 2.7). The resulting ‘wringing motion’ during ejection is known as ‘LV twist’. This mechanism facilitates efficient contraction through the generation of high intraventricular systolic pressures with minimal fibre shortening thus minimising myocardial energy expenditure and O$_2$ demand (Bloechlinger et al., 2011). The integrity of this physical process is pivotal to the generation of systolic contraction, which naturally provides rationale for the measurement of this motion in the evaluation of functional LV remodelling and reverse remodelling.

Figure 2.7 Generation of left ventricular twist during systole. Contraction of opposingly aligned subepicardial and subendocardial fibres results in the generation of rotational torque. The subendocardial radius is greater than the subepicardial radius ($r_2 > r_1$) resulting in greater rotational torque in the subepicardium compared to the subendocardium ($RT_2 > RT_1$). The result is clockwise rotation at the base and counterclockwise rotation at the apex during systole. (from Nakatani, 2011)
During isovolumic relaxation and early diastole, the subendocardial helix relaxes from apex to base and the subepicardial helix vice-versa causing the LV to lengthen and widen. This opposing relaxation sequence causes a negative intraventricular apex to base pressure gradient resulting in diastolic suction (Sengupta et al., 2006a). Furthermore, potential energy stored, during deformational shearing of subendocardial fibres during systolic LV wall thickening, is released during rapid early diastolic ‘untwist’, thus enhancing elastic recoil and ventricular filling (Sengupta et al., 2008b). As such, each diastolic untwist is heavily influenced by the nature of the preceding systolic twist (Notomi et al., 2006, Notomi et al., 2008) to which a number of mechanisms are known to contribute including compression of ‘spring like’ sarcomeric proteins such as titin (LeWinter and Granzier, 2010). Collectively, the multidirectional deformation of the LV over the course of the cardiac cycle has become known as LV mechanics and, as such, this terminology will be adopted for this thesis.

2.5.2 Left ventricular mechanics – strain and strain rate
Myocardial strain and shear strain are normalized, dimensionless measures of deformation defined as the percentage change in length of a particular myocardial segment, parallel to a given line in the former and perpendicular in the latter (Geyer et al., 2010). The coordinated electrical and mechanical activation of the obliquely wound laminar myofibres dictates deformation (strain) in 3 planes: circumferential shortening (-ve strain), longitudinal shortening (-ve strain) and radial thickening (+ve strain) (Dandel and Hetzer, 2009) (figure 2.8). The rate at which the deformation occurs is termed strain rate (SR). By definition, shear strain refers to myofibre distortion associated with the sliding of the transmural cleavage planes over one another, the consequence of which is the conversion of 15% myocyte shortening into 40% thickening and >60% volume ejection in a healthy heart (Covell, 2008). Radial thickening is predominantly achieved through the interaction between myocardial planes rather than through myocyte contraction per se (Rademakers et al., 1994, Stoylen, 2013). Longitudinal LV shortening, or atrial-ventricular plane displacement, describes the movement of the base towards
the apex during systole which accounts for ~60% of SV, the remainder being achieved through radial thickening and LV twisting (Carlsson et al., 2007, Esch and Warburton, 2009). With such an intricate dependency between myocardial architecture and function, cardiac pathology is likely to interfere with normal LV mechanics.

![Image](image.png)

**Figure 2.8** Left ventricular mechanics. Myocardial deformation in three planes; longitudinal, circumferential and radial (from Peterson, Forder et al., 2011 adapted with permission from D’hoode, Heimdal et al., 2000).

### 2.5.3 Cardiovascular pathology and left ventricular mechanics

The effects of the full spectrum of cardiovascular pathologies on LV mechanics are yet to be fully described. Although the primary pathological focus of this review is MI, a brief overview of the literature pertaining to the effects of other common cardiac pathologies on LV mechanics will first be provided, to identify the key mechanisms relevant to MI. Many authors have examined the extent to which LV mechanics are altered with pathology, and whilst this area is incompletely understood, it is clear that the site and transmurality of myocardial disease dictate the severity of LV mechanical impairment and the development and progression of diastolic and/or systolic dysfunction. In general, the subendocardium, which governs longitudinal mechanics, is the most susceptible to myocardial disease (Feigenbaum et al., 2012). The mid-myocardial and epicardial walls, and therefore circumferential strain and twist, may initially be unaffected, although may increase to compensate for loss in subendocardial function (Geyer et al., 2010). Accordingly, a compensatory increase in LV twist maintains systolic function in
diabetics, for example, where preclinical subendocardial microvascular disease is thought to be responsible for reduced longitudinal strain (Shivu et al., 2009, Nakai et al., 2009, Ng et al., 2009). Likewise, in the early stages of hypertensive heart disease, patients with a component of adaptive cardiac hypertrophy and normal LVEF, also exhibit reduced longitudinal strain whilst circumferential strain, radial strain and twist are initially unaffected (Chen et al., 2007, Kang et al., 2008). However, with a coexistent increase in myocardial stiffness, hypertensive heart disease may be associated with a loss of early diastolic longitudinal relaxation, a progressive delay in LV untwisting (directly correlated to extent of LVH) and increased LV filling pressures (Geyer et al., 2010, Takeuchi et al., 2007b). With advancing disease, maladaptive transmural fibrosis in concentric remodelling and hypertrophy is associated with reduced circumferential and radial strain, a compensatory increase in LV twist and untwisting rate, and commonly a supranormal LVEF (Ahmed et al., 2012). Ultimately, however, depression of twist and untwist parameters, and thus systolic function, is inevitable with progression to eccentric hypertrophy (Cameli et al., 2012).

As previously described, fibre orientation plays a significant role in governing LV mechanics (Dandel and Hetzer, 2009). With increasing sphericity (eccentric remodelling/hypertrophy), such as in dilated cardiomyopathy (DCM), transmural fibre angle progressively shifts from an oblique to transverse alignment resulting in global impairment of systolic and diastolic mechanics (Nakatani, 2011, Zeng et al., 2009, Meluzin et al., 2009). Essentially, the progressive departure from an oblique orientation decreases, by approximately half, atrio-ventricular plane displacement, which in a healthy LV accounts for 60% of SV (Carlsson et al., 2007). Accordingly, in DCM, peak LV twist is impaired in proportion to LVEF (Kanzaki et al., 2006) and impairment of longitudinal parameters appears to correlate directly with severity of symptoms (Jasaityte et al., 2009). Table 2.1 summarises changes in LV mechanics observed across the HF population (Geyer et al., 2010). As displayed, subendocardial, subepicardial or transmural dysfunction dictates the extent of longitudinal, circumferential, radial and torsional impairment, and consequently the presentation of systolic and/or diastolic heart failure.
Table 2.1 Classification of left ventricular mechanics in heart failure.

<table>
<thead>
<tr>
<th>Functional impairment</th>
<th>Predominant subendocardial dysfunction</th>
<th>Predominant subepicardial Dysfunction</th>
<th>Transmural dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal mechanics</td>
<td>Marked impairment</td>
<td>Preserved/minimal impairment</td>
<td>Marked impairment</td>
</tr>
<tr>
<td>Circumferential mechanics</td>
<td>Preserved</td>
<td>Marked impairment</td>
<td>Marked impairment</td>
</tr>
<tr>
<td>Radial mechanics</td>
<td>Preserved/minimal impairment</td>
<td>Minimal impairment</td>
<td>Marked impairment</td>
</tr>
<tr>
<td>Torsional mechanics</td>
<td>Minimal impairment</td>
<td>Marked impairment</td>
<td>Marked impairment</td>
</tr>
<tr>
<td>Global LVEF</td>
<td>Preserved/minimal impairment</td>
<td>Preserved/minimal impairment</td>
<td>Marked impairment</td>
</tr>
<tr>
<td>Diastolic filling pressures</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Clinical syndrome</td>
<td>Diastolic HF</td>
<td>Diastolic HF</td>
<td>Systolic HF</td>
</tr>
</tbody>
</table>

The extent to which left ventricular function is impaired, and the subsequent presentation of systolic or diastolic heart failure (HF), is related to the transmurality of the pathological dysfunction. (Adapted from Geyer, Caracciolo et al., 2010).

2.5.4 Left ventricular mechanics in myocardial infarction and remodelling

Following MI, as in HF above, the extent to which LV mechanics are impaired is predominantly dictated by transmurality of infarct. Subendocardial infarctions with preserved LVEF, result in reduced longitudinal and radial strain, however, have little, measurable effect on circumferential strain or twist mechanics (Takeuchi et al., 2007a). Infarcts extending to the midwall and subepicardium result not only in reduced longitudinal strain, but also radial strain, circumferential strain and twist mechanics (Geyer et al., 2010). Longitudinal strain is affected proportionally to infarct mass and LVEF and is impaired to a greater extent in the specific area of infarction (Helle-Valle et al., 2009, Delgado et al., 2008, Park et al., 2008b). As previously discussed, generation of high intra-ventricular pressure is reliant on LV twist. As such, peak LV twist and untwist have been shown to correlate directly with impairment in LVEF. Similarly, LV twist rate is related to the degree of systolic function and LV untwist rate with the degree of diastolic function (Chen et al., 2007, Takeuchi et al., 2007a, Bertini et al., 2009b).

A number of studies have examined the clinical applicability of LV mechanics in the assessment and treatment of MI. Echocardiographically derived longitudinal strain has been
found to correlate closely with commonly utilised prognostic parameters such as wall motion score index (WMSI), infarct size and LVEF (Stanton et al., 2009, Mistry et al., 2011, Mignot et al., 2010). The ability of LV mechanics to predict cardiovascular morbidity, mortality and LV remodelling is, therefore, of significant interest to clinicians. This is highlighted by the potential advantages of strain over conventional echo measures, such as lower inter and intra-observer variation (global longitudinal strain (GLS) vs. LVEF) and semi-automated derivation (Sjoli et al., 2011, Munk et al., 2012). In comparison to LVEF and ESVI, longitudinal strain and strain rate measured on admission and within 24 hours of MI has demonstrated equal or superior ability to predict composite endpoints of death, rehospitalisation, reinfarction, unstable angina and life threatening arrhythmia, at 24 and 36 month follow up (Hung et al. 2010; Sjoli et al. 2011; Munk et al. 2012). Furthermore, the progression to LV remodelling at 3-6 months (as defined by >15% increase in LVESV or >20% increase in LVEDV) can also be identified with the measurement of twist and GLS on admission with MI and up to 5 days thereafter (Zaliaduonyte-Peksiene et al., 2012, Bochenek et al., 2011, Jang et al., 2010, Nucifora et al., 2010). Likewise, Spinelli and colleagues (2012) concluded that twist measured post-revascularisation for MI was the greatest predictor of reverse LV remodelling, defined as >10% reduction in LVESV at 2 yrs post-MI. However, there is currently no data relating to the application of LV mechanics in the long term assessment of post-MI reverse LV remodelling in response to medical or rehabilitative intervention.

2.5.5 Summary of left ventricular deformation and mechanics

Left ventricular architecture and geometry is characterised by an intricate arrangement of myofibres which facilitates complex three dimensional deformation during systole and diastole. Recent advances in imaging technology (STE) have allowed the investigator to non-invasively quantify this motion in unprecedented detail. A rapidly expanding body of literature has begun to unravel the pathophysiological determinants of LV mechanics, including the effects of pathological structural LV remodelling. Given the reported association between conventional
measures of remodelling and LV mechanics, and the ability of LV mechanics to predict outcome in patients with recent MI, it is plausible to assume a future role for these measures in assessing reverse LV remodelling and defining adaptation to therapeutic intervention such as pharmacology and CR exercise training.

2.5.6 Overall summary of left ventricular remodelling, B-type-natriuretic peptide and left ventricular mechanics

Previous sections of this chapter have reviewed the underpinning theory of the development and reversal of post-MI LV remodelling. This has been discussed both in the context of the biomarker NT-pro-BNP and in relation to conventional and novel echocardiographic measures. The potential for both these areas to further our understanding of the effects of CR exercise training has been highlighted. Subsequent sections will address the evidence relating to the effects that CR exercise training may have on these physiological concepts prior to presenting the aims of this thesis.

2.6 The physiological effects of cardiac rehabilitation exercise training

As previously stated in section 2.1, recently published meta-analyses have overwhelmingly demonstrated significant reductions in cardiovascular and all cause mortality following exercise training in the general CR population (excluding CHF) (Heran et al., 2011), and specifically in patients with MI (Lawler et al., 2011). Studies in CHF are less conclusive, but reductions in hospitalisation and improvements in health related quality of life (HRQL) have been clearly identified (Davies et al., 2010a, Davies et al., 2010b). As a generalised measure of cardiorespiratory and metabolic fitness, VO₂peak has been shown to improve by 2.6 ml/kg/min in mixed pathology CR patients compared with only 0.3 ml/kg/min in controls (Valkeinen et al., 2010). Greater improvement was noted with earlier initiation of training and extended programme duration. Despite considerable understanding of the extra-cardiac effects of CR exercise training in post MI patients (Gielen et al., 2010), and a modest appreciation of structural LV adaptation (Haykowsky et al., 2011), surprisingly little is known of the
corresponding changes that may occur in LV function, for which a historical lack of appropriate
and sensitive cardiac imaging modalities may in part be responsible. Moreover, a lack of data
examining the effects of CR exercise training on NT-pro-BNP in this patient group is also
evident as research has primarily focussed on CHF. As such, the following section will firstly
appraise the evidence relating to the effects of CR exercise training on LV remodelling,
secondly summarise the literature pertaining to CR exercise training and NT-pro-BNP, and
finally, provide an overview of studies examining the effects of exercise training on LV
mechanics in health and disease.

2.6.1 The effect of cardiac rehabilitation exercise training on left ventricular
remodelling

The effect of exercise training on the pathologically remodelled LV has been previously studied
in a variety of settings. Early, somewhat misleading, animal and human studies initiated debate
as to whether post-infarction exercise training may in fact exacerbate remodelling and lead to
further ventricular dilation (Jugdutt et al., 1988, Gaudron et al., 1994, Oh et al., 1993). This
belief was dispelled with the advent of higher resolution imaging modalities which allowed
more accurate quantification of myocardial chamber dimensions and wall thicknesses. In a high
intensity exercise training study involving early post-MI patients with significant LV systolic
dysfunction (EF<35%), Dubach and colleagues (1997) used magnetic resonance imaging (MRI)
to demonstrate that there was no change in LV volumes or wall thickness in intervention or
control patients, despite improvements in VO$_2$ peak. Over the subsequent decade, the
heterogeneity of study populations, differences in exercise intervention design and the potential
inaccuracy of measurement techniques have limited the rigour with which systematic review
and meta-analyses have been able to provide consensus. Nevertheless, two notable recent meta-
analyses have been published.

Chen and colleagues (2012) revised a previous meta-analyses by Haykowsy and co-authors
(2007) examining the effects of exercise training on LV remodelling in CHF patients. The meta-
analysis comprised 813 predominantly male patients (425 exercise trained and 338 control) from a total of 15 trials. Mean age ranged from 54 – 75 yrs, CHF aetiology was mixed and mean LVEF was <45%. Exercise modality varied between aerobic exercise training alone, strength training alone or a combination of the two, with intensity ranging from 60-70% VO₂ peak and a programme duration of between 2 and 14 months. Overall, results indicated a favourable effect of exercise training on LVEF despite an absence of statistical reduction in ESV or EDV. Aerobic training alone (12 studies), however, was associated with significant improvements in LVEF, EDV and ESV whereas the analyses for strength training alone (1 study) and combined aerobic and strength training alone (3 studies) were inconclusive due to the small number of studies included. Long term aerobic training (>6 months) resulted in greater improvements in LVEF than short term training (<6 months) and the beneficial effects of aerobic exercise on ESV and EDV were only witnessed following longer term training. The authors concluded, in line with previous findings (Haykowsky et al., 2007), that long-term, moderate intensity aerobic exercise training reversed LV remodelling in stable CHF and that strength training had no adverse effect.

In patients with recent-MI (≤ 3 months), Haykowsky and colleagues (2011) published a further meta-analysis. Previously in this patient group, a lack of consensus was apparent. Aerobic training had been shown to either decrease EDV and ESV and increase LVEF (Giallauria et al., 2008, Giallauria et al., 2009, Giannuzzi et al., 1997), increase volumes and decrease LVEF (Jugdutt et al., 1988, Kubo et al., 2004), or have no impact on parameters of LV remodelling (Giannuzzi et al., 1993, Dubach et al., 1997, Giallauria et al., 2006a, Giallauria et al., 2006b, Koizumi et al., 2003). The meta-analysis included 12 trials, consisting of 647 predominantly male patients with a mean age of 55 yrs and a weighted mean LVEF of 44%. Exercise programmes were conducted at approx. 60-70% VO₂ peak for 20-180 min per session for 1 to 6 months (table 2.2). The authors acknowledged that all included studies demonstrated high levels of statistical, clinical and methodological heterogeneity and tended to be assessed as low to moderate quality, as dictated by the lack of description of randomisation and blinding.
procedures. Moreover, exercise capacity was not accurately quantified in the majority of studies. Analysis of three standard variables was performed; LVEF (12 trials), ESV (9 trials) and EDV (10 trials). All three were positively affected by exercise training, the magnitude of which was determined by time post-MI to initiation of exercise training and the exercise programme duration. Those studies in which exercise was commenced approximately one week post-MI and continued for six months had the greatest beneficial effect. Furthermore, for every week that passed prior to commencing exercise training, an additional month was required to ultimately attain the same reduction in ESV and improvement in EF.

Table 2.2 Description of exercise training programmes in the meta-analysis of the effects of exercise training on left ventricular remodelling in patients with recent MI - (Haykowsky et al., 2011)

<table>
<thead>
<tr>
<th>Study</th>
<th>Frequency (days/week)</th>
<th>Intensity</th>
<th>Exercise duration (min/session)</th>
<th>Mode</th>
<th>Programme length (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giallauria et al. (2009)</td>
<td>3</td>
<td>60 – 70% VO$_2$ peak</td>
<td>30</td>
<td>Cycle</td>
<td>6</td>
</tr>
<tr>
<td>Giallauria et al. (2008)</td>
<td>3</td>
<td>60 – 70% VO$_2$ peak</td>
<td>30</td>
<td>Cycle</td>
<td>6</td>
</tr>
<tr>
<td>Giallauria et al. (2006a)</td>
<td>3</td>
<td>70% VO$_2$ peak</td>
<td>30</td>
<td>Cycle</td>
<td>3</td>
</tr>
<tr>
<td>Giallauria et al. (2006b)</td>
<td>3</td>
<td>60% VO$_2$ peak</td>
<td>30</td>
<td>Cycle</td>
<td>3</td>
</tr>
<tr>
<td>Giannuzzi et al. (1997)</td>
<td>3 - 7</td>
<td>80% peak HR</td>
<td>30</td>
<td>Cycle</td>
<td>6</td>
</tr>
<tr>
<td>Koizumi et al. (2003)</td>
<td>7</td>
<td>Moderate speed</td>
<td>30</td>
<td>Walk</td>
<td>3</td>
</tr>
<tr>
<td>Kubo et al. (2004)</td>
<td>3</td>
<td>HR at VT</td>
<td>20 min, twice/day</td>
<td>Cycle</td>
<td>3</td>
</tr>
<tr>
<td>Dubach et al. (1997)</td>
<td>4 – 7</td>
<td>60 – 70 % HRR</td>
<td>45</td>
<td>Cycle</td>
<td>2</td>
</tr>
<tr>
<td>Gianuzzi et al. (1993)</td>
<td>3 – 7</td>
<td>80% peak HR</td>
<td>30</td>
<td>Cycle</td>
<td>6</td>
</tr>
<tr>
<td>Heldal et al. (2000)</td>
<td>5</td>
<td>85% peak HR</td>
<td>120</td>
<td>Cycle</td>
<td>1</td>
</tr>
<tr>
<td>Jette et al. (1991)</td>
<td>7</td>
<td>70 – 80% peak HR</td>
<td>45 – 105</td>
<td>Cycle, jogging, walk, calisthenics</td>
<td>1</td>
</tr>
<tr>
<td>Grodzinski et al. (1987)</td>
<td>5</td>
<td>80% peak HR</td>
<td>30 – 180</td>
<td>Cycle, jog, walk, swim, calisthenics</td>
<td>1</td>
</tr>
</tbody>
</table>

VO$_2$ peak, peak oxygen consumption; HR, heart rate; VT, ventilatory threshold; HRR, heart rate reserve.

From the meta-analytical data in CHF and MI, it can be concluded that exercise training appears to have a degree of efficacy in improving LVEF, ESV and EDV, all of which are highly
clinically relevant parameters of LV remodelling. However, the striking differences between studies in all aspects of exercise programme design, the level of clinical impairment and the time to initiation of exercise training in post-MI patients, all prevent definitive conclusions being drawn. In patients with recent MI, there is also a distinct lack of evidence relating to the reverse LV remodelling effects of CR exercise training when LV systolic function is mildly abnormal i.e. LVEF >45%. With advancement in percutaneous coronary artery revascularisation technology, rapid access to 24hr PPCI, more sensitive cardiac biomarkers and increased public awareness of chest pain management, this population is increasingly prevalent in CR exercise programmes (Kim et al., 2011b, Furman et al., 2001). This highlights the need for research to specifically focus on the effects of CR exercise training on reverse LV remodelling in post-MI patients with mildly abnormal LVEF.

2.6.2 The effect of cardiac rehabilitation exercise training on B-type natriuretic peptide

To complement data relating to echocardiographically measured reverse LV remodelling, an understanding of the effects of CR exercise training on NT-pro-BNP, as a surrogate measure of LV wall stress, may also provide further insight into reverse LV remodelling. In a population with mildly abnormal LVEF, change in LV structural and functional indices, whilst perhaps of clinical significance, may be relatively small, and thus potentially difficult to detect with standard echocardiographic techniques. Alternative means of analysis such as NT-pro-BNP, may be useful in quantifying the response to exercise training in these patients. A number of previous studies have indicated that exercise training can reduce NT-pro-BNP in patients with cardiac pathology (Maria Sarullo et al., 2006, Passino et al., 2006, Wisloff et al., 2007). As with reverse LV remodelling, however, the majority of research has been directed at those with significant and chronic left ventricular systolic dysfunction (LVSD) and thus the highest resting NT-pro-BNP. A recent individual patient meta-analysis of 10 randomised control trials reported data on 313 exercise trained HF patients and 252 controls (Smart et al., 2011). Whilst there was no change in controls, resting NT-pro-BNP was significantly reduced by 37% following
exercise training. Collectively, this cohort was typical of an optimally managed, stable HF population with a mean \( \text{VO}_2 \text{peak} \) of 14 ml.kg.min\(^{-1} \) and LVEF of 35\%, and a median resting NT-pro-BNP of 1114 pg/mL.

Two studies (Giallauria et al., 2006a, Giallauria et al., 2008) in the meta-analyses by Smart and Colleagues (2011) differed significantly from the other eight in that patients had a diagnosis of recent MI (<14 days), as opposed to stable CHF. The pathophysiological contrast between these two populations and the differences in their medical treatment should prevent their direct comparison. Further examination of these two studies indicates a 68-70\% reduction in resting NT-pro-BNP which is considerably greater than that witnessed in the remainder of the studies in the analysis. This appears to confirm a differential response of exercise training on NT-pro-BNP in recent post MI patients and those with CHF. Therefore, the results of the meta-analysis may be exaggerated by the inclusion of these two studies and the data showing a reduction in NT-pro-BNP in patients with CHF may be questioned. Indeed, a number of studies have not reported improved NT-pro-BNP (Arad et al., 2008, Prescott et al., 2009, Nilsson et al., 2010), two of which (Jonsdottir et al., 2006, Butterfield et al., 2008) were included in the meta-analysis by Smart and colleagues (2011). This apparent disagreement throughout the literature is most likely related to differences in the baseline clinical characteristics of CHF study populations. In particular, outcome may be dependent upon HF aetiology, degree of LVSD, length of treatment, \( \text{VO}_2 \text{peak} \) and medication. Therefore, both baseline characteristics and differences in the structure and content of training interventions ultimately hinder direct comparison and may prevent definitive conclusion as to the effect of CR exercise training on NT-pro-BNP in patients with CHF.

Only two studies appear to have specifically examined the effects of CR exercise training on NT-pro-BNP in patients with recent MI (Giallauria et al., 2006a, Giallauria et al., 2008). Patients in these studies had moderate LVSD (LVEF ~45\%), resting NT-pro-BNP of ~1400 pg/ml and \( \text{VO}_2 \text{peak} \) of ~16ml/kg/min at baseline, characteristics commensurate with moderate
clinical and functional impairment. As previously discussed, NT-pro-BNP was significantly reduced (~70%) in both studies following CR compared to controls, indicating the efficacy of exercise training interventions in patients with LVSD following recent MI. Moreover, whilst not exclusive to MI, data from Berent and colleagues (2009) indicated that NT-pro-BNP was reduced in response to exercise training in patients with mixed aetiology cardiovascular disease (MI, elective PCI, coronary artery bypass surgery (CABG), valve surgery, diabetes mellitus) irrespective of, LVEF and baseline resting NT-pro-BNP level. Cumulative data, from the above trials in patients with recent MI, therefore, suggests that exercise training may have a favourable effect on NT-pro-BNP and could be used to evaluate the efficacy of exercise training interventions. The available data is, however, insufficient to offer definitive conclusion and patients with mildly abnormal LV function following MI have not been studied. A need exists to further investigate the effects of CR exercise training on NT-pro-BNP, particularly in less compromised patients.

2.6.3 The effect exercise training on left ventricular mechanics

To date, little is known of the effects of exercise training on LV mechanics in healthy and diseased populations. Due to the complexity of interactions between cardiovascular physiology and LV mechanics, and the relative infancy of this area of research, data from cross-sectional and longitudinal studies is limited, and findings are inconsistent. In the following section, a summary of the data relating to the effects of exercise training on resting LV mechanics in healthy individuals will precede a synopsis of the literature in diseased populations, including IHD.

Cross-sectional studies examining LV twist in trained and untrained individuals have reported contrasting results. In comparison to healthy controls, reduced resting apical rotation and/or twist has been demonstrated in highly trained footballers, cyclists, mixed endurance trained individuals and those with high VO\textsubscript{2}\text{peak} (Stohr et al., 2012, Zocalo et al., 2007, Nottin et al.,
2008). To the contrary, LV twist has been reported to be the same as healthy controls in elite rowers (Stuber et al., 1999), and higher endocardial and epicardial LV twist has been observed in elite cyclists (De Luca et al., 2011). In the majority of these studies, despite differences in LV mechanical adaptation, structural parameters were consistent with physiological LV remodelling. Imaging modality and methodology, demographics, current and historical training status and inter-individual variation in cardiac structural parameters are likely responsible for the inconsistency of these findings. Furthermore, it has been proposed that the overall systemic cardiovascular response to endurance training i.e. reduced heart rate and blood pressure may influence LV mechanics (Weiner et al., 2010, Zocalo et al., 2007, Nottin et al., 2008). This assumption, whilst offering a logical physiological rationale, does not explain the differences in LV twist adaptation between cross-sectional studies, in which the systemic cardiovascular response to chronic training was comparable. As such, recent work has questioned this proposition.

In a comparison between highly and moderately fit young men, Stohr and colleagues (2012) reported reduced resting and exercise apical rotation in high-fit individuals despite any differences in arterial hemodynamics or heart rate between groups. These findings would seemingly indicate myocardial specific adaptation, independent of accompanying alterations in cardiovascular hemodynamics. Furthermore in the study by Stohr, gross LV structure and stroke volume did not differ between groups, highlighting that LV mechanical adaptation was not only independent of cardiovascular hemodynamics, but also independent of systolic function. Essentially this adaptation could be considered to represent improved myocardial efficiency, as evidenced by the production of similar LV stroke volume with a lower contribution from twist mechanics and therefore a lower myocardial energy demand (Stohr et al., 2012).

In a longitudinal training study in healthy individuals, Weiner and colleagues (2010) demonstrated an increase in resting apical rotation, twist and peak early untwisting rate following 90 days of rowing training in young, previously untrained individuals. The results of
this study are at odds with the majority of cross-sectional studies. However, whilst cross-sectional studies have evaluated LV mechanics in chronically trained individuals, the study by Weiner et al. (2010) performed baseline STE prior to initiating a training regime in untrained individuals. As LV mechanics have been shown to be preload dependant (Burns et al., 2009, Hodt et al., 2011), the increase in LV twist mechanics may reflect the influence of the well documented increase in blood volume associated with the onset of chronic endurance training (Green et al., 1991). It may be hypothesised that continued chronic training could ultimately have reduced LV twist, in line with data from the majority of cross-sectional studies (Stohr et al., 2012, Zocalo et al., 2007, Nottin et al., 2008).

Studies assessing LV mechanics following exercise training in clinical populations are limited. In type II diabetics with subclinical myocardial dysfunction, due most likely to coronary microvascular disease, two studies have examined the effects of 12 months of moderate intensity exercise training (Loimaala et al., 2007, Hordern et al., 2009). In comparison to population based norms, both cohorts were characterised by reduced values of tissue doppler imaging (TDI) derived tissue velocity, strain and strain rate. Despite improvements in metabolic, cardiovascular and functional indices, neither cohort displayed reversal of myocardial dysfunction in comparison to usual care. In the study by Hordern and colleagues (2009), however, those who reported the greatest increase in physical activity participation showed the greatest increase in strain rate and improvement in diastolic function (tissue velocities). This may indicate a relationship between volume of physical activity and improvement in myocardial function. Likewise, in an obese population with documented subclinical diastolic dysfunction, improvements in TDI derived diastolic indices and increases in STE derived strain and strain rate measurements were noted following a low-level, 8 week exercise training programme (Schuster et al., 2012). Although data are limited, these studies may indicate an effect of exercise on subclinical myocardial dysfunction, which may be exaggerated by longer duration or higher intensity exercise training programmes.
For those with clinical cardiac pathology, the data is equally scarce. Firstly, in stable CHF patients (LVEF ≤35%), 16 weeks of exercise training, whilst improving exercise capacity and peak exercise LVEF, had no effect on the conventional echocardiographic measures of resting LVEF, LVEDV, LVESV or on TDI derived parameters of strain and strain rate (Smart et al., 2006). Improved exercise capacity, however, did correlate positively with baseline strain and the increase in strain following training, potentially indicating an underlying interdependence.

Secondly, a recent pilot study reported improvements in diastolic function following three months of CR exercise training (Wuthiwaropas et al., 2012). In this cohort of predominantly NSTEMI patients with normal LVEF (61%), improved six-minute walk distance was accompanied by significant improvements in LVEF, grade of diastolic dysfunction and E/e’ ratio (a surrogate of LV filling pressure). Post-hoc comparison of STE derived LV mechanics revealed an increased peak untwisting rate and decreased left atrial volume index (LAVI) in those with improved diastolic function and the reverse in those with unchanged diastolic function. Although peak systolic twist remained unchanged in the population as a whole, there was a marked trend towards an increased twist in those with improved diastolic function and a decrease in those without. Finally, TDI derived strain analysis was conducted in a group of transmural MI patients with triple vessel disease, revascularised with CABG (Claessens et al., 2009). Four months of exercise training did not result in any change in conventional measures of myocardial structure or function. Furthermore, no change was reported in end systolic or diastolic strain values in the cohort as a whole. Comparison of inferior versus anterior MI, however, did reveal adaptation. On regional analysis it was noted that non-infarcted segments demonstrated increased end systolic and diastolic strain values whereas infarcted segments exhibited decreased strain values. This led the authors to propose a beneficial effect of CR exercise training on non-infarcted myocardium with a corresponding deleterious effect on the performance of infarcted regions. In the absence of an appropriate control group, however, this observation cannot be confirmed. With such limited and inconclusive data relating to the effects of CR exercise training on LV mechanics in patients with MI, there is a clear need for research to be conducted in this area.
2.6.4 Summary of the effects of exercise training on left ventricular remodelling, B-type-natriuretic peptide and left ventricular mechanics

Cardiac rehabilitation exercise training improves cardiorespiratory and metabolic fitness in post-MI patients, with resultant improvements in morbidity and mortality. The contribution of exercise induced changes in LV structure and function to these long term outcomes is not known. This is a surprising observation given that improvements in structural LV parameters and reductions in the counterregulatory neurohormone BNP are highly prognostically significant. Whilst large scale clinical trials have demonstrated the efficacy of medical therapies in this regard, significant heterogeneity and small sample sizes prevent definitive conclusion as to the effects of CR exercise training in this patient group. It is reasonable to conclude from the current literature that CR exercise training does, to an extent, favourably influence both of these measures. Larger scale trials are required to confirm these findings, and little is known of the effects in patients with mildly abnormal LVEF. A lack of appropriate imaging modalities may historically have prevented accurate assessment of LV functional change following CR exercise training. The advent of STE allows characterisation of complex LV mechanics and may have the potential to quantify the response of these parameters to a period of exercise training. Currently, very little research has been conducted to examine the response of LV mechanics to exercise training in healthy or chronically diseased individuals.

2.7 Overall summary of literature review and thesis aims

Improved functional capacity and reduced cardiovascular and all cause mortality are proven outcomes of CR exercise training in patients with MI. The effects of this intervention specifically on LV structure and function are poorly understood, particularly in the increasingly prevalent group of patients with mildly abnormal LVEF. Importantly, indices of LV structure and function are of high prognostic significance and, as such, are a target of medical intervention. An understanding of the potential effects of CR exercise training on these parameters may, therefore, inform holistic treatment strategies and aid in the design of appropriate exercise training programmes for the management of post-MI patients. With the
measurement of NT-pro-BNP, conventional echocardiography and novel STE derived indices
of LV mechanics, it may be possible to assess the impact of CR exercise training on
neurohormonal activation, LV structure and LV function. As such, in post-MI patients with
mildly abnormal LVEF, the overall aims of the studies presented in this thesis were to:

1) Assess the effect of CR exercise training on NT-pro-BNP
2) Assess the effect of CR exercise training on LV structural and functional parameters
   with conventional echocardiography
3) Assess the effect of CR exercise training on STE derived LV mechanics

In order that these aims be duly addressed, three experimental chapters are subsequently
presented, with specific hypotheses individually detailed in each chapter.
CHAPTER 3

General Methods
3.1 Introduction

To fulfil the overall aims of this thesis, a single longitudinal protocol was designed to facilitate collection of data for three separate experimental studies as follows:

Study 1) The effect of cardiac rehabilitation exercise training on resting and exercise induced NT-pro-BNP.

Study 2) The effect of cardiac rehabilitation exercise training on left ventricular structure and function.

Study 3) The effect of cardiac rehabilitation exercise training on left ventricular mechanics.

Given the likelihood of drop-out and the potential for logistical difficulties with data collection, it was decided a priori to recruit a large cohort to complete the experimental protocol, accepting that each participant may ultimately not provide data for each study. Data was collected at University Hospital, Coventry between September 2009 and December 2011. The following chapter provides an overview of the general experimental and statistical methods employed. Subsequent chapters (4 – 6) will provide additional detail of study specific methods. Firstly, in chapter four, information pertaining to the methods employed for the collection and analysis of whole blood samples will be presented. Secondly, in chapter five, specific methodology relating to the measurement of LV structure and function with transthoracic echocardiography will be described. Finally, in chapter six, the acquisition and analysis of data for the measurement of LV mechanics will be discussed.

3.2 General procedures

Prior to the start of the overall project, ethical approval was gained from the National Research Ethics Service (West Midlands – Coventry and Warwickshire) and Cardiff Metropolitan University (Appendix 1). In accordance with local protocol, the University Hospitals Coventry
and Warwickshire (UHCW) NHS Trust Research, Development and Innovation Department also approved the study (Appendix 2). Care was taken to ensure that the study complied with all aspects of the Declaration of Helsinki and the NHS Code of Practice. Experimental investigations were conducted in accordance with the principles of Good Clinical Practice (Great Britain. Department of Health, 2005) and all research personnel complied with the required level of qualification and experience to undertake their respective duties. An immediate life support (ILS) qualification was mandatory for personnel involved in exercise testing and training, and medical supervision was immediately available should it have been required. As a condition of ethical approval, incidental but potentially clinically significant findings were discussed with a consultant cardiologist or other clinician, as and when necessary. Written informed consent was gained prior to enrolment (appendix 3) and patients were made fully aware that participation was voluntary and could be ceased at any point without current and/or future medical treatment being affected in any way. All experimental procedures were performed at the Departments of Respiratory Physiology and Cardiac Investigations at the University Hospital, Coventry. The exercise training intervention was completed as part the University Hospital CR programme at the Coventry Sports Centre. Biochemical analysis was conducted at St George’s Hospital, Tooting, London.

3.3 Study design – overview

To address the previously presented aims, a prospective, longitudinal study was conducted to collect data for three individual but related investigations. Two non-randomised groups of post-MI patients; an exercise training intervention group and a non-exercising control group, were assessed at baseline and after 10 weeks (figure. 3.1). Assessments included cardiopulmonary exercise testing (CPEX), standardised individualised exercise session (SIES), resting transthoracic echocardiography and the collection of whole blood samples. Standard general physical activity advice was provided to both groups as a component of cardioprotective lifestyle education.
Figure 3.1 Study design flow chart. Patients undertook baseline testing 3-6 weeks following MI prior to populating an exercise training intervention group or a non-exercising control group. Follow-up testing was performed 10 weeks later with patient data subsequently allocated to one or more specific studies. MI, myocardial infarction; CPEX, cardiopulmonary exercise test; SIES, standardised individualised exercise session; Echo, echocardiogram; BD, blood draw for measurement of NT-pro-BNP

3.4 Participants
All patients with recent MI, who were eligible for the University Hospital, Coventry CR exercise programme were screened by the lead investigator. To be eligible for inclusion, patients were required to fulfil the following criteria.

3.4.1 General inclusion criteria:
1. Acute STEMI or NSTEMI at least three, but not more than six weeks previously
2. Successfully revascularised (determined by cardiology team) following percutaneous coronary intervention (PCI)
3. Left ventricular ejection fraction ≥ 45% (determined from in-patient clinical echocardiogram)
4. Male
5. Greater than 18 yrs of age
6. Able to provide written informed consent
3.4.2 General exclusion criteria:

1. Presence of symptoms of ischemia or heart failure
2. Chronic renal insufficiency
3. Inability to meet guidelines for participation in exercise testing and training
   (AACVPR, 2003, ACSM, 2009)
4. Significant limiting comorbidities that would prevent full participation
5. Significant time constraints that would prevent full participation

Further to the analysis of CPEX results at baseline, patients were prevented from continuing their involvement in the study if there was indication of:

1. Exercise induced ischemia
2. Clinical instability in accordance with CR guidelines (AACVPR, 2003)
3. Inability to comply with guidelines for participation in exercise testing and training
   (ACSM, 2009)

Between September 2009 and December 2011 a total of 70 patients were consented and undertook baseline testing. Figure 3.2 displays the patient pathway from recruitment to final analysis. Detection of exercise induced ischemia (n=1) prevented any further participation in the study. The intervention group was subsequently populated by those who attended CR exercise training (n=45) and the control group by those who did not (n=24) due to work or personal commitments. During the course of the study, some patients were lost to follow up (n= 8), some failed to meet the minimum exercise adherence targets (n=2) and some were excluded from the final analysis on the basis of clinical instability (n=3), as determined by excessively elevated NT-pro-BNP (>1500 pg/mL). Subsequently, 58 patients were eligible for inclusion in the analysis of one or more studies, dependent on the availability of study specific data. Due to logistical and technical limitations, it was not possible to attain full biochemical and echocardiographic datasets on all participants (fig. 3.2).
Figure 3.2 Schematic of patient pathway. Following recruitment, a number of patients were excluded (red boxes) at various stages throughout the duration of the study. The final cohort for each of the studies 1-3 (experimental chapters 4-6) was partially different, dependant on the availability of data. See text for details. Colour coding of boxes corresponds with colour coding in figure 3.1; blue, study 1; green, study 2; purple, study 3.

3.4.3 Overview of general study population – exercise training intervention and control groups

Prior to study specific exclusions, a total of 58 patients completed the study protocol in either the intervention group (n=36), or the control (n=22) group. Baseline clinical, demographic and exercise test characteristics for this total cohort are displayed in table 3.1. In subsequent experimental chapters, baseline characteristics for the intervention and control groups for each study specific analysis will be presented.
Table 3.1. Baseline demographic, clinical and exercise test characteristics for the final cohort of patients prior to study specific segregation

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Intervention (n=36)</th>
<th>Control (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>55.4 ± 8.9</td>
<td>57.0 ± 9.6</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 ± 0.1</td>
<td>1.8 ± 0.1</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>84.0 ± 11.6</td>
<td>89.6 ± 13.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.9 ± 2.8</td>
<td>29.0 ± 3.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical</th>
<th></th>
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<tbody>
<tr>
<td>STEMI (n)</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>NSTEMI (n)</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>Time post MI (days)</td>
<td>33.3 ± 8.4</td>
<td>34.7 ± 7.4</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55.8 ± 7.2</td>
<td>56.3 ± 7.9</td>
</tr>
<tr>
<td>HR_{rest} (bpm)</td>
<td>59 ± 8</td>
<td>58 ± 8</td>
</tr>
<tr>
<td>BP_{sys} (mmHg)</td>
<td>113 ± 17</td>
<td>119 ± 11</td>
</tr>
<tr>
<td>BP_{dia} (mmHg)</td>
<td>71 ± 9</td>
<td>71.3 ± 10.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPEX</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>VO₂_{peak} (L.min⁻¹)</td>
<td>2.0 ± 0.4</td>
<td>1.8 ± 0.5</td>
</tr>
<tr>
<td>VO₂_{peak} (ml.kg⁻¹.min⁻¹)</td>
<td>23.6 ± 4.2 §</td>
<td>20.2 ± 3.9</td>
</tr>
<tr>
<td>W_{max} (watts)</td>
<td>149 ± 27</td>
<td>139 ± 31</td>
</tr>
<tr>
<td>VT (ml.kg⁻¹.min⁻¹)</td>
<td>12.4 ± 2.6</td>
<td>11.1 ± 2.0</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>30.2 ± 4.3</td>
<td>32.2 ± 5.0</td>
</tr>
<tr>
<td>Exercise time (mins)</td>
<td>8.5 ± 0.9</td>
<td>8.3 ± 1.3</td>
</tr>
</tbody>
</table>

Data as mean ± SD. BMI, body mass index; STEMI, ST elevation myocardial infarction; NSTEMI, non ST elevation myocardial infarction; MI, myocardial infarction; LVEF, left ventricular ejection fraction; HR_{rest}, resting heart rate; BP_{sys}, systolic blood pressure; BP_{dia}, diastolic blood pressure; CPEX, cardiopulmonary exercise test; VO₂_{peak}, peak oxygen uptake; W_{max}, maximum workload; VT, ventilatory threshold; VE/VCO₂ slope, ventilatory efficiency slope. . § P<0.05 vs. control at baseline

3.5 Non-exercising control group

The control group was populated by patients who were unable to attend the 10-week CR exercise training programme due to work or personal commitments. Echocardiography and CPEX were performed at baseline and after 10 weeks. General physical activity advice was provided to all patients in the control group as a component of standard cardioprotective lifestyle education.

3.6 Exercise training intervention group

Exercise training was conducted twice weekly on Monday and Thursday mornings for a period of 10 weeks. An adherence rate of 85% (17 of 20 sessions) was designated as the required
standard for inclusion in the final analysis. A 10 min progressive treadmill or cycle warm-up was followed initially by 25 min of continuous cardiovascular exercise (outlined below). A five minute cool down walk was performed prior to and on completion of a standardised resistance training programme (outlined below).

3.6.1 Cardiovascular exercise component
Cardiovascular exercise was split equally between treadmill, cycle, rower and cross-trainer. Intensity was initially set at a heart rate (HR) corresponding to 60-80% VO$_2$ peak derived from CPEX. After the first two sessions, the supervising exercise physiologist ensured that patients were exercising at a HR equivalent to 80% VO$_2$ peak. To account for improvements in functional capacity as the programme progressed, exercise intensity and training heart rate range (THRR) were simultaneously re-prescribed every two weeks based on HR achieved during each individual exercise and patient reported rating of perceived exertion (RPE). Patients were extensively tutored, thus skilled in the use of RPE which allowed accurate assessment and adjustment of workload to maintain a training intensity of 80% VO$_2$ peak (Borg, 1998). A reported RPE of ≤14 signified the need to adjust THRR and workload accordingly. The duration of exercise was progressively increased from 25 to 40 min by the fifth week.

3.6.2 Resistance training exercise component
One set of 15 repetitions of seven core muscle group resistance training exercises was performed, as per recommended guidelines (ACSM, 2009). All exercises were executed using resistance training machines and the prescription comprised lateral pull down, bicep curl and tricep extension in the standing position and shoulder press, leg extension, leg curl and abdominal crunch in the seated position. The intensity of each set was regulated using RPE, with the aim of achieving a local muscular RPE of 15 by the 12th-15th repetition. A reported RPE of ≤15 signified the need to increase resistance accordingly.
3.7 Pre-experimental procedures
Data for CPEX and transthoracic echocardiography are reported in all three experimental chapters. Accordingly, the general methodology for these experimental procedures is described below. To minimise inconvenience for the participants, echocardiography and CPEX were conducted during the same testing session. On the day of testing, patients were directed to refrain from smoking, caffeine and food for three hours prior to their appointment and a 24 hour abstinence from vigorous exercise and alcohol was requested. All tests were conducted in a temperature controlled environment and, in the majority of cases, baseline and 10 week measures were conducted at the same time of day. Prior to each testing session, patients’ stature and mass were measured using appropriately calibrated equipment and recorded to the nearest 0.1 cm and 0.1kg respectively. Other than the removal of footwear, patients were dressed in the attire in which they undertook testing. Previous work has demonstrated that sustained post-exercise cardiac dysfunction can occur following maximal exercise in patients with heart disease (Morikawa et al., 1998). As such, echocardiography was performed in the resting state, prior to CPEX, or where this was not possible (<15%), a minimum of 1 ½ hours thereafter.

3.8 Cardiopulmonary Exercise Testing
Cardiopulmonary exercise testing (CPEX) was performed by all patients at baseline and 10 weeks later. Test protocols were in accordance with American Thoracic Society guidelines (Ross, 2003). A calibrated, electronically braked, upright exercise bicycle (Viasprint 150P, Care Fusion Corp., San Diego, California, USA) was used in combination with an exercise respiratory gas analysis system (Oxycon Pro, Care Fusion Corp., San Diego, California, USA). Gas analyser and volume calibrations were undertaken daily and prior to each test respectively, as dictated by manufacturer’s guidelines. Breath by breath respiratory gas exchange measurements of oxygen uptake (VO₂), carbon dioxide production (VCO₂) and minute ventilation (V̇E) were recorded and used to derive ventilatory threshold (VT) and ventilatory efficiency (VE/VCO₂ slope) (Guazzi et al., 2012). The ‘V slope’ method and/or the dual criteria
(Beaver et al., 1986, Wasserman et al., 1981) were utilised by the lead investigator to identify VT and the VE/VCO₂ slope was measured from the start of unloaded pedalling to maximal exercise and calculated using linear regression. Commonly, a true VO₂ max (as determined by a plateau in VO₂) is not achieved in cardiovascular disease populations and thus the measure of peak VO₂ (VO₂ peak) was preferred (Balady et al., 2010, Cooper and Storer, 2006). Peak VO₂ was determined in the last 30 seconds of exercise as the highest measured average of the mid five of every seven breaths. In addition to gas exchange variables, a twelve lead ECG was continuously monitored and blood pressure and rating of perceived exertion (RPE) were recorded every two minutes. A standard ramp protocol was employed with increments of 15, 20 or 25 W/min, calculated to ensure an optimal test duration of 9-12 minutes (Cooper and Storer, 2006). Three minutes of rest, followed by three minutes of unloaded pedalling, preceded the test and subjects were strongly encouraged to maintain a cadence of 70 rpm until symptom limited volitional fatigue. In accordance with published criteria, a respiratory exchange ratio (RER) of >1.15 was considered indicative of maximal effort (Balady et al., 2010).

3.9 Transthoracic echocardiography

To ensure standardisation and optimal image quality in a clinical population, all echocardiograms for the following investigations were performed by highly experienced clinical cardiac sonographers. It is not the intention of this thesis to describe in great detail the nuances of image acquisition, however, a synopsis of transthoracic echocardiographic procedures and image acquisition is warranted. Likewise, a detailed explanation of the scientific principles of echocardiography is out with the scope of this thesis but a general overview is required to demonstrate an appreciation of the physics involved in the production of echocardiographic images. All analyses were performed off-line by the lead investigator and thus a thorough explanation of image analysis and a definition of the measured parameters will be provided in the relevant study chapters (five and six).
3.9.1 General principles of transthoracic echocardiography

Transthoracic echocardiography is a long established technique by which the structure and function of the heart and great vessels can by noninvasively visualised (Crawford et al., 2010). Specifically, a focused beam of high frequency ultrasound emitted from piezoelectric crystals in the echocardiographic transducer is used to exploit the varying acoustic properties of the anatomical media through which it travels (Armstrong and Ryan, 2009). Two dimensional (2D) echocardiography, which provides the platform with which to define cardiac anatomy, relies on acoustic reflection at the boundary between two tissue structures, the magnitude of which depends primarily on tissue composition and thus impedance (Otto, 2009). Varying amplitudes and directions of reflected ultrasound are captured by the transducer and processed into real-time images. In contrast, for the assessment of cardiac function, the basis of Doppler imaging lies with the principle that the frequency of sound increases when reflected by media moving towards the transducer and decreases when reflected by media moving away from the transducer (Stoylen, 2013). Otherwise known as the Doppler shift, this principle allows echocardiography to interrogate the velocity of both blood flow and myocardial tissue.

For all imaging modalities, the maximisation of both spatial resolution (accurate distinction between two structures in close physical proximity) and temporal resolution (accurate distinction of moving targets over time) is central to the production of high quality echocardiographic images, and is dependent upon skilful manipulation of various operator defined ultrasound parameters i.e. frequency, frame rate (number of ultrasound waves emitted, received and analysed by the system per unit time), depth and sector width (Mathew et al., 2010). Limitations relating to the properties of ultrasound, dictate that optimisation of spatial resolution is often achieved at the expense of temporal resolution, and vice versa. Higher spatial resolution is attained with higher frequency ultrasound but the associated increase in attenuation limits the depth to which the ultrasound can accurately image. Similarly, imaging with an increased depth or sector width leads to a reduction in frame rate and a resultant compromise in temporal resolution (Mathew et al., 2010). With adjustment of spatial and temporal resolution to
suit the intended structural or functional analysis, transthoracic echocardiography is a highly competent and reliable tool for cardiac imaging and is used routinely in clinical practice (Douglas et al., 2011).

3.9.2 Acquisition and analysis of echocardiographic images
All images were acquired at rest using a commercially available ultrasound system (Vivid 7 or Vivid I, GE Medical Systems, Horten, Norway) and a 1.6 – 4 MHz phased array transducer. The patient was required to assume the left lateral decubitas position with the left arm situated above shoulder height. This orientation allows the heart to move closer to the chest wall (and thus the transducer) and the ribs to be spread, both of which help to maximise acoustic echocardiographic windows (Lang et al., 2005). To assess specific parameters in relation to the cardiac cycle, a three lead ECG was continuously monitored throughout and both conventional two dimensional (2D) and doppler imaging (DI) modalities were utilised.

A standardised systematic approach to the assessment of myocardial structure and function was adopted with grey-scale images obtained from the parasternal long axis view (PLAX), the parasternal short axis view (PSAX) at the base and the apex and both the apical two (A2C) and apical four-chamber (A4C) views (Henry et al., 1980). In accordance with recommended practice, excessive translational motion was avoided by acquiring images over five cardiac cycles during quiet respiration and/or held end-expiration, with care taken to avoid potential degradation of image quality from inadvertent valsalva manoeuvre (Lang et al., 2005). To ensure standardisation of image acquisition between baseline and post intervention measures, the cardiac sonographer was able to review the baseline images whilst simultaneously completing the post intervention examination. Blood pressure was recorded immediately post examination (Dinamap V100, GE Medical Systems, Horten, Norway).
3.10 General statistical methods

Baseline characteristics and continuous variables are presented as mean ± standard deviation (SD) and normality of data was assessed using the Kolmogorov-Smirnov test. Between group differences were determined using unpaired Student’s t-tests. The change in outcome variables by group over time was assessed with either a two-way mixed model analysis of variance (ANOVA) or multiple paired Student’s t-tests with Bonferroni correction as appropriate. All statistical analysis was conducted using SPSS, version 21 (IBM Corp., Armonk, NY) with α set at <0.05 unless otherwise stated. Study specific statistical methodology including relationship analyses and reliability will be further described in each experimental chapter, which follow hereafter.
CHAPTER 4

Study 1

The effect of cardiac rehabilitation exercise training on NT-pro-BNP
4.1 Introduction

Released in response to LV volume and pressure overload, NT-pro-BNP is representative of LV wall stress and thus indicative of LV hemodynamic compromise (Ruskoaho, 2003). Whilst the measurement of NT-pro-BNP is of little diagnostic value on presentation with acute MI, it is strongly predictive of long term cardiovascular outcome thereafter (de Lemos et al., 2001, James et al., 2003, Kim et al., 2011b). It is routinely used to quantify disease severity, establish prognosis and guide effective treatment strategies in both CHF and CHD (Thygesen et al., 2007, Hochholzer et al., 2010). With the development of post-MI remodelling, LV dysfunction in both the infarcted and non-infarcted territories is responsible for regional increases in LV wall stress (Hall, 2005, Konstam et al., 2011) and an increase in NT-pro-BNP. As such, NT-pro-BNP may provide a surrogate indication of structural and functional LV remodelling. Consequently, a reduction in NT-pro-BNP is a target of therapeutic intervention, correlating with improved functional status, reverse LV remodelling and mortality (Felker et al., 2009, Porapakkham et al., 2010, Weiner et al., 2013).

The therapeutic effects of CR exercise training are well described, particularly in relation to improvements in skeletal muscle metabolism, vascular endothelial function and aspects of neurohormonal and autonomic control (Gielen et al., 2010). As a marker of neurohormonal over-activation, there is a clear rationale for aiming to reduce NT-pro-BNP with CR exercise training. However, despite significant study in patients with CHF, findings are mixed (Arad et al., 2008, Prescott et al., 2009, Nilsson et al., 2010, Maria Sarullo et al., 2006, Passino et al., 2006, Wisloff et al., 2007) and data in post-MI patients are limited. Whilst studies have shown reductions in NT-pro-BNP in post-MI patients with moderate LV dysfunction (Giallauria et al., 2006a, Giallauria et al., 2008), there is insufficient data to be conclusive, and patients with mildly abnormal LVEF have, to date, not been studied. In light of the increasing prevalence of this category of MI survivors (Furman et al., 2001, Kim et al., 2011a), further study of the effect of CR exercise training on NT-pro-BNP is needed.
Data describing the response of NT-pro-BNP to acute exercise is equally inconclusive. With an acute bout of maximal exercise, an increase in NT-pro-BNP is commonly witnessed in CHD patients, although considerable heterogeneity is displayed (Maeder et al., 2011). Evaluation of this response may provide additional information to data obtained at rest. Whilst resting NT-pro-BNP provides an indication of dysfunction in the unstressed myocardium, it may not reflect the potential for hemodynamic compromise during maximal exercise. Furthermore, the effect of submaximal exercise on NT-pro-BNP has not been fully evaluated. Given the current advocacy of moderate intensity, submaximal exercise training in CR programmes (AACVPR, 2003, ACSM, 2009), an understanding of the NT-pro-BNP response to this stimulus may also be useful in informing exercise programming strategies. Recently, however, literature has reported greater improvement, in a number of cardiorespiratory parameters, with higher intensity exercise training in cardiac disease populations (Rognmo et al., 2012, Wisloff et al., 2009). Comparison of the NT-pro-BNP response to maximal versus submaximal exercise may, therefore, be of particular relevance as a way of establishing the level of LV wall stress associated with different exercise intensities.

The measurement of NT-pro-BNP at rest and following exercise, prior to commencing and on completion of a CR exercise training programme, may be of use as a therapeutic evaluation tool and may aid in the design of exercise training interventions for the management of post-MI patients. Accordingly, the aims of this study were to (1) assess the response of NT-pro-BNP to acute maximal and submaximal exercise, and (2) evaluate the therapeutic effects of CR exercise training on resting and exercise induced NT-pro-BNP, in patients with mildly abnormal LVEF.

4.2 Hypotheses

1) Ten weeks of CR exercise training will reduce resting NT-pro-BNP in post-MI patients.
2) Ten weeks of CR exercise training will attenuate the acute NT-pro-BNP response to maximal and submaximal exercise in post-MI patients.

3) The acute increase in NT-pro-BNP will be greater following maximal exercise than submaximal exercise in post-MI patients.

4.3 Methods

4.3.1 Study design – overview
As described in chapter three (General methods), consecutive, male, post-MI patients were prospectively assigned to either an exercise training intervention group or a non-exercising control group. At baseline, and 10 weeks later, resting echocardiography and cardiopulmonary exercise testing (CPEX) were undertaken by all patients, and a standardised individualised exercise session (SIES) was completed by the intervention group. Whole blood samples were obtained prior to and on completion of CPEX and SIES at baseline and at 10 weeks. As a component of standard cardioprotective lifestyle education, general physical activity advice was provided to both groups. The study commenced following ethical approval and receipt of informed consent.

4.3.2 Study population
Further to the exclusions described in chapter three, whole blood samples were collected for the present study in an intervention group (n=30) and a control group (n=16). Subsequent, exclusions in the intervention (n=2) and control (n=3) groups were necessary as a result of the inability to collect the full complement of CPEX blood data due to technical difficulties with peripheral venous cannulation. Technical difficulties with venepuncture also prevented collection of SIES data in a small proportion of the intervention group (n=4).
4.3.3 Cardiopulmonary exercise testing and exercise training

Cardiopulmonary exercise testing and exercise training were conducted as detailed in chapter three.

4.3.4 Standardised individualised exercise session

In addition to CPEX, an SIES was conducted by patients in the intervention group prior to and on completion of the exercise training programme. Twenty five minutes of mixed modality (treadmill, cycle, rower and cross-trainer) cardiovascular exercise was performed at 60-80% VO$_{2}$peak, calculated from the baseline CPEX. Each SIES was preceded by a standardised ten-minute warm-up, followed by a ten-minute cool down and did not include a resistance training component. Unfortunately due to participant burden, SIES data could not be collected in the control group. Two further outpatient appointments would have been required, which proved prohibitive for those not routinely attending CR.

4.3.5 Collection, handling and analysis of whole blood samples

The collection and storage of all research blood samples was conducted in line with the Human Tissue Authority guidelines (Great Britain. Human Tissue Authority, 2009). In accordance with local policy, a peripheral venous cannula was inserted into the right antecubital vein. Whole blood samples were collected into ethylene diamine teracetic acid (EDTA) tubes, via the cannula using a 5 ml syringe and extension set. To obtain serum, clotted samples were centrifuged at 3000rpm for 10 minutes prior to being aliquoted and stored frozen at -80 °C. at University Hospital, Coventry. Frozen samples were transported to St Georges Hospital, Tooting, London where they were analysed for NT-pro-BNP concentration in a single batch at the end of data collection. NT-pro-BNP was determined using the Immulite 2500 electrochemiluminescent immunoassay (Siemens Healthcare Diagnostics, Frimley, UK). The assay has a linear calibration range from 20 to 35,000 pg/mL; analytical sensitivity of 10 pg/mL.
with no high dose hook effect up to 425,000 pg/mL. The total coefficient of variation (CV) is 3.4 to 5.6% between 40.9 and 32,096 pg/mL.

Whole blood samples were collected prior to and following CPEX and SIES. Samples were obtained after 15 minutes of seated rest, within three minutes of exercise cessation, at one and two hours following CPEX and at two hours following SIES. To help minimise inconvenience, and thus aid recruitment, blood samples were not taken at one hour post SIES. As peripheral venous cannulation was not permitted at the exercise training venue (non-NHS facility), SIES samples were obtained using standard venepuncture techniques in accordance with local protocol. To avoid the potential influence of prior activity on NT-pro-BNP concentration (Conraads et al., 2008), patients were requested to refrain from exercise for 24 hours prior to each testing session and were informally questioned with regards to their physical activity pattern in the preceding 24 hours.

4.3.6 Statistical analyses

General statistical analysis was performed as outlined in chapter three. Further to confirmation of normality with the Kolmogorov-Smirnov test, a two-way mixed model analysis of variance (ANOVA) was used to assess the effect of the 10-week exercise training intervention or control period on exercise test parameters. Group × time interaction was used to establish differences between groups, and paired Student’s *t*-tests were applied to assess within group change. The biological variability of NT-pro-BNP combined with the relatively small sample size (particularly in the control group), dictated that multiple *t*-tests be applied to the NT-pro-BNP data as opposed to a two-way ANOVA. Paired Student’s *t*-tests were used to examine within group differences in: (1) the NT-pro-BNP concentration at rest, peak, 1 hr and 2 hr within the same test (i.e. the acute response to exercise), (2) the NT-pro-BNP concentration at each time point between the pre and post intervention tests (i.e. the chronic response to the 10-week training intervention or control period). To control for the risk of type 1 statistical error when
conducting multiple comparisons, a Bonferroni correction was applied, with $\alpha$resultantly set at <0.01. Where of interest, relative change is expressed as a percentage, with the group mean calculated from percentage change for each individual subject.
4.4 Results

There were no significant differences in demographic, clinical or exercise test characteristics between the intervention and control groups at baseline \( (P > 0.05) \) (table 4.1). During the 10-week period, there were no changes in prescribed medications in either group.

Table 4.1. Baseline demographic, clinical and exercise test characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=28)</th>
<th>Control (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>55.1 ± 9.4</td>
<td>59.1 ± 5.0</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 ± 0.1</td>
<td>1.7 ± 0.1</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>85.3 ± 12.0</td>
<td>87.5 ± 9.6</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>28.0 ± 3.1</td>
<td>28.8 ± 3.6</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI (n)</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>NSTEMI (n)</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Time post MI (days)</td>
<td>32.1 ± 6.9</td>
<td>34.6 ± 6.7</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55.6 ± 7.8</td>
<td>56.3 ± 8.0</td>
</tr>
<tr>
<td>( \text{HR}_{\text{rest}} ) (bpm)</td>
<td>59 ± 8</td>
<td>59 ± 9</td>
</tr>
<tr>
<td>( \text{BP}_{\text{sys}} ) (mmHg)</td>
<td>115 ± 17</td>
<td>118 ± 11</td>
</tr>
<tr>
<td>( \text{BP}_{\text{dia}} ) (mmHg)</td>
<td>72 ± 9</td>
<td>71 ± 11</td>
</tr>
<tr>
<td><strong>CPEX</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{VO}_2 \text{peak} ) (L.min(^{-1}))</td>
<td>2.0 ± 0.2</td>
<td>2.0 ± 0.4</td>
</tr>
<tr>
<td>( \text{VO}_2 \text{peak} ) (ml.kg(^{-1}).min(^{-1}))</td>
<td>23.9 ± 4.3</td>
<td>22.4 ± 4.3</td>
</tr>
<tr>
<td>( W_{\text{max}} ) (watts)</td>
<td>148 ± 25</td>
<td>132 ± 29</td>
</tr>
<tr>
<td>VT (ml.kg(^{-1}).min(^{-1}))</td>
<td>13.0 ± 2.6</td>
<td>12.1 ± 1.9</td>
</tr>
<tr>
<td>VE/VCO(_2) slope</td>
<td>30.6 ± 4.6</td>
<td>33.4 ± 4.2</td>
</tr>
<tr>
<td>Exercise time (mins)</td>
<td>8.4 ± 0.9</td>
<td>8.9 ± 1.6</td>
</tr>
<tr>
<td><strong>Resting cardiac biomarkers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-pro-BNP (pg/mL)</td>
<td>257 ± 226</td>
<td>231 ± 300</td>
</tr>
</tbody>
</table>

Data as mean ± SD. BMI, body mass index; STEMI, ST elevation myocardial infarction; NSTEMI, non ST elevation myocardial infarction; MI, myocardial infarction; LVEF, left ventricular ejection fraction; \( \text{HR}_{\text{rest}} \), resting heart rate; \( \text{BP}_{\text{sys}} \), systolic blood pressure; \( \text{BP}_{\text{dia}} \), diastolic blood pressure; CPEX, cardiopulmonary exercise test; \( \text{VO}_2 \text{peak} \), peak oxygen uptake; \( W_{\text{max}} \), maximum workload; VT, ventilatory threshold; VE/VCO\(_2\) slope, ventilatory efficiency slope; NT-pro-BNP, N-terminal-pro-b-type natriuretic peptide.

4.4.1 Effect of cardiac rehabilitation exercise training on demographic, clinical and exercise test parameters

All exercise testing and training sessions were completed without any incidence of cardiovascular complication or other adverse events. Average exercise session attendance per patient was 89.5%. After 10 weeks of exercise training, \( \text{VO}_2 \text{peak}, W_{\text{max}}, \text{VT} \) and exercise time all
increased in comparison to controls (all $P<0.05$). Exercise training increased $\dot{V}O_2\text{peak}$ by 14%, $W_{\text{max}}$ by 18%, exercise time by 18% (all $P<0.0001$) and VT by 11% ($P<0.01$) (table 4.2). In the control group, however, $W_{\text{max}}$, $\dot{V}O_2\text{peak}$, VT and exercise time all remained unchanged ($P>0.05$). The change in the VE/VCO$_2$ slope also differed between groups ($P<0.05$). A 2% increase was noted in the intervention group and a 2% decrease in the control group, neither of which independently reached statistical significance ($P>0.05$). Furthermore, there were no statistical differences in body mass, BMI, HR$\text{rest}$, BP$_{\text{sys}}$ or BP$_{\text{dia}}$ in either group between the baseline and 10-week assessments (table 4.2).

Table 4.2 Demographic, clinical and exercise test parameters at baseline and 10 weeks

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=28)</th>
<th></th>
<th>Control (n=13)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 10</td>
<td>Baseline</td>
<td>Week 10</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>85.0 ± 12.0</td>
<td>85.3 ± 12.0</td>
<td>87.5 ± 9.6</td>
<td>86.4 ± 8.8</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>27.9 ± 3.0</td>
<td>28.0 ± 3.1</td>
<td>28.8 ± 3.6</td>
<td>28.4 ± 3.7</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR$\text{rest}$ (bpm)</td>
<td>59 ± 8</td>
<td>59 ± 8</td>
<td>59 ± 9</td>
<td>58 ± 13</td>
</tr>
<tr>
<td>BP$_{\text{sys}}$ (mmHg)</td>
<td>115 ± 17</td>
<td>112 ± 15</td>
<td>118 ± 11</td>
<td>123 ± 19</td>
</tr>
<tr>
<td>BP$_{\text{dia}}$ (mmHg)</td>
<td>72 ± 9</td>
<td>71 ± 8</td>
<td>71 ± 11</td>
<td>67 ± 9</td>
</tr>
<tr>
<td>CPEX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\dot{V}O_2\text{peak}$ (L.min$^{-1}$)†‡</td>
<td>2.0 ± 0.2</td>
<td>2.3 ± 0.4***</td>
<td>2.0 ± 0.4</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>$\dot{V}O_2\text{peak}$ (ml.kg$^{-1}$.min$^{-1}$)†‡</td>
<td>23.9 ± 4.3</td>
<td>27.2 ± 4.9****</td>
<td>22.4 ± 4.3</td>
<td>21.0 ± 4.8</td>
</tr>
<tr>
<td>$W_{\text{max}}$ (watts)†‡</td>
<td>148 ± 25</td>
<td>173 ± 29****</td>
<td>132 ± 29</td>
<td>131 ± 36</td>
</tr>
<tr>
<td>VT (ml.kg$^{-1}$.min$^{-1}$)†‡</td>
<td>13.0 ± 2.6</td>
<td>14.4 ± 3.4**</td>
<td>12.1 ± 1.9</td>
<td>11.9 ± 2.0</td>
</tr>
<tr>
<td>VE/VCO$_2$ slope ‡</td>
<td>30.6 ± 4.6</td>
<td>31.1 ± 4.6</td>
<td>33.4 ± 4.2</td>
<td>32.8 ± 5.2</td>
</tr>
<tr>
<td>Exercise time (mins)†‡</td>
<td>8.4 ± 0.9</td>
<td>9.9 ± 1.3****</td>
<td>8.9 ± 1.6</td>
<td>9.2 ± 2.0</td>
</tr>
</tbody>
</table>

Data as mean ± SD. BMI, body mass index; HR$\text{rest}$, resting heart rate; BP$_{\text{sys}}$, systolic blood pressure; BP$_{\text{dia}}$, diastolic blood pressure; CPEX, cardiopulmonary exercise test; $\dot{V}O_2\text{peak}$, peak oxygen uptake; $W_{\text{max}}$, maximum workload; VT, ventilatory threshold; VE/VCO$_2$ slope, ventilatory efficiency slope; NT-pro-BNP, N-terminal-pro-b-type natriuretic peptide. † $P<0.05$ time effect (ANOVA), ‡ $P<0.05$ group × time interaction effect (ANOVA), ** $P<0.01$ vs. baseline, **** $P<0.0001$ vs. baseline.

### 4.4.2 Effect of cardiac rehabilitation exercise training on resting NT-pro-BNP

Ten weeks of exercise training resulted in a 24% reduction in resting NT-pro-BNP ($P<0.01$), whereas no change was observed in the control group ($P>0.05$) (figure 4.1).
4.4.3 Acute response of NT-pro-BNP to maximal and submaximal exercise

Completion of baseline CPEX in both the intervention and control groups resulted in an increase in NT-pro-BNP ($P<0.01$) followed by a gradual return towards baseline levels by two hours post CPEX (figure 4.2). As depicted in figure 4.2c, NT-pro-BNP also increased following SIES in intervention group patients ($P<0.01$), but in contrast to CPEX, remained elevated at two hours post SIES ($P<0.01$). The maximal observed NT-pro-BNP level following CPEX and SIES did not differ ($P>0.05$). As previously stated, SIES was not performed in control group patients. At the end of the 10-week exercise training intervention, the acute elevation in NT-pro-BNP was not observed following CPEX in either group, or following SIES in the intervention group ($P>0.05$). In relative terms, completion of CPEX at baseline resulted in a 21% increase in NT-pro-BNP in both the intervention and control group ($P<0.01$) with a subsequent return to within 10% of baseline levels after two hours (figure 4.3). After 10 weeks, CPEX was not associated with a statistically significant increase in NT-pro-BNP in either the intervention or control groups despite a 13% and 20% increase respectively. Further to the 10-week exercise training intervention, the relative increase from rest to 1 hr post CPEX was reduced (19% vs. 1%, $P<0.001$) indicating a faster return to baseline levels in the intervention group. This change was not observed in the control group.
Figure 4.2 Post exercise NT-pro-BNP levels (pg/mL) at baseline (dark grey bars) and after 10 weeks (light grey bars) at (a) rest, peak, 1 hr and 2 hr post CPEX in the intervention group, (b) rest, peak, 1 hr and 2 hr post CPEX in the control group (striped bars) and (c) rest, peak and 2 hr post SIES in the intervention group. Data as Mean ± SEM. **P<0.01, ***P<0.001.

Figure 4.3 Post-exercise relative increase (∆) in NT-pro-BNP (%) at baseline (dark grey bars) and after 10 weeks (light grey bars) at (a) peak, 1 hr and 2 hr post CPEX in the intervention group (solid bars) and (b) peak, 1 hr and 2 hr post CPEX in the control group (striped bars). Data as Mean ± SEM. **P<0.01, ***P<0.001.
4.4.4 Comparison of the acute response of NT-pro-BNP to CPEX and SIES

The profile of the relative NT-pro-BNP response to maximal and submaximal exercise in the intervention group demonstrated different characteristics (figure 4.4). At baseline, CPEX resulted in a relative increase from rest to peak exercise (21%, $P<0.01$) followed by a return towards baseline levels at two hours (10%, $P>0.05$ vs. rest). In contrast, a continual increase was observed following SIES, with a relative increase from rest to peak exercise (14%, $P<0.01$) and rest to two hours (25%, $P<0.01$). A very similar profile was witnessed at 10 weeks although none of the changes were statistically significant.

![Figure 4.4](image)

**Figure 4.4** Post-exercise relative increase ($\Delta$) in NT-pro-BNP (%) at baseline (dark grey bars) and after 10 weeks (light grey bars) at peak, 1 hr and 2hr post CPEX in the intervention group (solid bars) and at peak, 1 hr and 2hr post SIES in the intervention group (striped bars). Data as Mean ± SEM. **$P<0.01$.**
4.5 Discussion

This study aimed to comprehensively evaluate the effects of exercise on NT-pro-BNP in a cohort of patients with mildly abnormal LVEF following recent MI. Firstly, the acute response of NT-pro-BNP to bouts of sub-maximal and maximal exercise was studied and, secondly, the therapeutic effect of 10 weeks of CR exercise training was examined with respect to the effect this conferred on both resting and exercise induced NT-pro-BNP. The main finding from the study was that 10 weeks of CR exercise training had a significant therapeutic effect as evidenced by 1) improved VO_{peak}, CPEX exercise time and workload, 2) a 24% reduction in resting NT-pro-BNP and 3) an attenuation of the post exercise NT-pro-BNP response.

4.5.1 Effect of cardiac rehabilitation exercise training on resting NT-pro-BNP

NT-pro-BNP, secreted predominantly by ventricular wall myocytes in response to increased LV wall stress, is associated with worsened prognosis throughout the spectrum of CHD (Bibbins-Domingo et al., 2007, de Lemos et al., 2001, James et al., 2003, Kim et al., 2011b). A reduction in NT-pro-BNP is, therefore, considered an important therapeutic target (Januzzi et al., 2011). The current study is the first to show a reduction in resting NT-pro-BNP (24%) following CR exercise training in relatively fit (VO_{peak} 24.0 ± 4.3 ml.kg^-1.min^-1) post-MI patients with moderately raised resting NT-pro-BNP (257 ± 226 pg/mL) and mildly abnormal LVEF (55.6 ± 7.8 %). All patients, including the controls, were on optimal post-MI pharmacological therapy, thus the positive change in NT-pro-BNP can likely be attributed to the effects of exercise training. Similar reductions in resting NT-pro-BNP have been previously demonstrated in a meta-analysis of CHF patients with a lower VO_{peak} (mean = 14 ml.kg^{-1}.min^{-1}), higher resting NT-pro-BNP (median = 1114 pg/mL) and greater LVSD (mean LVEF = 35%) than the current population (Smart et al., 2011). However, due to the different underlying pathophysiology, it is inappropriate to draw comparison between the results of studies in chronic, stable, optimally managed HF and the current study population of recent post-MI patients. Furthermore, data in the CHF population demonstrates considerable heterogeneity, with a number of studies reporting increased or unchanged resting NT-pro-BNP (Arad et al., 2008, Butterfield et al., 2009, Arad et al., 2010, Arad et al., 2011).
A reduction in resting NT-pro-BNP has also been previously shown in post-MI patients (Giallauria et al., 2008, Giallauria et al., 2006a, Berent et al., 2009), although data is limited. In the studies by Giallauria and colleagues (2008, 2006a), a reduction of approximately 70% was observed following early initiation of CR exercise training (<14 days post-MI). Whilst similar to the current study with respect to diagnosis, patients were significantly more functionally and clinically compromised, with lower VO$_2$peak (~16 ml.kg$^{-1}$min$^{-1}$), lower LVEF (~45%) and higher resting NT-pro-BNP (~1400 pg/mL). This greater impairment was likely a result of more severe MI and the limited time between MI and baseline assessment (<14 days). Likewise, the greater reduction in NT-pro-BNP reported in the Giallauria studies (70% vs. 24%) may be partly explained by the fact that exercise training was commenced earlier post-MI, at which time NT-pro-BNP would have been higher. The current study commenced exercise training considerably later (32 ± 7 days) which may have allowed time for improvement in VO$_2$peak, LVEF and NT-pro-BNP, further to natural recovery and pharmacological therapy. It is possible that earlier initiation of exercise training in the present study may have resulted in an even lower NT-pro-BNP value at 10 weeks. Alternatively, a similar endpoint may have been achieved which, from a higher baseline value, would have represented a greater overall reduction. Nevertheless, the present data are the first to indicate that significant improvement in NT-pro-BNP is possible, even when initiation of training is relatively ‘delayed’ in line with current UK practice (National Audit of Cardiac Rehabilitation, 2012). Furthermore, this adaptation was observed in post-MI patients with only mildly reduced LVEF.

The nature of the exercise training employed in the current and previous studies may have had an effect on the magnitude of NT-pro-BNP reduction. With exercise training interventions in all clinical populations, a condition specific prescription is required to ensure optimal benefit. As
such, it is likely that there exists an ideal exercise prescription for reducing NT-pro-BNP. For 10 weeks, the current study required patients to perform twice weekly, mixed modality cardiovascular exercise for up to one hour (including warm up and cool down) at 60-80% VO\textsubscript{2} peak. In addition, a resistance training programme was also completed. In contrast, Giallauria and co-authors (2008, 2006a) employed a three to six month exercise cycle training programme conducted for 30 minutes, three times per week at 70% VO\textsubscript{2} peak. Data are clearly insufficient to provide recommendation as to what intensity, frequency, duration and modality of CR exercise training confers optimal benefit. Indeed, it was not the intention of the current study to specifically examine this area and it is unlikely that exercise programmes would ever be constructed with the primary intention of reducing NT-pro-BNP. Nevertheless, it appears that a variety of formats of exercise training are effective at reducing resting NT-pro-BNP in post-MI patients. However, in the current and previous studies, where improvements in NT-pro-BNP have been shown, the training intensity was considerably greater than that recommended in accepted CR guidelines i.e. 40-65% VO\textsubscript{2} peak (AACVPR, 2003). This may highlight the importance of administering a sufficient intensity of exercise, in order to facilitate a reduction in NT-pro-BNP. Moreover, this may be particularly important when, as in the current study, exercise frequency was low (twice per week) and time to initiation was prolonged (five weeks).

4.5.2 Acute response of NT-pro-BNP to maximal and submaximal exercise

Previous work has predominantly focussed on the effect of CR exercise training on resting NT-pro-BNP. The present study was designed, not only to assess resting NT-pro-BNP, but also to characterise the response of NT-pro-BNP to maximal and submaximal exercise. A significant rise in absolute and relative NT-pro-BNP was evident with maximal exercise in both the intervention and control groups at baseline. This likely indicates an increase in LV wall stress in response to maximal exercise. However, this response was not observed in either group at week 10, suggesting that the exercise training intervention had little beneficial effect on LV wall stress during exercise. Rather, the attenuation of exercise-induced LV wall stress may be
secondary to pharmacological therapy and natural recovery, and independent of improvements in cardiovascular fitness. However, on completion of CPEX at week 10, the intervention group achieved a greater absolute workload and exercise duration (both 18%), and thus a greater attenuation of LV wall stress may be assumed. The relative change in NT-pro-BNP may also be indicative of reduced LV wall stress. In the intervention group, the difference between the rest and 1 hr values at baseline (19%) was significantly reduced after exercise training (1%), suggesting a faster return to baseline levels. In contrast, a greater difference was observed in the control group at 10 weeks (22% vs. 17%), indicating sustained elevation. It may be that this differential response reflects lower LV wall stress, during maximal exercise, as a result of exercise training.

It is unclear whether the release of NT-pro-BNP during exercise is pathological or, indeed, physiological. Moreover, the clinical or physiological characteristics most likely to promote or inhibit NT-pro-BNP release are yet to be fully confirmed. It has recently been suggested that rapid release may, in fact, have a beneficial effect on exercise performance, perhaps due to the vasodilatory properties of BNP (Maeder et al., 2011). Whilst studies have generally demonstrated exercise induced NT-pro-BNP release in patients with CHD and CHF (Maeder et al., 2011, Koc et al., 2008, Conraads et al., 2008), the response is mixed (Pascual-Figal et al., 2007). Some studies in CHF have demonstrated an absence of BNP release during exercise which appeared to be related to advanced age, lower VO$_{2\text{peak}}$, higher NYHA class and in particular, higher resting BNP (Kruger et al., 2004, Ciampi et al., 2009). This, the authors speculated, could be due to patients having exhausted their limited myocardial reserve of BNP. Equally, several studies have identified positive relationships between NT-pro-BNP release during exercise and higher cardiovascular fitness i.e. low resting heart rate, peak workload and peak oxygen consumption (Maeder et al., 2011, Pascual-Figal et al., 2007, Ciampi et al., 2009) in CHF patients. The results of the present study, showing increased exercise capacity but an attenuated acute NT-pro-BNP response, therefore seem to be at odds with previous work. This is most likely due to clinical differences between study populations. However, the potential for
acute physiological benefit from NT-pro-BNP release during exercise remains speculative. It is more likely that in the present population, a reduction in the exercise induced NT-pro-BNP response, is indicative of improved hemodynamic status and lower wall stress and thus represents a beneficial physiological outcome.

At baseline, the significant increase in absolute and relative NT-pro-BNP observed following maximal exercise was also evident following submaximal exercise in the intervention group, as previously reported in CHF and mixed aetiology CR patients (Conraads et al., 2008, Montiel-Trujillo et al., 2011). However, in contrast to maximal exercise, completion of 45 minutes of submaximal exercise resulted in sustained absolute and relative NT-pro-BNP elevation at two hours post exercise. Whilst the maximum release of NT-pro-BNP was very similar following both types of exercise (in both absolute and relative terms), it occurred at one hour following maximal exercise in comparison to two hours following submaximal exercise. This finding follows previous data in healthy individuals which showed a greater NT-pro-BNP release with prolonged endurance exercise in comparison to short duration exercise (Scharhag et al., 2008, Neumayr et al., 2005). The exercise stimulus in this previous work is clearly different from the current study. However, the effect of prolonged exercise on the myocardium in recreational athletes could be similar to the exaggerated LV wall stress that may occur in the dysfunctional post-MI myocardium during CR endurance exercise training. This novel and important finding suggests that prior to completion of a CR exercise training programme, the increase in LV wall stress associated with maximal exercise (in patients with mildly abnormal LVEF following recent MI), is no greater than that resulting from 45 minutes of submaximal exercise. It may be that the duration of the exercise performed, rather than the intensity, has a more pronounced effect on LV hemodynamics and thus NT-pro-BNP release in this population. This may offer additional support to emerging evidence of equally low exercise-related adverse event rates and greater cardiovascular benefit when comparing higher intensity, shorter duration exercise with conventional CR exercise prescription (Rognmo et al., 2012, Wisloff et al., 2009).
As with maximal exercise, the acute response to submaximal exercise was attenuated further to 10 weeks of CR exercise training. This may corroborate findings in healthy trained individuals. A reduced post-exercise NT-pro-BNP response has been shown following completion of exercise training programmes, most likely as a result of myocardial preconditioning (Neilan et al., 2006, Scharhag et al., 2006). In the current study, however, the attenuation of the submaximal NT-pro-BNP response may not be unique to the exercise training group as this data was not collected in the control group, thus preventing comparison. With reference to the relative increase in NT-pro-BNP following submaximal exercise at 10 weeks, whilst statistical significance was not apparent, it is possible that the substantial 15% increase at two hours (as opposed to 2% following CPEX) may have reached significance with a larger study population. It is, therefore, proposed, that at 10 weeks, an acute response in NT-pro-BNP would have been witnessed following submaximal exercise thus confirming the increased LV wall stress associated with this form of exercise (in comparison to shorter duration, maximal exercise).

Whilst these findings may offer some insight into the LV wall stress associated with different intensities and durations of exercise, it must be viewed in the context of a biologically variable biomarker for which the stimulus, mechanisms and indeed purpose of acute release are incompletely understood. Further studies are required before CR exercise programmes consider the inclusion of higher-intensity, short duration exercise on the basis of these findings, but similar data from future studies may provide a highly relevant addition to a topical area of research.

4.5.3 Mechanisms for reduced NT-pro-BNP with cardiac rehabilitation exercise training

The mechanisms by which exercise training reduces resting and exercise induced NT-pro-BNP are poorly understood. It is likely, however, that this reflects a reduction in LV wall stress as a result of interplay between autonomic and neurohormonal activation and vascular and myocardial structure and function (Smart and Steele, 2010). Left ventricular wall stress, and thus NT-pro-BNP, is increased in the presence of pathologic LV dysfunction (Hall, 2004,
Konstam et al., 2011). The accompanying autonomic and neurohormonal overexpression is ultimately destructive to cardiac myocytes and the extracellular matrix (Bonow et al., 2012, Solomon et al., 2011). Pharmacological attenuation of these compensatory responses has provided evidence of reduced cardiomyocyte dysfunction and restoration of LV structural and functional integrity (St John Sutton et al., 2003, Koitabashi and Kass, 2012, Fraccarollo et al., 2003). A reduction in LV wall stress is likely concomitant with this improved hemodynamic environment. A recent review provided evidence of normalised autonomic and neurohormonal derangement following exercise training in CHF patients, reporting reduced sympathetic outflow, plasma catecholamines, angiotensin II and vasopressin (Gademan et al., 2007). There is, therefore, reasonable rationale to suggest an association between exercise induced reductions in autonomic and neurohormonal overexpression, improved LV structural and functional integrity, reduced LV wall stress, and ultimately reduced NT-pro-BNP. Furthermore, evidence of this association has been provided by studies demonstrating correlation between exercise induced reductions in NT-pro-BNP and improved diastolic function and LV volumes (Giallauria et al., 2008, Giallauria et al., 2006a) in patients with recent MI.

4.5.4 Clinical significance of findings

Data from the current study provide indication of important clinical significance in two areas. Firstly, it is well documented that NT-pro-BNP is highly prognostically significant throughout the IHD continuum, regardless of baseline levels and degree of LVSD (Bibbins-Domingo et al., 2007, de Lemos et al., 2001, James et al., 2003, Berent et al., 2009, Kim et al., 2011b). Furthermore, a reduction of this biomarker in CHF has been shown to markedly improve clinical outcome (Januzzi et al., 2011). Research is currently underway to establish the role of NT-pro-BNP in the long term management of post-MI stable CHD; however, there is insufficient data in this population to confirm a link between reductions in NT-pro-BNP and prognosis. It is highly likely, as in CHF and in other cardiac pathologies, that a chronic reduction in NT-pro-BNP will prove to be clinically relevant (Kim et al., 2011b), thus
confirming the significance of the data from the current study. Secondly, it is well known that NT-pro-BNP is reflective of hemodynamic status, particularly LV filling pressure (Matsumoto et al., 1995, Friedl et al., 1999). By virtue of its relationship with LV wall stress, it has been shown to correlate with indices of structural and functional reverse LV remodelling following medical treatment in CHF (Weiner et al., 2013) and exercise training in post-MI patients (Giallauria et al., 2008, Giallauria et al., 2006a, Malfatto et al., 2009). Reverse LV remodelling has a well established prognostic significance in patients with LVSD (Konstam et al., 2011) and consequently it is realistic to propose that the reductions in NT-pro-BNP in the present study, which are likely representative of improved hemodynamic status and reverse LV remodelling, should be associated with positive changes to outcome.

4.5.5 Hypotheses

1) Ten weeks of CR exercise training will reduce resting NT-pro-BNP in post-MI patients – ACCEPTED

2) Ten weeks of CR exercise training will attenuate the acute NT-pro-BNP response to maximal and submaximal exercise in post-MI patients - ACCEPTED

3) The acute increase in NT-pro-BNP will be greater following maximal exercise than submaximal exercise in post-MI patients – REJECTED

4.5.6 Conclusion

In conclusion, a 10-week CR exercise training programme, in post-MI patients with mildly abnormal LVEF, significantly improved functional capacity and reduced NT-pro-BNP at rest and following maximal and submaximal exercise. These findings further confirm the therapeutic effect of CR exercise training and suggest an important role for the measurement of this biomarker in the evaluation and design of CR exercise training programmes for the management of post-MI patients. Furthermore, it is plausible that these data are indicative of reverse LV remodelling which, to date, has not been demonstrated in this population and may
contribute to the impressive reductions in morbidity and mortality associated with CR exercise training. Finally, the observation of the different NT-pro-BNP responses to acute maximal and submaximal exercise may be a valuable contribution to the current debate relating to the optimal exercise intensity and duration of CR exercise training.
CHAPTER 5

Study 2

The effect of cardiac rehabilitation exercise training

on left ventricular remodelling
5.1 Introduction

Independently and collectively, LV structural and functional parameters provide the clinician with vital information on which to base treatment strategies for the acute and chronic management of patients with MI. In particular, LVESV, LVEDV, LVEF and E/e’ represent powerful prognostic indicators (Hillis et al., 2004, Solomon et al., 2005). Furthermore, measures of relative wall thickness and LV mass can accurately quantify the extent and nature of global LV remodelling (Gaasch and Zile, 2011). Pharmacological and electrophysiological interventions attenuate, and reverse the process of structural and functional LV remodelling, resulting in measurable improvement in cardiovascular and all cause mortality (Konstam et al., 2011, Cho et al., 2012). A number of mechanisms contribute to this reverse LV remodelling, not least a reduction in systemic neurohormonal and autonomic derangement (Gielen et al., 2010, Koitabashi and Kass, 2012). As an indicator of neurohormonal activation, a reduction in the counterregulatory hormone NT-pro-BNP is, therefore, indicative of improved survival (Felker et al., 2009, Porapakkham et al., 2010). It has been proposed that this may be as a result of its association with increased LV wall stress (Ruskoaho, 2003), a feature of the abnormally loaded, adversely remodelled LV.

In the previous chapter, for the first time, clear indication was provided of the positive effect of exercise training on NT-pro-BNP in patients with mildly abnormal LVEF following recent MI. It was concluded that this likely reflects the reverse remodelling effect of CR exercise training, a finding which is supported by previous literature, albeit in a different clinical population (Giaffauria et al., 2006a, Giaffauria et al., 2008). However, whilst NT-pro-BNP appears to be a surrogate measure of reverse LV remodelling in patients with moderate LVSD, this relationship has not been investigated in the current cohort. Direct measurement of LV structural and functional indices is therefore required to provide more accurate determination of reverse LV remodelling.
A number of longitudinal studies using transthoracic echocardiography have shown a reverse remodelling effect with exercise training in post MI patients (Giallauria et al., 2009, Giannuzzi et al., 1997, Giallauria et al., 2008). However, conflicting data exists (Kubo et al., 2004, Giallauria et al., 2006b), and a recent meta-analysis, whilst confirming the positive effect of CR exercise training on LV remodelling, was limited by the poor methodological quality of the included studies (Haykowsky et al., 2011). Further evaluation of the reverse remodelling effects of exercise training in post-MI patients is therefore warranted and an understanding of the relationship between echocardiographic indices and NT-pro-BNP would be useful. Previously, studies have exclusively focussed on patients with moderate to severe impairment of LV systolic function (LVEF ≤45%). There is, therefore, a need to investigate patients with mildly abnormal LVEF who represent an increasing proportion of MI survivors (Furman et al., 2001). Finally, the available studies have employed training protocols of moderate intensity (60-70% VO$_2$peak) which may be an insufficient stimulus to result in marked reverse LV remodelling.

In light of the current evidence and experimental findings from chapter four of this thesis, the aims of the present study in patients with mildly abnormal LVEF were 1) to investigate the effects of a higher intensity CR exercise training programme on structural and functional LV remodelling using transthoracic echocardiography and (2) to investigate the association between exercise induced reductions in NT-pro-BNP and changes in LV structural and functional parameters.

### 5.2 Hypotheses

1) Ten weeks of CR exercise training will decrease LVEDV and LVESV in patients with recent MI.

2) Ten weeks of CR exercise training will increase LVEF in patients with recent MI.

3) Reductions in NT-pro-BNP will be related to an improvement in LVEDV, LVESV and LVEF following 10 weeks of CR exercise training in patients with recent MI.
5.3 Methods

5.3.1 Study design – overview
As described in chapter three (General methods), consecutive, male, post-MI patients were prospectively assigned to either an exercise training intervention group or a non-exercising control group. At baseline, and 10 weeks later, resting echocardiography and cardiopulmonary exercise testing (CPEX) were undertaken by all patients and whole blood samples at rest and post-exercise were obtained. As a component of standard cardioprotective lifestyle education, general physical activity advice was provided to both groups. The study commenced following ethical approval and receipt of informed consent.

5.3.2 Study population
Further to the exclusions described in chapter three, transthoracic echocardiography was performed in 58 patients. Additional exclusions in the intervention (n=3) and control (n=5) groups were necessary due to poor echocardiographic windows. Therefore, the final population for the present study (n=50) comprised 33 exercise training intervention patients and 17 controls. Biochemical analysis for resting NT-pro-BNP was possible in a sub-group of the intervention cohort (n=21).

5.3.3 Cardiopulmonary exercise testing and exercise training
Cardiopulmonary exercise testing and exercise training were conducted as detailed in chapter three.

5.3.4 Transthoracic echocardiography
The general procedures for the acquisition and analysis of images with transthoracic echocardiography are described in chapter three. All analyses were performed off-line by the lead investigator using commercially available software (Echo-pac, GE Medical Systems, Horten, Norway, version 7.0.0) with measurements averaged over two to three cardiac cycles.
In the following sections, echocardiographic measures are presented and described in relation to the echocardiographic modality employed and the view from which the images were acquired. Firstly, from the parasternal long axis view (PLAX), 2D echocardiography was used to determine LV internal diameter in systole and diastole (LVIDs, LVIDd), inter-ventricular septal wall thickness in systole and diastole (SWTs, SWTd), posterior wall thickness in systole and diastole (PWTs, PWTd), percentage fractional shortening (FS), relative wall thickness (RWT) and LV mass. Secondly, 2D echocardiography was applied in the apical 4-chamber (A4C) and 2-chamber (A2C) views to calculate LV end diastolic volume (LVEDV), LV end systolic volume (LVESV), LV stroke volume (SV) and LV ejection fraction (LVEF). Thirdly, from the A4C view, pulse waved doppler echocardiography of mitral inflow was employed to measure early mitral inflow velocity (E), late mitral inflow velocity (A), ratio of early to late mitral inflow velocity (E/A) and E-wave deceleration time (DT). Finally, tissue doppler echocardiography of the mitral annulus in the A4C view was utilised to establish peak systolic mitral annulus tissue velocity (s’), peak early diastolic mitral annulus tissue velocity (e’), peak late diastolic mitral annulus tissue velocity (a’), isovolumic relaxation time (IVRT), ratio of early to late peak mitral annulus tissue velocity (e’/a’) and ratio of peak early mitral inflow velocity to peak early mitral annulus tissue velocity (E/e’).

5.3.4.1 Measurement of left ventricular linear dimensions – parasternal long axis view
Left ventricular internal dimensions and wall thicknesses were determined from the PLAX view. Measurements were taken at the tissue-blood interface, perpendicular to the long axis of the LV at the level of the LV minor axis i.e. approximately at the mitral leaflet tips (mitral chordal level) (Otto, 2009). The following parameters were recorded in mm at end systole (s) and end diastole (d): left ventricular internal diameter (LVIDs, LVIDd), inter-ventricular septal wall thickness (SWTs, SWTd) and left ventricular posterior wall thickness (PWTs, PWTd) (figure 5.1). End-diastole was defined as the frame in which the cardiac dimension was largest, immediately following mitral valve closure and, similarly, end systole as the frame in which the
cardiac dimension was smallest, immediately prior to mitral valve opening (Armstrong and Ryan, 2009).

Figure 5.1 Parasternal long axis view. Left ventricular diameters were measured in diastole (left panel) and systole (right panel). LV, left ventricular cavity; LA, left atrial cavity; PW, posterior wall; SW, interventricular septal wall; AV, aortic valve. Dashed white line indicates the level at which measurements were acquired (adapted from British Society of Echocardiography (2012)).

In addition, fractional shortening (FS), relative wall thickness (RWT) and LV mass were derived using the following formulae (Lang et al., 2005):

1. FS (%) = \( \frac{\text{LVIDd} - \text{LVIDs}}{\text{LVIDd}} \times 100\% \)
2. RWT (no units) = \( \frac{2 \times \text{PWTd}}{\text{LVIDd}} \)
3. LV mass (g/m^2) = \( 0.8 \times \left(1.04 \left(\text{LVIDd} + \text{PWTd} + \text{SWTd}\right)^3 - \text{LVIDd}^3\right) + 0.6\) g

5.3.4.2 Measurement of left ventricular volumes – apical 4-chamber and 2-chamber views

The Simpsons bi-plane method was used to objectively quantify LV volumes (Lang et al., 2005). Accordingly, the LV endocardial border was traced at end-systole and end-diastole (as previously defined) in both the A4C and A2C views (figure 5.2). Care was taken to ensure exclusion of papillary muscles and trabeculae from the LV cavity. The basal border was delineated as a straight line between the mitral valve annuli of the lateral and septal walls in the A4C view and the anterior and inferior walls in the A2C view (Lang et al., 2005).
ventricular end diastolic volume (LVEDV) and end systolic volume (LVESV) in ml were subsequently calculated by the software using ‘Simpson’s rule of disks’, and the difference between the two reported in absolute terms (ml) as stroke volume (SV) and in relative terms (%) as left ventricular ejection fraction (LVEF).

![Figure 5.2](image)

**Figure 5.2** Apical 4-chamber and apical 2-chamber views. To determine LV volumes, the LV endocardium was manually traced in diastole and systole respectively in the A4C view (top panels) and A2C view (bottom panels) (from Lang, Bierig et al. 2005).

### 5.3.4.3 Pulsed wave doppler measurements of mitral inflow velocity – apical 4-chamber view

In the present study, pulse wave doppler echocardiography was utilised to measure mitral inflow velocity from the A4C view i.e. blood flow through the mitral valve. Early mitral inflow velocity as a result of the trans-mitral pressure gradient is commonly known as the E-wave (E), and late mitral inflow velocity due to atrial contraction, the A-wave (A). The units of measurement for both these indices is mm/s, and their unitless ratio (E/A) provides an indication of the relationship between the peak early and late diastolic, atrial to ventricular pressure (LA-
LV) gradient. Furthermore, the rate of deceleration of early mitral inflow, or E-wave deceleration time (DT), in ms, provides insight into LV chamber compliance (Armstrong and Ryan, 2009). When examined collectively, these parameters are indicative of varying degrees of global LV diastolic function. Both E and A were measured as the peak height of the corresponding doppler mitral inflow waveform, and the deceleration time as the time interval between peak E and the baseline intersection of the E-wave deceleration slope line (Otto, 2007) (figure 5.3).

![Figure 5.3](image.jpg)

**Figure 5.3** Transmitral doppler signal from the apical 4-chamber view. Peak early mitral inflow velocity (E), peak late mitral inflow velocity (A) and the rate of deceleration of early mitral inflow (DT) were determined as depicted.

### 5.3.4.4 Mitral annuli tissue doppler measurements – apical 4-chamber view

Doppler imaging of the septal and lateral mitral annuli in the A4C view provides quantification of systolic (s’), early diastolic (e’) and late diastolic (a’) peak mitral annulus tissue velocities in cm/s. All three measures are determined from the tissue doppler recordings of the lateral and septal mitral annuli by identifying the peak positive deflection (s’), first peak negative deflection (e’) and second peak negative deflection (a’) (figure 5.4). Subsequently, the derived ratios of e’/a’ and E/e’ are clinically relevant parameters, the former, representing LV relaxation and the latter, LV filling pressure (Kasner et al., 2007). Mitral annuli tissue doppler recordings can also be used to measure the isovolumic relaxation time (IVRT) which provides indication of the rate
of early active diastolic LV relaxation. This parameter is measured as the time interval (ms) between the intersection of the positive s’ wave with the baseline (after peak s’ has been achieved) and the point at which the e’ wave commences its negative deflection from the baseline (figure 5.4). In line with current international guidelines, this thesis will report all tissue velocities and associated timings as the average of septal and lateral annulus measurements (Nagueh et al., 2009) which is particularly important in the presence of regional LV wall motion abnormalities i.e. post-MI (Rivas-Gotz et al., 2003). However, lateral measurements will also be independently reported on the basis of their superior correlation with invasive indices of LV filling and stiffness in patients with normal LVEF (Rivas-Gotz et al., 2003, Kasner et al., 2007).

![Figure 5.4](image)

**Figure 5.4** Mitral annuli tissue doppler signal of the inter-ventricular septum from the apical 4-chamber view. Systolic (s’), early diastolic (e’), late diastolic (a’) peak mitral annulus tissue velocities and isovolumic relaxation time (IVRT) were measured as identified.

### 5.3.4.5 Reliability of transthoracic echocardiography

The reliability of transthoracic echocardiography has been comprehensively assessed over the past 40 years. When performed within the boundaries of an established framework (Oxborough, 2008, Lang et al., 2005), by suitably qualified and experienced sonographers, it is widely accepted that the level of reliability achieved with this technique is sufficient to justify its application as a clinical and research tool. All echocardiograms performed for this thesis were undertaken by highly experienced cardiac sonographers with significant research experience. Off-line analysis was performed by the lead investigator for whom intra-observer coefficient of
variation (CoV) data is presented in table 5.1. To obtain CoV data, images acquired for 10 patients were analysed twice. For each parameter, the within subject standard deviation was determined by calculating the square root of the residual mean square from the one-way analysis of variance. This value was then divided by the group mean of values from both analyses and multiplied by a hundred to establish a percentage CoV (Bland, 2003).

Table 5.1 Coefficient of variation for the analysis of echocardiographic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean of analysis 1 &amp; 2</th>
<th>SD of analysis 1 &amp; 2</th>
<th>CoV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LV size</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>5.0 ± 1.5</td>
<td>± 1.5</td>
<td>3</td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>3.5 ± 2.4</td>
<td>± 2.4</td>
<td>6</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>99.4 ± 4.2</td>
<td>± 4.2</td>
<td>4</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>43.2 ± 2.1</td>
<td>± 2.1</td>
<td>5</td>
</tr>
<tr>
<td><strong>LV mass and geometry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>241 ± 19</td>
<td>± 19</td>
<td>8</td>
</tr>
<tr>
<td>RWT (cm)</td>
<td>0.44 ± 0.04</td>
<td>± 0.04</td>
<td>9</td>
</tr>
<tr>
<td><strong>LV systolic function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>56.8 ± 1.7</td>
<td>± 1.7</td>
<td>3</td>
</tr>
<tr>
<td>Mean s’ (cm/s)</td>
<td>8.5 ± 0.6</td>
<td>± 0.6</td>
<td>7</td>
</tr>
<tr>
<td><strong>LV diastolic function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.87 ± 0.3</td>
<td>± 0.3</td>
<td>3</td>
</tr>
<tr>
<td>Mean E/e’ ratio</td>
<td>8.0 ± 0.6</td>
<td>± 0.6</td>
<td>7</td>
</tr>
<tr>
<td>Mean IVRT (ms)</td>
<td>87.3 ± 11.8</td>
<td>± 11.8</td>
<td>13</td>
</tr>
</tbody>
</table>

Data as mean ± SD. LV, left ventricular; LVIDd, LV internal diameter in diastole; LVIDs, LV internal diameter in systole; LVEDV, LV end diastolic volume; LVESV, LV end systolic volume; RWT, relative wall thickness; s’, peak systolic mitral annulus tissue velocity; E/A ratio, ratio of peak early (E) to late (A) mitral inflow velocity; E/e’ ratio, ratio of peak early (E) mitral inflow velocity to peak early diastolic mitral annulus tissue velocity (e’); IVRT, iso-volumic relaxation time.

5.3.5 Collection and handling of whole blood samples

Resting blood samples were collected prior to CPEX as per procedures outlined in chapter four. For the assessment of the relationship between resting NT-pro-BNP and LV volumetric parameters, biochemical analysis was conducted in a sub-group of intervention group patients (n=21).
5.3.6 Statistical analyses

General statistical methods are outlined in chapter three. Further to confirmation of normality with the Kolmogorov-Smirnov test, a two-way mixed model ANOVA was used to assess the effect of the 10-week exercise training intervention or control period on LV structure and function. Group × time interaction was used to establish differences between groups, and paired Student’s t-tests were applied to assess within group change. Pearson’s product-moment correlation coefficient was used to determine relationships between the relative change (Δ) in NT-pro-BNP and the absolute change (Δ) in LV volumetric parameters over the 10 week period. Relative change is expressed as a percentage, with the group mean calculated from percentage change for each individual subject.
5.4 Results

Overall, the intervention and control groups were well matched for clinical, demographic and exercise test characteristics (table 5.2). Despite the small difference in relative VO₂ peak, \((P<0.05)\) there was no statistical difference between the groups in absolute VO₂ peak \((P>0.05)\).

Tables 5.3 and 5.4 demonstrate that there was no difference between the intervention and control groups in LV structural and functional parameters at baseline \((P>0.05)\), and displays the effect of the 10-week exercise training intervention or control period. During the 10 weeks, there were no changes in prescribed medications in either group.

### Table 5.2 Demographic, clinical and exercise test parameters at baseline and 10 weeks

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=33)</th>
<th>Control (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>55.8 ± 9.2</td>
<td>56.2 ± 10.8</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 ± 0.1</td>
<td>1.8 ± 0.1</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>82.7 ± 10.2</td>
<td>83.1 ± 10.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 ± 2.6</td>
<td>27.6 ± 2.7</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>2.0 ± 0.1</td>
<td>2.0 ± 0.1</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI (n)</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>NSTEMI (n)</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Time post MI (days)</td>
<td>33.7 ± 8.9</td>
<td>35.7 ± 7.7</td>
</tr>
<tr>
<td>HRrest (bpm)</td>
<td>59 ± 8</td>
<td>58 ± 7</td>
</tr>
<tr>
<td>BPsys (mmHg)</td>
<td>113 ± 17</td>
<td>110 ± 16</td>
</tr>
<tr>
<td>BPdia (mmHg)</td>
<td>71 ± 8</td>
<td>71 ± 8</td>
</tr>
<tr>
<td><strong>CPEX</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO₂ peak (L.min⁻¹)</td>
<td>2.0 ± 0.4</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>VO₂ peak (ml.kg⁻¹.min⁻¹)</td>
<td>24.0 ± 4.1</td>
<td>27.5 ± 4.6</td>
</tr>
<tr>
<td>Wmax (watts)</td>
<td>148 ± 27</td>
<td>175 ± 30</td>
</tr>
<tr>
<td>VT (ml.kg⁻¹.min⁻¹)</td>
<td>12.5 ± 2.8</td>
<td>14.6 ± 3.5</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>30.3 ± 4.4</td>
<td>31.3 ± 4.4</td>
</tr>
<tr>
<td>Exercise time (mins)</td>
<td>8.6 ± 1.0</td>
<td>9.9 ± 1.2</td>
</tr>
</tbody>
</table>

Data as mean ± SD. BMI, body mass index; BSA, body surface area; STEMI, ST elevation myocardial infarction; NSTEMI, non ST elevation myocardial infarction; MI, myocardial infarction; HRrest, resting heart rate; BPsys, systolic blood pressure; BPdia, diastolic blood pressure; CPEX, cardiopulmonary exercise test; VO₂ peak, peak oxygen uptake; Wmax, maximum workload; VT, ventilatory threshold; VE/VCO₂ slope, ventilatory efficiency slope. § \(P<0.05\) vs. control at baseline, † \(P<0.05\) time effect (ANOVA), ‡ \(P<0.05\) group × time interaction effect (ANOVA), ****\(P<0.0001\) vs. baseline.
Table 5.3 Left ventricular structural parameters at baseline and 10 weeks

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=33)</th>
<th>Control (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Week 10</td>
<td>Baseline Week 10</td>
</tr>
<tr>
<td><strong>LV size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVId (cm)</td>
<td>4.8 ± 0.5 4.8 ± 0.5</td>
<td>4.9 ± 0.5 4.9 ± 0.5</td>
</tr>
<tr>
<td>LVId (cm)</td>
<td>3.2 ± 0.5 3.2 ± 0.5</td>
<td>3.4 ± 0.6 3.4 ± 0.5</td>
</tr>
<tr>
<td>LVId/BSA (cm²)</td>
<td>2.2 ± 0.6 2.4 ± 0.2</td>
<td>2.4 ± 0.6 2.4 ± 0.2</td>
</tr>
<tr>
<td>LVId/BSA (cm²)</td>
<td>1.7 ± 0.3 1.7 ± 0.2</td>
<td>1.6 ± 0.3 1.7 ± 0.2</td>
</tr>
<tr>
<td><strong>LV mass and geometry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>209 ± 46 217 ± 57</td>
<td>234 ± 51 217 ± 45</td>
</tr>
<tr>
<td>IVSd (cm)</td>
<td>1.3 ± 0.2 1.3 ± 0.2</td>
<td>1.4 ± 0.3 1.3 ± 0.2</td>
</tr>
<tr>
<td>LVPWd (cm)</td>
<td>1.1 ± 0.2 1.1 ± 0.2</td>
<td>1.1 ± 0.2 1.1 ± 0.2</td>
</tr>
<tr>
<td>IVSs (cm)</td>
<td>1.7 ± 0.2 1.7 ± 0.2</td>
<td>1.8 ± 0.3 1.8 ± 0.3</td>
</tr>
<tr>
<td>LVPWs (cm)</td>
<td>1.5 ± 0.3 1.5 ± 0.2</td>
<td>1.5 ± 0.3 1.5 ± 0.3</td>
</tr>
<tr>
<td>RWT (cm)</td>
<td>0.45 ± 0.08 0.45 ± 0.08</td>
<td>0.46 ± 0.11 0.45 ± 0.10</td>
</tr>
<tr>
<td>LV mass/BSA (g/m²)</td>
<td>106 ± 20 109 ± 25</td>
<td>115 ± 26 105 ± 19</td>
</tr>
</tbody>
</table>

Data as mean ± SD. LV, left ventricular; LVId, LV internal diameter in diastole; BSA, body surface area; LVId, LV internal diameter in systole; LVEn, LV end diastolic volume; LVEn, LV end systolic volume; IVSd, inter-ventricular septal wall in diastole; LVPWs, LV posterior wall in diastole; IVSs, inter-ventricular septum in systole; LVPWs, LV posterior wall in systole; RWT, relative wall thickness.

Table 5.4 Left ventricular functional parameters at baseline and 10 weeks

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=33)</th>
<th>Control (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Week 10</td>
<td>Baseline Week 10</td>
</tr>
<tr>
<td><strong>LV systolic function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>31.9 ± 7.2 32.1 ± 5.3</td>
<td>31.9 ± 7.2 31.5 ± 7.3</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>46.8 ± 9.5 46.3 ± 8.3</td>
<td>52.9 ± 11.9 53.1 ± 9.8</td>
</tr>
<tr>
<td>Lateral s’(cm/s)</td>
<td>8.1 ± 2.9 8.3 ± 2.4</td>
<td>9.1 ± 2.3 8.5 ± 3.0</td>
</tr>
<tr>
<td>Mean s’(cm/s)</td>
<td>8.0 ± 1.9 8.0 ± 1.6</td>
<td>8.4 ± 1.6 8.1 ± 2.0</td>
</tr>
<tr>
<td><strong>LV diastolic function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.15 ± 0.33 1.06 ± 0.24</td>
<td>1.14 ± 0.36 1.17 ± 0.37</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>215 ± 34 224 ± 44</td>
<td>217 ± 67 245 ± 67</td>
</tr>
<tr>
<td>Lateral e’(cm/s)</td>
<td>9.5 ± 3.3 10.0 ± 3.1</td>
<td>10.0 ± 3.3 9.8 ± 2.9</td>
</tr>
<tr>
<td>Lateral a’(cm/s)</td>
<td>8.6 ± 2.4 9.2 ± 2.4</td>
<td>8.9 ± 1.4 8.8 ± 2.3</td>
</tr>
<tr>
<td>Lateral e’/a’ ratio</td>
<td>1.2 ± 0.5 1.1 ± 0.4</td>
<td>1.2 ± 0.4 1.2 ± 0.5</td>
</tr>
<tr>
<td>Lateral E/e’ ratio</td>
<td>7.3 ± 2.6 6.6 ± 2.0</td>
<td>6.6 ± 2.0 6.2 ± 2.8</td>
</tr>
<tr>
<td>Mean e’(cm/s)</td>
<td>8.1 ± 2.3 8.6 ± 2.1</td>
<td>8.9 ± 2.4 8.8 ± 2.1</td>
</tr>
<tr>
<td>Mean a’(cm/s)</td>
<td>8.9 ± 1.6 9.2 ± 1.3</td>
<td>8.9 ± 1.2 8.6 ± 1.9</td>
</tr>
<tr>
<td>Mean e’/a’ ratio</td>
<td>1.0 ± 0.3 1.0 ± 0.2</td>
<td>1.0 ± 0.3 1.1 ± 0.4</td>
</tr>
<tr>
<td>Mean E/e’ ratio</td>
<td>8.4 ± 2.0 7.6 ± 1.6</td>
<td>7.5 ± 1.7 7.0 ± 2.9</td>
</tr>
<tr>
<td>Lateral IVRT (ms)</td>
<td>80 ± 30 77 ± 26</td>
<td>75 ± 24 89 ± 20</td>
</tr>
<tr>
<td>Mean IVRT (ms) †</td>
<td>83 ± 26 88 ± 24</td>
<td>85 ± 24 96 ± 19 **</td>
</tr>
</tbody>
</table>

Data as mean ± SD. s’, peak systolic mitral annulus tissue velocity; E/A ratio, ratio of peak early (E) to late (A) mitral inflow velocity; DT, rate of deceleration of early mitral inflow; e’ peak early diastolic mitral annulus tissue velocity; a’, peak late diastolic mitral annulus tissue velocity; e’/a’ ratio, ratio of peak early to late diastolic mitral annulus tissue velocity; E/e’ ratio, ratio of peak early mitral inflow velocity to peak early diastolic mitral annulus tissue velocity; IVRT, iso-volumic relaxation time. † P<0.05 time effect (ANOVA), **P<0.01 vs. baseline.
5.4.1 Effect of cardiac rehabilitation exercise training on demographic, clinical and exercise test parameters

All exercise testing and training sessions were completed without any incidence of cardiovascular complication or other adverse events. Average exercise session attendance per patient was 88.3%. In comparison to the control group, \( W_{\text{max}} \), \( \text{VO}_2 \text{peak} \), VT and exercise time all increased in response to exercise training (all \( P<0.05 \)) (table 5.1). In the intervention group, \( \text{VO}_2 \text{peak} \) increased by 16%, \( W_{\text{max}} \) by 19%, VT by 18%, and exercise time by 16% (all \( P<0.0001 \)) (table 5.1). In the control group, however, no changes were noted. The change in VE/VCO\(_2\) slope also differed between groups (\( P<0.05 \)). A 4% increase was noted in the intervention group and a 3% decrease in the control group, neither of which independently reached statistical significance (\( P>0.05 \)). There were no statistical changes in demographic or clinical variables in either group over the course of the study period (\( P>0.05 \)) (table 5.1).

5.4.2 Effect of cardiac rehabilitation exercise training on left ventricular structure and function

On completion of the exercise training intervention, LVEDV and LVEDV/BSA (both \( P<0.05 \)), and LVESV and LVESV/BSA (both \( P<0.01 \)) were decreased in comparison to the control group. As depicted in figure 5.5, 10 weeks of exercise training resulted in a 5% reduction in LVEDV and LVEDV/BSA (both \( P<0.001 \)) and a 9% reduction in LVESV and LVESV/BSA (both \( P<0.001 \)), whereas volumetric parameters remained unchanged in the control group (\( P>0.05 \)). For ease of presentation for the remainder of this thesis, the change in end diastolic volumes (i.e. LVEDV) and the equivalent change in indexed LV volumes (i.e. LVEDV/BSA) will be collectively described as the non-indexed variable (i.e. LVEDV). No changes were observed in LV linear dimensions, mass or geometry during the 10-week intervention or control period (\( P>0.05 \)). Furthermore, other than mean IVRT, which was prolonged in the cohort as a whole (\( P<0.05 \)), the exercise training intervention had no impact on systolic or diastolic function (table 5.4).
Figure 5.5. Left ventricular (LV) volumetric parameters at baseline (dark grey bars) and at 10 weeks (light grey bars) in the intervention group (solid bars) and control group (striped bars) (a) LV end diastolic volume (ml) (b) LV end diastolic volume/BSA (ml/m\(^2\)), (c) LV end systolic volume (ml), (d) LV end systolic volume/BSA (ml/m\(^2\)), (e) LV ejection fraction (%). Data as mean ± SD. ***\(P<0.001\).

5.4.3 Relationship between NT-pro-BNP and left ventricular volumetric parameters

In a sub group of intervention group patients (n=21), resting NT-pro-BNP prior to the CR exercise training intervention (267 ± 232 pg/mL), was significantly reduced after 10 weeks (158 ± 121pg/mL, \(P<0.01\)). Furthermore, the relative change in resting NT-pro-BNP (%) over the course of the 10-week intervention demonstrated significant positive correlation with the absolute change in LVEDV (ml) (\(r = 0.58, P<0.01, r^2 = 0.33\)) (figure 5.6a). There was no
significant relationship between the relative change in NT-pro-BNP and the absolute change in either LVESV \((r = 0.10, P>0.05, r^2 = 0.01)\) or LVEF \((r = 0.17, P>0.05, r^2 = 0.03)\) (figure 5.6).

Figure 5.6 Correlation between the relative change \((\Delta)\) in NT-pro-BNP (%) and the absolute change \((\Delta)\) in left ventricular (LV) (a) end diastolic volume (EDV) (ml), (b) end systolic volume (ESV) (ml) and (c) ejection fraction (EF) (%) in the intervention group
5.5 Discussion

The aims of the current study, in post-MI patients with mildly abnormal LVEF, were to investigate the reverse LV remodelling effect of CR exercise training and to determine the association between exercise induced reductions in NT-pro-BNP and changes in LV structural and functional parameters. The three main findings from the study were: 1) 10 weeks of CR exercise training improved VO$_{2peak}$, CPEX exercise time and workload 2) the exercise training intervention was effective in volumetrically reverse remodelling the LV as evidenced by significant reductions in LVEDV and LVESV, and 3) there was a positive correlation between the relative change in resting NT-pro-BNP and the absolute change in LVEDV.

5.5.1 Effect of cardiac rehabilitation exercise training on reverse LV remodelling

The present study demonstrated that, in addition to improved functional capacity, completion of a 10-week CR exercise training programme resulted in reverse LV remodelling in post-MI patients with mildly abnormal LVEF. The study measured a broad spectrum of echocardiographic variables with a view to examining the effects of CR exercise training on LV size, mass, geometry, systolic function and diastolic function. Following completion of the exercise training intervention, the most notable finding was a significant 5% and 9% reduction in LVEDV and LVESV respectively. Moreover, no change was witnessed in the control group, and with medication equally administrated in both groups, the change in LV volumes can likely be attributed to the exercise training intervention. Interestingly, there was no appreciable change in any other measure of LV size, mass or geometry.

The results of the current study are in keeping with previous reports. In a recent meta-analysis, Haykowsky and colleagues (2011) reported a positive effect of exercise training on LVEDV and LVESV in an exclusively post-MI population. However, the included studies displayed significant clinical and methodological heterogeneity in relation to patient demographic, clinical status and exercise training intervention design. The authors concluded, that this may have limited the quality of the analysis. Nevertheless, a measurable reduction was reported in LV
volumes, indicating the efficacy of various formats of exercise training. Most closely matched to the cohort in the present investigation is a study by Koizumi and colleagues (2003) in which exercise training commenced four weeks post-MI in a small cohort of patients with mildly abnormal LVEF (56 ± 5%). However, in contrast to the findings of the current study, completion of 30 min of daily walking at ‘moderate pace’ did not result in improvements in LVEDVI, LVESVI or LVEF. It is possible that the difference in these studies, despite similar clinical characteristics, was due to the lack of formal assessment of exercise capacity and the non-specific nature of the exercise training intervention in the study by Koizumi. Without appropriately prescribed exercise intensity (i.e. with reference to the results of a graded exercise text), and in the absence of an accurate method of monitoring during the exercise intervention (i.e. HR), it is possible that an exercise stimulus sufficient to result in reverse LV remodelling was not achieved.

The positive change in LV volumes in the present study was not accompanied by a change in functional parameters, i.e. SV and LVEF. This finding is at odds with the Haykowsky review which reported improved LVEF with exercise training. However, within group analysis in the current study did indicate a tendency towards improvement in the intervention group (P=0.011), whilst there was no change in the control group. It is, therefore, likely that with greater statistical power, the improvement in LVEF in the intervention group may have achieved significance. Alternatively, the mildly abnormal LVEF in this cohort, as opposed to the marked dysfunction in previous studies may, by definition, dictate limited scope for improvement. This relatively preserved function may also be responsible for the absence of any improvement in diastolic function. Whilst mean IVRT was prolonged in the cohort as a whole, this was not considered to represent a functional diastolic adaptation. In the absence of change in any other diastolic parameters this measurement is non-specific (Armstrong and Ryan, 2009), and, therefore, the relevance of this finding is unclear.
The meta-regression in the analysis by Haykowsky and colleagues also identified early initiation and longer duration of exercise training as predictors of greater improvement in LVEDV, LVESV and LVEF. Commencement of exercise training in the current study was relatively delayed (five weeks post-MI) and the intervention was considerably shorter (10 weeks) than the most effective protocols (six months) in the Haykowsky study. In the absence of early initiation of training and prolonged programme duration in the present study, it would seem realistic to identify the higher exercise intensity as the overriding factor responsible for the improvement in LV volumes. Whilst the exercise intensity was not higher than 70% VO$_{2\text{peak}}$ in previous studies, the current protocol was rigorously conducted at an intensity of at least 80% VO$_{2\text{peak}}$. In accordance with emerging literature in the CHF population, higher exercise intensities are more likely to promote reverse LV remodelling (Wisloff et al., 2009, Wisloff et al., 2007). Whilst it was not the intention of the current study to determine the most appropriate intensity of exercise training required to provoke reverse LV remodelling, it is possible that the improved LV volumes witnessed, are indicative of the higher intensity of exercise performed.

### 5.5.2 Mechanisms for reverse left ventricular remodelling with cardiac rehabilitation exercise training

Current knowledge of the effect of medical therapy and exercise training on LV remodelling is limited. However, several key mechanisms have been investigated in human models, and experimentation in animal models has provided insight into molecular and cellular adaptation. As previously discussed, LV systolic and diastolic function is, in part, mediated by systemic autonomic and neurohormonal overexpression (Bonow et al., 2012, Solomon et al., 2011). In an effort to maintain hemodynamic equilibrium, enhanced and sustained neurohormonal activation is both compensatory in the short term and detrimental in the long term (Mann and Bristow, 2005, Floras, 2003). Over expression of other biologically active molecules associated with this process (i.e. endothelin, angiotensin II) directly contributes to the destruction of myocardial integrity, increasing extra-cellular myocardial collagen content and stimulating fibrotic and
hypertrophic maladaptation of the LV (Gray et al., 1998). Exercise training has been shown to exert beneficial effect in a number of key areas in this counterproductive pathological cascade.

There is good evidence of the counteractive effect of exercise training on compensatory neurohormonal mechanisms (Gademan et al., 2007). It is well known from pharmacological trials that suppression of these mechanisms can reduce their destructive effects (St John Sutton et al., 2003, Koitabashi and Kass, 2012, Fraccarollo et al., 2003). This appears to be important in preventing the progression of maladaptive LV remodelling. In addition, in combination with specific vascular adaptation to exercise i.e. improved endothelial function, reduced neurohormonal activation contributes to the normalisation of LV afterload (Hambrecht et al., 2000, Hambrecht et al., 1998). It is likely that this helps restore normal LV loading conditions and thus facilitates the process of reverse LV remodelling. The magnitude of this effect, however, may prove less significant than originally thought, in light of findings from recent animal investigations (Gielen et al., 2010). The direct effect of exercise training on the myocardium has been demonstrated in a number of animal models and is increasingly verified as a key contributor to the process of reverse LV remodelling (Kemi and Wisloff, 2010, Schober and Knollmann, 2007, Kemi et al., 2007, McMullen et al., 2007). A plethora of exercise induced, biomolecular adaptations interfere with maladaptive signalling pathways which results in attenuation of hypertrophy, fibrosis and apoptosis. It is, therefore, likely that the reverse remodelling effect attributed to CR exercise training in the current study, is a result of the combined influence of the above potential mechanisms in addition to other, as yet, unquantified processes.

5.5.3 Relationship of NT-pro-BNP with left ventricular reverse remodelling
In the CR exercise training group, the current study demonstrated a moderate, significant correlation between the relative change in NT-pro-BNP and the absolute change in LVEDV. Those, in whom a greater relative reduction in NT-pro-BNP was observed, had a greater
reduction in absolute LVEDV. In the previous chapter, it was shown that NT-pro-BNP can be reduced with CR exercise training. Not only was NT-pro-BNP reduced at rest, but the acute response of NT-pro-BNP to maximal and submaximal exercise was attenuated following the exercise training intervention. It was proposed, in line with limited previous research, that these changes may represent reverse structural and functional LV remodelling (Giallauria et al., 2008, Giallauria et al., 2006a, Malfatto et al., 2009). Data from the present study provides some confirmation of this association, and is the first study to do so in patients with mildly abnormal LVEF.

The current findings are supported by data from Giallauria and colleagues (2008) who demonstrated a positive correlation between changes in NT-pro-BNP and LVEDVI (r=0.86, P<0.001) in patients with more pronounced LV dysfunction (LVEF<45%). Furthermore, reduced NT-pro-BNP has been shown to correlate with improved early diastolic filling (E-wave) (r= -0.44, P<0.001) (Giallauria et al., 2008), E/A ratio (r= -0.59, P<0.001) (Giallauria et al., 2006a) and LV elastance (r= -0.58, P<0.01), an index of ‘LV stiffness’ derived from transmitral doppler deceleration time (Malfatto et al., 2009). The direct and indirect molecular and cellular adaptations associated with exercise training (as described in 5.5.3) are likely implicated in reducing LV wall stress and NT-pro-BNP, with a coexistent reduction in LV volumes and an improvement in diastolic filling.

5.5.4 Clinical significance of findings

In a population presenting with mildly abnormal LVEF but with LV volumes within normal limits, the prognostic significance of reverse volumetric LV remodelling is yet to be fully evaluated. Investigation has focussed on those with more significant LVSD, in whom a reduction in LV volumes is a highly desirable outcome, demonstrating a clear relationship with improved survival (Solomon et al., 2005). However, prognostic benefit may also result from reduced LV volumes in less compromised patients. Abnormal hemodynamics following MI are
a product of the pathological imbalance between LV pressures, dimensions and wall thicknesses and result in functional impairment (Mann et al., 2012). Ultimately, left untreated, this may lead to progressive functional decline in some patients with resultant prognostic implications (Konstam et al., 2011). A reduction in LV volumes provides the environment for restoration of normal LV hemodynamics and thus offers the potential for improved prognosis. The raised resting NT-pro-BNP prior to exercise training in the current study further indicates hemodynamic compromise by virtue of its relationship with increased LV wall stress (Ruskoaho, 2003). Therefore, the significant decrease in NT-pro-BNP, and the moderate correlation of this change with a reduction in LV volumes, shows an improvement in the overall neurohormonal and hemodynamic environment in response to exercise training. The improvement in VO$_2$peak witnessed in the current study is also highly clinically significant (Arena et al., 2004, Francis et al., 2000). The concurrent reduction in LV volumes and NT-pro-BNP may be evidence of a cardiac contribution to improved VO$_2$peak and the associated improvements in prognosis reported with participation in CR exercise training (Lawler et al., 2011).

### 5.5.5 Hypotheses

1) Ten weeks of CR exercise training will decrease LVEDV and LVESV in patients with recent MI - **ACCEPTED**

2) Ten weeks of CR exercise training will increase LVEF in patients with recent MI - **REJECTED**

3) Reductions in NT-pro-BNP will correlate with improvement in LVEDV, LVESV and LVEF following 10 weeks of CR exercise training in patients with recent MI – **PARTIALLY ACCEPTED.** Reduced NT-pro-BNP correlated with improved LVEDV but not with LVESV or LVEF
5.5.6 Conclusion

To conclude, 10 weeks of CR exercise training improved functional capacity and had a significant reverse LV remodelling effect, reducing LVEDV and LVESV. These findings, in an increasingly prevalent CR population of post-MI patients with mildly abnormal LVEF, extend previous knowledge of reverse remodelling with CR exercise training in more compromised patients. Not only does this serve to confirm the general therapeutic benefit of CR exercise training, but may also indicate the potential contribution of cardiac adaptation to the well documented reductions in cardiovascular and all cause mortality. Furthermore, a reduction in LVEDV occurred alongside a reduction in NT-pro-BNP, providing further insight into the association of LV wall stress with reverse LV remodelling. The potential role of NT-pro-BNP as a measure of therapeutic benefit in its own right and as a surrogate indicator of reverse LV remodelling has, to an extent, been confirmed by the results of the current and preceding study. It is, therefore, tentatively recommended that NT-pro-BNP be considered as a routine measurement in CR exercise training programmes as a measure of efficacy and an aid to the long term management of post-MI patients.
CHAPTER 6

Study 3
The effect of cardiac rehabilitation exercise training
on left ventricular mechanics
6.1 Introduction

The assessment of LV structure and function is a key component of the integrated care pathway for the management of patients following acute MI (O’Gara et al., 2013). Serial assessment allows the clinician to quantify chronic LV remodelling and determine the efficacy of therapeutic intervention, modifying treatment strategies accordingly (Fihn et al., 2012). Post-MI LV remodelling, the progressive structural and functional maladaptation associated with infarcted myocardium, is predominantly evaluated through the measurement of LV volumetric parameters such as LVEDV and LVESV (Cheng and Vasan, 2011, Gaasch and Zile, 2011). These measures, in addition to LVEF, are prognostically significant (Verma et al., 2008) and thus their improvement is an aggressively pursued therapeutic target. However, whilst structural LV remodelling appears relatively well defined, the ability of LVEF and Doppler derived indices to adequately assess LV functional remodelling has long been debated (Feigenbaum et al., 2012). These techniques are inherently limited and unable to characterise the multidirectional deformation of the LV during systole and diastole.

During systolic contraction, the transmural laminar construction of obliquely and opposingly wound endocardial and epicardial myofibres respond to an apex to base electrical activation sequence with longitudinal, circumferential and radial deformation (LV strain) and the consequent production of LV rotation and twist (Sengupta et al., 2007). Similarly, diastolic relaxation is characterised by the development of a high intraventricular pressure gradient and subsequent ‘suction’ of blood into the LV, generated predominantly by the untwisting of the LV during isovolumic relaxation and early diastole (Sengupta et al., 2008b). The assessment of LV mechanics with speckle tracking echocardiography (STE) allows this complex motion to be characterised in the post-MI population. Indices such as longitudinal strain and LV rotation, have been shown to reflect LV impairment acutely post-MI (Geyer et al., 2010). They may also demonstrate superior discrimination over conventional echocardiographic indices for the prediction of chronic LV remodelling (Spinelli et al., 2012). Over and above the greater sensitivity of these measurements, the potential advantage of LV mechanics over conventional
measures may extend to improved inter-observer variability (Global longitudinal strain (GLS) vs. LVEF) and more automated, less subjective quantification of LV systolic and diastolic dysfunction (Sjoli et al., 2011, Munk et al., 2012). In light of these benefits, and some acceptance of these techniques in clinical practice, the measurement of LV mechanics has been used in the evaluation of chronic therapeutic intervention. The optimisation of cardiac resynchronisation therapy in advanced CHF is one such area in which LV mechanics has been shown to offer superior clinical insight in comparison to conventional echocardiographic measures (Saba et al., 2013). It is possible that the characterisation of LV functional remodelling following chronic CR exercise training may also be better represented by LV mechanics.

Cardiac rehabilitation exercise training has proven benefits including increased functional capacity and reduced cardiovascular mortality (Lawler et al., 2011, Valkeinen et al., 2010). Whilst much is known of the peripheral adaptation to this therapeutic intervention (Gielen et al., 2010), comparatively little is known of cardiac adaptation, which in part may relate to a historical lack of appropriate methods of measurement. As discussed in chapter two, the literature pertaining to the effects of CR exercise training on LV structural and functional remodelling is equivocal, particularly in relation to LV functional adaptation (Haykowsky et al., 2011). Whilst CR exercise training led to an improvement in LVEF in a number of studies in post-MI patients, this potentially arbitrary measure may not represent true functional adaptation. Further study of LV function is required to assess the efficacy of CR exercise training in this regard. Indices of LV mechanics, with the ability to quantify regional LV systolic and diastolic function, offer the potential to further develop our understanding of cardiac adaptation to CR exercise training.

In the previous experimental chapters of this thesis, clear indication of the therapeutic benefit of CR exercise training was demonstrated in patients with mildly abnormal LVEF following recent MI. Firstly, in addition to improved functional capacity in chapter four, a reduction in resting
NT-pro-BNP was shown. This indicated improvement in the neurohormonal and hemodynamic environment of the post-MI LV, in keeping with reduced LV wall stress and reverse remodelling. Secondly, in chapter five, conventional echocardiographic assessment revealed improvement in LV volumetric but not functional indices, providing insight into reverse LV remodelling following CR exercise training. Finally, the potential link between reduced NT-pro-BNP and reverse LV remodelling was to some extent confirmed by the correlation between reduced NT-pro-BNP and reduced LVEDV in a subgroup of patients in chapter five. Overall, an effect of CR exercise training on neurohormonal activation and LV volumetric remodelling was identified in preceding chapters although little indication of LV functional adaptation was evident. This may be a consequence of the lack of sensitivity offered by conventional functional echocardiographic parameters such as LVEF. The assessment of LV mechanics, therefore, has clear rationale in potentially identifying functional reverse remodelling following CR exercise training. Whilst this is an interesting area of research, the study of LV mechanics in response to exercise training is extremely limited, primarily due to the relative novelty of STE. However, longitudinal exercise training studies in healthy individuals have observed LV mechanical adaptation, characterised predominantly by an increase in LV twist (Aksakal et al., 2013, Weiner et al., 2010). Currently there are no studies that have examined the effects of CR exercise training on LV mechanics in the post-MI population.

Understanding of LV functional adaptation to CR exercise training is currently limited and there is a lack of scientific literature dedicated to the effects of CR exercise training on LV mechanics. With a view to extending the experimental findings of chapters four and five of this thesis, the aim of the present study, in patients with mildly abnormal LVEF, was to assess the effects of 10 weeks of CR exercise training on LV mechanics.

6.2 Hypotheses

1. Resting LV twist will increase in response to ten weeks of CR exercise training
2. Resting LV longitudinal, radial and circumferential strain will increase in response to ten weeks of CR exercise training

3. Resting LV longitudinal, radial and circumferential strain rate will increase in response to ten weeks of CR exercise training

6.3 Methods

6.3.1 Study design – overview
As described in chapter three (General methods), consecutive, male, post-MI patients were prospectively assigned to either an exercise training intervention group or a non-exercising control group. At baseline, and 10 weeks later, resting echocardiography and cardiopulmonary exercise testing (CPEX) were undertaken by all patients. As a component of standard cardioprotective lifestyle education, general physical activity advice was provided to both groups. The study commenced following ethical approval and receipt of informed consent.

6.3.2 Study population
In addition to the exclusions outlined in chapter three, further patients were excluded in the intervention (n=17) and control (n=5) groups due to poor echocardiographic windows. Therefore, the final population for the present study (n=36) comprised 19 exercise training intervention patients and 17 controls.

6.3.3 Cardiopulmonary exercise testing and exercise training
Cardiopulmonary exercise testing and exercise training were conducted as detailed in chapter three.

6.3.4 Transthoracic echocardiography
Procedures for image acquisition and analysis of conventional transthoracic echocardiography parameters are introduced in chapter three and further detailed in chapter five.
6.3.5 Speckle tracking echocardiography (STE)

In addition to the standard echocardiography techniques, discussed in chapter three, STE was used to assess LV mechanics, the principles of which are described in chapter two. Speckle tracking echocardiography was used to derive indices of LV mechanics from the A4C view and the basal and apical PSAX views. Images were acquired at a frame rate between 45 and 100 frames/s to avoid image decorrelation (Bertini et al., 2009a, Hoit, 2011). Care was taken to ensure that basal images were recorded at the tips of the mitral valve leaflets (Park et al., 2008a), apical images recorded just proximal to the level of LV luminal closure at end systole (Helle-Valle et al., 2005) and that the LV cross-section was as circular as possible (Helle-Valle et al., 2009). Furthermore, inter-individual basal and apical images and repeated measure images were acquired at the same frame rates. Analysis of STE in the A4C view was conducted as follows. The endocardium was manually traced from the septal to lateral mitral annuli. A region of interest (ROI) was automatically applied by the software, which if necessary, was manually adjusted to ensure inclusion of the full thickness of myocardium, whilst excluding the pericardium. By identifying unique, stable blocks of pixels or ‘speckles’, (Gorcsan and Tanaka, 2011), echocardiographic analysis software (Echo-pac, GE Medical Systems, Horten, Norway, version 7.0.0) tracked the motion of the adopted ROI frame-by-frame throughout the cardiac cycle and delineated six specific myocardial segments: basal septum, mid septum, apical septum, apical lateral, mid lateral and basal lateral (figure 6.1). Automated indication was given of segmental tracking quality. The lead investigator modified the ROI and/or the endocardial tracing to improve tracking, or otherwise exclude segments which inadequately tracked. Records were made of excluded segments and the same segments were excluded from repeated measurements. Patients were excluded where more than two segments were deemed to have insufficient tracking quality or where visual inspection of the automatically constructed strain curves indicated unacceptable tracking (Kim et al., 2007). The endocardial border was tracked in similar fashion at the basal and apical levels in the PSAX view (figure 6.2) and six segments were once more identified: anterior, lateral, posterior, inferior, septal and antero-septal.
Figure 6.1 Example of the region of interest (ROI) applied with LV speckle tracking echocardiography (STE) in the apical 4-chamber view (A4C). The LV endocardium was manually traced and an automatically generated ROI was manually adjusted to ensure inclusion of the full thickness of the myocardium and exclusion of the pericardium. Coloured dots represent myocardial segments: yellow, basal septum; turquoise, mid septum; green, apical septum; pink, apical lateral; blue, mid lateral; red, basal lateral.

Figure 6.2 Example of the region of interest (ROI) applied with LV speckle tracking echocardiography (STE) in the basal parasternal short axis view (PSAX) (left panel) and (b) the apical PSAX view (right panel). The LV endocardium was manually traced and an automatically generated ROI was manually adjusted to ensure inclusion of the full thickness of the myocardium and exclusion of the pericardium. Coloured dots represent myocardial segments: yellow, antero-septal; turquoise, anterior; green, lateral; pink, posterior; blue, inferior; red, septal.

Data were exported as the average of 4 - 6 segments to bespoke software (2D Strain Analysis Tool, Stuttgart, Germany) for further automated and operator processing. To accommodate inter and intra-individual variations in heart rate, data were normalised to the percentage of systolic and diastolic duration using cubic spline interpolation (Stohr et al., 2012). Systolic values were
taken from the peak of the R-wave on the ECG to aortic valve closure and vice-versa for diastolic values. Raw frame-by-frame data were converted to 1200 data points in total, 600 representing systole and 600 representing diastole. Each parameter was graphically illustrated (y-axis) against time (x-axis), (figure 6.3) with results presented as the mean for each group (intervention and control), pre and post intervention/control period. It should be noted, that due to the inter-individual variation in LV dysfunction, the peak value for a specific parameter i.e. peak twist, may have been achieved at a different time point in systole for each patient. Therefore, further to normalisation for heart rate (in relation to aortic valve closure), the graphically presented peak mean value represents the mean of the peak values relative to the time of the cardiac cycle as opposed to the mean of the actual peak for the group. Subsequently, for indices of LV mechanics, the peak values displayed in the tables of results differ from those on the graphs. The tables of results display the mean of the peak values achieved by each patient, irrespective of the time point at which it was achieved.
Figure 6.3 Annotated example of temporal LV strain and rotation curves. Each panel displays data for a single participant over one cardiac cycle as a percentage of systole and diastole for (a) LV longitudinal strain, (b) LV longitudinal strain rate (c) LV apical rotation, (d) LV apical rotation velocity, (e) LV basal rotation, (f) LV basal rotation velocity, (g) LV twist, (h) LV twist velocity. LV, left ventricular; AVC, aortic valve closure; °, degrees.
6.3.5.1 Measurement of strain and strain rate

Various interchangeable terms have been proposed as descriptors of myocardial strain indices. For the purpose of this thesis, strain indices were derived from STE analysis and defined and calculated as described in the following subsections. Speckle tracking echocardiography measures Lagrangian strain, which can be defined as the motion around a ‘given point’ in tissue as it traverses through space and time (Geyer et al., 2010). For the software package used in the present study, the ‘given point’ was the end-diastolic tissue dimension (D’Hooge et al., 2000). Positive strain (+ve) was indicative of tissue lengthening and negative strain (-ve) of tissue shortening, and all values were calculated by the software as relative change (%) (Hoit, 2011). Peak mean systolic strain was defined as the highest absolute value of peak positive or peak negative strain attained during systole (Grenne et al., 2011) and was measured in 3 planes; circumferential shortening (-ve strain) from the basal and apical PSAX image, radial thickening (+ve strain) from the basal and apical PSAX image, and longitudinal shortening (-ve strain) from the A4C view. Systolic and diastolic strain rates (SR) were simply the change in strain over time in sec\(^{-1}\) (Hoit, 2011).

6.3.5.2 Measurement of systolic rotation, twist and torsion

LV rotational displacement, the myocardial rotation around the LV long axis (Mor-Avi et al., 2011), was measured as the angular displacement of short axis LV sections (basal and apical), as viewed from the apex (Nuñifora et al., 2010). Specifically, peak rotation was measured as the angle between radial lines connecting the centre of the LV (in a specific cross-sectional plain) to a specific point in the myocardial wall at end-diastole and end-systole (Sengupta et al., 2008a). By convention, systolic rotation was measured in degrees (°) at the base and apex and represented as positive (anti-clockwise) and negative (clockwise) values respectively. Systolic twist was calculated by subtracting peak basal rotation from peak apical rotation, thus defining the variable, in degrees, as the net apex-base difference in rotation angle along the longitudinal axis of the left ventricle (Geyer et al., 2010). Left ventricular torsion was further calculated by indexing LV twist according to the LV length at end diastole.
6.3.5.3 Measurement of the timing and velocity of rotation, twist and untwist

Both rotation and twist can be further classified in relation to their duration and velocity. Duration of rotation and twist, as defined by the elapsed time between end diastole and the respective peak value, is expressed in ms (Notomi et al., 2005) and can also be quantified as a percentage of systolic duration (%). Accordingly, the values of time to peak basal and apical rotation (ms and %) and time to peak systolic twist (ms and %) are reported in this thesis. Likewise, the combination of the magnitude of movement (°) and the time interval during which this is achieved (sec), provides a measure of velocity for both rotation and twist in °sec\(^{-1}\) (Notomi et al., 2005). The diastolic component of rotational mechanics is commonly described in terms of diastolic untwist velocity (°sec\(^{-1}\)). In accordance with Perry et al. (2008), peak untwist velocity was determined as the first negative inflection of the velocity curve occurring following the peak positive inflection i.e. peak systolic twist velocity (figure 6.4). Finally, the time taken to achieve other peak values (ms and %) i.e. time to peak longitudinal strain, is reported.

6.3.5.4 Reliability of speckle tracking echocardiography

The methods employed for calculating intra-observer CoV for standard echocardiographic analysis are described in chapter three. The addition of STE to the study protocol requires that the issue of reliability be further addressed. All STE image acquisition was undertaken by highly experienced clinical cardiac sonographers whilst the analysis was performed by the lead investigator for whom intra-observer CoV data are presented below (table 6.1). As previously discussed, considerable attention was paid to minimising the variability attributed to the technical aspects of image acquisition and analysis. However, the reliability of STE derived indices of LV mechanics remains the focus of ongoing discussion (Oxborough et al., 2012). Previous literature reports wide variation in intra-observer reliability (Burns et al., 2010, Hurlburt et al., 2007, van Dalen et al., 2009, Mavinkurve-Groothuis et al., 2009, Notomi et al., 2005), which in addition to the potential technical issues of STE, may be confounded by different methodological approaches to assessing reliability and, indeed, the different statistical
techniques employed (Oxborough et al., 2012). With previously reported variability of up to 25% for apical and basal rotation and up to 15% for LV twist, the respective values of 13%, 21% and 18% for the current study are considered acceptable. Likewise values of 11% for longitudinal strain, ~11% for circumferential strain and ~25% for radial strain for the present study are comparable to a recent report which indicated variability of 7%, 6% and 19% respectively (Oxborough et al., 2012).

Table 6.1 Coefficient of variation for lead investigator analysis of parameters derived from speckle tracking echocardiography

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean of analysis 1 &amp; 2</th>
<th>SD of analysis 1 &amp; 2</th>
<th>CoV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak systolic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twist (°)</td>
<td>12.1 ± 1.8</td>
<td>± 1.8</td>
<td>15</td>
</tr>
<tr>
<td>Twist velocity (°.sec⁻¹)</td>
<td>68.9 ± 12.7</td>
<td>± 12.7</td>
<td>18</td>
</tr>
<tr>
<td><strong>Peak basal systolic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotation (°)</td>
<td>-4.7 ± 1.0</td>
<td>± 1.0</td>
<td>21</td>
</tr>
<tr>
<td>Rotation velocity (°.sec⁻¹)</td>
<td>-40.1 ± 9.9</td>
<td>± 9.9</td>
<td>24</td>
</tr>
<tr>
<td>Radial strain (%)</td>
<td>40.5 ± 8.3</td>
<td>± 8.3</td>
<td>20</td>
</tr>
<tr>
<td>Radial strain rate (sec⁻¹)</td>
<td>0.6 ± 0.2</td>
<td>± 0.2</td>
<td>14</td>
</tr>
<tr>
<td>Circ. strain (%)</td>
<td>-13.3 ± 1.5</td>
<td>± 1.5</td>
<td>11</td>
</tr>
<tr>
<td>Circ. strain rate (sec⁻¹)</td>
<td>-0.8 ± 0.1</td>
<td>± 0.1</td>
<td>14</td>
</tr>
<tr>
<td><strong>Peak apical systolic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotation (°)</td>
<td>7.9 ± 1.0</td>
<td>± 1.0</td>
<td>13</td>
</tr>
<tr>
<td>Rotation velocity (°.sec⁻¹)</td>
<td>44.4 ± 3.8</td>
<td>± 3.8</td>
<td>9</td>
</tr>
<tr>
<td>Radial strain (%)</td>
<td>17 ± 5.3</td>
<td>± 5.3</td>
<td>31</td>
</tr>
<tr>
<td>Radial strain rate (sec⁻¹)</td>
<td>1.0 ± 0.3</td>
<td>± 0.3</td>
<td>29</td>
</tr>
<tr>
<td>Circ. strain (%)</td>
<td>-20.3 ± 2.5</td>
<td>± 2.5</td>
<td>12</td>
</tr>
<tr>
<td>Circ. strain rate (sec⁻¹)</td>
<td>-1.14 ± 0.2</td>
<td>± 0.2</td>
<td>14</td>
</tr>
<tr>
<td><strong>Peak longitudinal systolic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strain (%)</td>
<td>-16.1 ± 1.7</td>
<td>± 1.7</td>
<td>11</td>
</tr>
<tr>
<td>Strain rate (sec⁻¹)</td>
<td>-0.8 ± 0.1</td>
<td>± 0.1</td>
<td>13</td>
</tr>
<tr>
<td><strong>Peak diastolic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untwisting velocity (°.sec⁻¹)</td>
<td>-75.8 ± 10.6</td>
<td>± 10.6</td>
<td>14</td>
</tr>
<tr>
<td><strong>Peak basal diastolic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotation velocity (°.sec⁻¹)</td>
<td>47.7 ± 5.7</td>
<td>± 5.7</td>
<td>12</td>
</tr>
<tr>
<td>Radial strain rate (sec⁻¹)</td>
<td>-1.6 ± 0.5</td>
<td>± 0.5</td>
<td>33</td>
</tr>
<tr>
<td>Circ. strain rate (sec⁻¹)</td>
<td>0.9 ± 0.1</td>
<td>± 0.1</td>
<td>13</td>
</tr>
<tr>
<td><strong>Peak apical diastolic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotation velocity (sec⁻¹)</td>
<td>-47.8 ± 6.4</td>
<td>± 6.4</td>
<td>13</td>
</tr>
<tr>
<td>Radial strain rate (sec⁻¹)</td>
<td>-1.47 ± 0.3</td>
<td>± 0.3</td>
<td>23</td>
</tr>
<tr>
<td>Circ. strain rate (sec⁻¹)</td>
<td>1.7 ± 0.2</td>
<td>± 0.2</td>
<td>14</td>
</tr>
<tr>
<td><strong>Peak Longitudinal diastolic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strain rate (sec⁻¹)</td>
<td>1.1 ± 0.1</td>
<td>± 0.1</td>
<td>14</td>
</tr>
</tbody>
</table>

Data as mean ± SD. Circ, circumferential.
6.4 Statistical analyses

General statistical methods are outlined in chapter three. Further to confirmation of normality with the Kolmogorov-Smirnov test, a two-way mixed model ANOVA was used to assess the effect of the 10-week exercise training intervention or control period on indices of LV mechanics. Group × time interaction was used to establish differences between groups, and paired Student’s *t*-tests were applied to assess within group change. Relative change is expressed as a percentage, with the group mean calculated from percentage change for each individual subject.
6.5 Results

At baseline the intervention and control groups were well matched for clinical and demographic parameters (table 6.2). Likewise, LV structural and functional parameters did not differ between the two groups (tables 6.3 and 6.4). Exercise testing further confirmed the similarity of the groups, other than a small difference in VO$_{2\text{peak}}$ relative to body weight ($P<0.05$) (table 6.2).

Despite this there was no difference in absolute VO$_{2\text{peak}}$ ($P>0.05$). Left ventricular mechanical indices were also comparable at baseline (table 6.5), however, peak LV twist, peak LV twist velocity, peak apical rotation and peak apical rotation velocity were lower in the control group (all $P<0.05$). There were no changes in prescribed medications in either group.

Table 6.2 Demographic, clinical and exercise test parameters at baseline and 10 weeks

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=19)</th>
<th>Control (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 10</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>53.5 ± 9.8</td>
<td>-</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 ± 0.1</td>
<td>-</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>84.5 ± 9.8</td>
<td>84.6 ± 10.3</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>27.9 ± 2.6</td>
<td>28.0 ± 2.8</td>
</tr>
<tr>
<td>BSA (m$^2$)</td>
<td>2.0 ± 0.1</td>
<td>2.0 ± 0.1</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI (n)</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>NSTEMI (n)</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Time post MI (days)</td>
<td>34.2 ± 7.0</td>
<td>-</td>
</tr>
<tr>
<td>HR$_{\text{rest}}$ (bpm)</td>
<td>58 ± 8</td>
<td>58 ± 8</td>
</tr>
<tr>
<td>BP$_{\text{sys}}$ (mmHg)</td>
<td>112 ± 16</td>
<td>109 ± 15</td>
</tr>
<tr>
<td>BP$_{\text{dia}}$ (mmHg)</td>
<td>70 ± 7</td>
<td>71 ± 8</td>
</tr>
<tr>
<td><strong>CPEX</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO$_{2\text{peak}}$ (L.min$^{-1}$) $\dagger$ $\ddagger$</td>
<td>2.0 ± 0.4</td>
<td>2.3 ± 0.4***</td>
</tr>
<tr>
<td>VO$_{2\text{peak}}$ (ml.kg$^{-1}$.min$^{-1}$) $\dagger$ $\ddagger$</td>
<td>24.5 ± 3.9 $\S$</td>
<td>27.8 ± 4.9***</td>
</tr>
<tr>
<td>W$_{\text{max}}$ (watts) $\dagger$ $\ddagger$</td>
<td>152 ± 26</td>
<td>181 ± 30***</td>
</tr>
<tr>
<td>VT (ml.kg$^{-1}$.min$^{-1}$) $\ddagger$</td>
<td>12.8 ± 2.9</td>
<td>14.1 ± 3.1**</td>
</tr>
<tr>
<td>VE/VCO$_2$ slope $\ddagger$</td>
<td>29.0 ± 3.8</td>
<td>30.4 ± 4.0</td>
</tr>
<tr>
<td>Exercise time (mins) $\dagger$ $\ddagger$</td>
<td>8.5 ± 1.0</td>
<td>10.4 ± 1.4****</td>
</tr>
</tbody>
</table>

Data as mean ± SD. BMI, body mass index; BSA, body surface area; STEMI, ST elevation myocardial infarction; NSTEMI, non ST elevation myocardial infarction; MI, myocardial infarction; HR$_{\text{rest}}$, resting heart rate; BP$_{\text{sys}}$, systolic blood pressure; BP$_{\text{dia}}$, diastolic blood pressure; CPEX, cardiopulmonary exercise test; VO$_{2\text{peak}}$, peak oxygen uptake; W$_{\text{max}}$, maximum workload; VT, ventilatory threshold; VE/VCO$_2$ slope, ventilatory efficiency slope. $\S$ $P<0.05$ vs. control at baseline, $\dagger$ $P<0.05$ time effect (ANOVA), $\ddagger$ $P<0.05$ group x time interaction effect (ANOVA), **$P<0.01$ vs. baseline, ***$P<0.001$ vs. baseline, ****$P<0.0001$ vs. baseline.
Table 6.3 Left ventricular structural parameters at baseline and 10 weeks

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=19)</th>
<th>Control (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 10</td>
</tr>
<tr>
<td><strong>LV size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>4.8 ± 0.5</td>
<td>4.9 ± 0.5</td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>3.2 ± 0.6</td>
<td>3.3 ± 0.5</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>86.0 ± 20.8</td>
<td>80.5 ± 17.7**</td>
</tr>
<tr>
<td>LVEDV/BSA (ml/m²)</td>
<td>43.1 ± 9.2</td>
<td>40.3 ± 7.9**</td>
</tr>
<tr>
<td>LV mass and geometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>220 ± 43</td>
<td>222 ± 56</td>
</tr>
<tr>
<td>LV mass/BSA (g/m²)</td>
<td>110 ± 19</td>
<td>111 ± 24</td>
</tr>
<tr>
<td>IVSd (cm)</td>
<td>1.3 ± 0.2</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>LVPWd (cm)</td>
<td>1.1 ± 0.2</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>IVSs (cm)</td>
<td>1.7 ± 0.2</td>
<td>1.7 ± 2.1</td>
</tr>
<tr>
<td>LVPWs (cm)</td>
<td>1.5 ± 0.2</td>
<td>1.5 ± 2.0</td>
</tr>
<tr>
<td>RWT (cm)</td>
<td>0.46 ± 0.09</td>
<td>0.44 ± 0.08</td>
</tr>
</tbody>
</table>

Data as mean ± SD. LV, left ventricular; LVIDd, LV internal diameter in diastole; BSA, body surface area; LVIDs, LV internal diameter in systole; LVEDV, LV end diastolic volume; LVESV, LV end systolic volume; IVSDd, inter-ventricular septal wall in diastole; LVPWd, LV posterior wall in diastole; IVSs, inter-ventricular septum in systole; LVPWs, LV posterior wall in systole; RWT, relative wall thickness.† P<0.05 time effect (ANOVA), ‡ P<0.05 group×time interaction effect (ANOVA), ** P<0.01 vs. baseline.
Table 6.4 Left ventricular functional parameters at baseline and 10 weeks

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=19)</th>
<th>Control (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 10</td>
</tr>
<tr>
<td><strong>LV systolic function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>32.7 ± 6.6</td>
<td>32.0 ± 4.5</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>55.5 ± 7.1</td>
<td>58.2 ± 6.7**</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>47.3 ±10.4</td>
<td>46.4 ± 9.0</td>
</tr>
<tr>
<td>Lateral s’ (cm/s)</td>
<td>7.7 ± 2.6</td>
<td>7.9 ± 1.9</td>
</tr>
<tr>
<td>Mean s’ (cm/s)</td>
<td>7.7 ± 1.6</td>
<td>7.7 ± 1.2</td>
</tr>
<tr>
<td><strong>LV diastolic function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.17 ± 0.31</td>
<td>1.05 ± 0.2</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>220 ± 31</td>
<td>222 ± 41</td>
</tr>
<tr>
<td>Lateral e’ (cm/s)</td>
<td>9.2 ± 3.4</td>
<td>9.7 ± 2.8</td>
</tr>
<tr>
<td>Lateral a’ (cm/s)</td>
<td>8.4 ± 2.5</td>
<td>8.6 ± 2.2</td>
</tr>
<tr>
<td>Lateral e’/a’ ratio</td>
<td>1.2 ± 0.5</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Lateral E/e’ ratio</td>
<td>7.5 ± 2.8</td>
<td>6.6 ± 2.2</td>
</tr>
<tr>
<td>Mean e’ (cm/s)</td>
<td>8.1 ± 2.3</td>
<td>8.3 ± 1.8</td>
</tr>
<tr>
<td>Mean a’ (cm/s)</td>
<td>8.7 ± 1.6</td>
<td>8.9 ± 1.4</td>
</tr>
<tr>
<td>Mean e’/a’ ratio</td>
<td>1.0 ± 0.3</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Mean E/e’ ratio</td>
<td>8.3 ± 2.0</td>
<td>7.7 ± 1.8</td>
</tr>
<tr>
<td>Lateral IVRT (ms)</td>
<td>84 ± 33</td>
<td>79 ± 26</td>
</tr>
<tr>
<td>Mean IVRT (ms) †</td>
<td>83 ± 23</td>
<td>86.7 ± 18.5</td>
</tr>
</tbody>
</table>

Data as mean ± SD. s’, peak systolic mitral annulus tissue velocity; E/A ratio, ratio of peak early (E) to late (A) mitral inflow velocity; DT, rate of deceleration of early mitral inflow; e’ peak early diastolic mitral annulus tissue velocity; a’, peak late diastolic mitral annulus tissue velocity; e’a’ ratio, ratio of peak early to late diastolic mitral annulus tissue velocity; E/e’ ratio, ratio of peak early mitral inflow velocity to peak early diastolic mitral annulus tissue velocity; IVRT, iso-volumic relaxation time. † P<0.05 time effect (ANOVA), ‡ P<0.05 group×time interaction effect (ANOVA), ** P<0.01 vs. baseline.
Table 6.5 Left ventricular mechanics at baseline and 10 weeks

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n=19)</th>
<th>Control (n=17)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 10</td>
<td>Baseline</td>
<td>Week 10</td>
</tr>
<tr>
<td><strong>Peak systolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twist (°) §</td>
<td>19.1 ± 9.5 §</td>
<td>15.4 ± 9.3**</td>
<td>12.6 ± 4.4</td>
<td>15.2 ± 6.3*</td>
</tr>
<tr>
<td>Twist velocity (°.sec⁻¹) §</td>
<td>109 ± 40 §</td>
<td>91 ± 37*</td>
<td>72 ± 23</td>
<td>83 ± 26*</td>
</tr>
<tr>
<td><strong>Peak basal systolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotation (°)</td>
<td>-6.2 ± 3.3</td>
<td>-5.0 ± 2.3</td>
<td>-4.6 ± 2.8</td>
<td>-5.0 ± 2.5</td>
</tr>
<tr>
<td>Rotation velocity (°.sec⁻¹)</td>
<td>-54.2 ± 23.9</td>
<td>-49.3 ± 15.0</td>
<td>-43.5 ± 18.8</td>
<td>-44.4 ± 16.7</td>
</tr>
<tr>
<td>Radial strain (%)</td>
<td>43.7 ± 12.8</td>
<td>42.2 ± 15.1</td>
<td>36.4 ± 10.4</td>
<td>38.9 ± 16.3</td>
</tr>
<tr>
<td>Radial strain rate (sec⁻¹)</td>
<td>1.82 ± 0.48</td>
<td>1.67 ± 0.45</td>
<td>1.72 ± 0.86</td>
<td>1.54 ± 0.35</td>
</tr>
<tr>
<td>Circ. strain (%)</td>
<td>-13.9 ± 4.2</td>
<td>-13.1 ± 3.8</td>
<td>-14.2 ± 3.3</td>
<td>-14.3 ± 4.7</td>
</tr>
<tr>
<td>Circ. strain rate (sec⁻¹)</td>
<td>-0.97 ± 0.24</td>
<td>-0.92 ± 0.31</td>
<td>-0.88 ± 0.23</td>
<td>-0.94 ± 0.27</td>
</tr>
<tr>
<td><strong>Peak apical systolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotation (°)</td>
<td>14.1 ± 7.5 §</td>
<td>11.5 ± 7.8*</td>
<td>8.8 ± 4.6</td>
<td>10.7 ± 5.4*</td>
</tr>
<tr>
<td>Rotation velocity (°.sec⁻¹)</td>
<td>77.6 ± 31.4 §</td>
<td>65.5 ± 29.3*</td>
<td>53.2 ± 22.9</td>
<td>54.1 ± 21.5</td>
</tr>
<tr>
<td>Radial strain (%)</td>
<td>19.5 ± 13.8</td>
<td>18.6 ± 13.2</td>
<td>17.8 ± 11.3</td>
<td>18.3 ± 12.3</td>
</tr>
<tr>
<td>Radial strain rate (sec⁻¹)</td>
<td>0.98 ± 0.45</td>
<td>1.04 ± 0.44</td>
<td>0.97 ± 0.26</td>
<td>0.92 ± 0.46</td>
</tr>
<tr>
<td>Circ. strain (%)</td>
<td>-22.7 ± 5.7</td>
<td>-23.1 ± 6.3</td>
<td>-21.1 ± 5.9</td>
<td>-20.6 ± 6.0</td>
</tr>
<tr>
<td>Circ. strain rate (sec⁻¹)</td>
<td>-1.36 ± 0.38</td>
<td>-1.42 ± 0.45</td>
<td>-1.22 ± 0.4</td>
<td>-1.22 ± 0.36</td>
</tr>
<tr>
<td><strong>Peak longitudinal systolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strain (%)</td>
<td>-17.5 ± 2.7</td>
<td>-17.4 ± 3.2</td>
<td>-17.4 ± 2.9</td>
<td>-17.2 ± 2.4</td>
</tr>
<tr>
<td>Strain rate (sec⁻¹)</td>
<td>-0.93 ± 0.17</td>
<td>-0.90 ± 0.17</td>
<td>-0.89 ± 0.17</td>
<td>-0.85 ± 0.16</td>
</tr>
<tr>
<td><strong>Peak diastolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untwisting velocity (°.sec⁻¹)</td>
<td>-90.5 ± 38.1</td>
<td>-89.2 ± 48.4</td>
<td>-75.9 ± 24.1</td>
<td>-81.9 ± 20.8</td>
</tr>
<tr>
<td><strong>Peak basal diastolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotation velocity (°.sec⁻¹)</td>
<td>53.4 ± 31.1</td>
<td>51.1 ± 24.3</td>
<td>42.9 ± 20.7</td>
<td>44.0 ± 18.8</td>
</tr>
<tr>
<td>Radial strain rate (sec⁻¹)</td>
<td>-1.35 ± 0.69</td>
<td>-1.33 ± 0.52</td>
<td>-1.57 ± 0.83</td>
<td>-1.36 ± 0.47</td>
</tr>
<tr>
<td>Circ. strain rate (sec⁻¹)</td>
<td>0.90 ± 0.37</td>
<td>0.76 ± 0.18</td>
<td>0.93 ± 0.36</td>
<td>0.94 ± 0.32</td>
</tr>
<tr>
<td><strong>Peak apical diastolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotation velocity (sec⁻¹)</td>
<td>-61.6 ± 27.6</td>
<td>-62.8 ± 32.2</td>
<td>-53.9 ± 22.0</td>
<td>-59.0 ± 19.6</td>
</tr>
<tr>
<td>Radial strain rate (sec⁻¹)</td>
<td>-1.35 ± 0.61</td>
<td>-1.21 ± 0.4</td>
<td>-1.49 ± 0.53</td>
<td>-1.32 ± 0.50</td>
</tr>
<tr>
<td>Circ. strain rate (sec⁻¹)</td>
<td>1.75 ± 0.59</td>
<td>1.57 ± 0.54</td>
<td>1.66 ± 0.66</td>
<td>1.51 ± 0.52</td>
</tr>
<tr>
<td><strong>Peak Longitudinal diastolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strain rate (sec⁻¹)</td>
<td>1.04 ± 0.27</td>
<td>0.93 ± 0.28</td>
<td>1.03 ± 0.39</td>
<td>1.03 ± 0.34</td>
</tr>
</tbody>
</table>

Data as mean ± SD. Circ, circumferential. § P<0.05 vs. control at baseline, ‡ P<0.05 group × time interaction effect (ANOVA), **P<0.05 vs. baseline, ***P<0.01 vs. baseline
Table 6.6 Left ventricular mechanics – selected ‘time to peak’ indices at baseline and 10 weeks

<table>
<thead>
<tr>
<th>Time to peak (ms)</th>
<th>Intervention (n=19)</th>
<th>Control (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal systolic rotation vel. †</td>
<td>199 ± 82</td>
<td>212 ± 82</td>
</tr>
<tr>
<td>Basal diastolic rotation vel. ‡</td>
<td>458 ± 82</td>
<td>443 ± 56</td>
</tr>
<tr>
<td>Apical rotation †</td>
<td>357 ± 70</td>
<td>383 ± 53</td>
</tr>
<tr>
<td>Longitudinal systolic SR †</td>
<td>145 ± 36*</td>
<td>167 ± 37</td>
</tr>
<tr>
<td>Basal radial strain ‡</td>
<td>103 ± 14</td>
<td>107 ± 9</td>
</tr>
<tr>
<td>Longitudinal strain †</td>
<td>104 ± 6*</td>
<td>100 ± 6</td>
</tr>
<tr>
<td>Longitudinal diastolic SR ‡</td>
<td>121 ± 5**</td>
<td>125 ± 6</td>
</tr>
</tbody>
</table>

Data as mean ± SD. † P<0.05 time effect (ANOVA), ‡ P<0.05 group × time interaction effect (ANOVA), *P<0.05 vs. baseline, **P<0.01 vs. baseline. Vel, velocity; SR, strain rate.

6.5.1 Effect of cardiac rehabilitation exercise training on demographic, clinical and exercise test parameters

All exercise testing and training sessions were completed without any incidence of cardiovascular complication or other adverse events. Average exercise session attendance per patient was 87.9%. In comparison to controls, exercise training resulted in an increase in $W_{max}$, $V_{O2peak}$, VT, VE/VCO₂ slope, and exercise time (all P<0.05) (table 6.2). In the intervention group, $V_{O2peak}$ increased by 14% (P<0.001), $W_{max}$ by 20% (P<0.0001), VT by 12% (P<0.01), and exercise time by 19% (P<0.0001) (table 6.2). In the control group, however, no changes were noted. The change in VE/VCO₂ slope over the 10 week period was also group dependent (P<0.05). Independently, however, a 4% increase in the intervention group and a 3% decrease in the control group, did not reach statistical significance (P>0.05). There were no changes in demographic or clinical variables in either group over the course of the study period (P>0.05) (table 6.2).

6.5.2 Effect of cardiac rehabilitation exercise training on left ventricular structure and function

In comparison to the control group, CR exercise training reduced LVEDV (P<0.05) and LVESV (P<0.01) and increased LVEF (P<0.05) (table 6.4). Whilst volumetric parameters...
remained unchanged in the control group ($P>0.05$), a 6% reduction in LVEDV ($P<0.001$), an 11% reduction in LVESV ($P<0.001$) (table 6.3) and a 5% increase in LVEF ($P<0.01$) was evident following the exercise training intervention. No changes were observed in LV linear dimensions, mass or geometry during the 10-week intervention or control period ($P>0.05$). Finally, IVRT was prolonged by 13% and 23% in the intervention ($P>0.05$) and control ($P<0.01$) groups respectively, which collectively constituted an increase over the 10 weeks ($P<0.05$).

### 6.5.3 Effect of cardiac rehabilitation exercise training on left ventricular mechanics

Exercise training resulted in reduced apical rotation ($P<0.01$), apical rotation velocity ($P<0.05$), LV twist ($P<0.001$) and LV twist velocity ($P<0.01$) in comparison to controls (table 6.5, figures 6.4 and 6.5). In the intervention group there was a decrease in, apical rotation (14%, $P<0.05$) and apical rotation velocity (9%, $P<0.05$) in contrast to an increase in apical rotation (17%, $P<0.01$) and unchanged apical rotation velocity ($P>0.05$) in controls. Basal rotational parameters remained unchanged in both groups ($P>0.05$) with a consequent decrease in LV twist (16%, $P<0.01$), and LV twist velocity (12%, $P<0.05$) in the intervention group and an increase in LV twist (23%, $P<0.05$) and LV twist velocity (19%, $P<0.5$) in the control group. Left ventricular torsion (LV twist indexed for LV length at end diastole) is not reported based on the absence of change in LV length in either group over the 10-week period. Finally, there was no change in the intervention or control groups in longitudinal, radial or circumferential strain or strain rate.

### 6.5.4 Effect of cardiac rehabilitation exercise training on timings of LV mechanics

Over the 10-week period, a number of differences in time to peak indices were identified between the intervention and control group. For clarity, only those indices demonstrating significance are presented (table 6.6), with additional results available in appendix four. In comparison to controls, the intervention group demonstrated a reduced time to peak basal
diastolic rotation velocity (ms), increased time to peak basal radial strain (%) and increased peak longitudinal diastolic SR (%) (all $P<0.05$). Furthermore, the cohort as a whole displayed an increase in the time to peak basal systolic rotation velocity (ms), apical rotation (ms), longitudinal systolic SR (ms) and longitudinal strain (%) (all $P<0.05$).
Figure 6.4 Group mean data over one cardiac cycle as a percentage of systole and diastole for (a) LV apical rotation (red lines), (b) LV basal rotation (blue lines) and (c) LV twist (black lines) in the intervention (left column) and control group (right column) at baseline (solid lines) and at 10 weeks (dashed lines). Peak values do not match those presented in the table 6.5 due to normalisation of data for heart rate (see section 6.3.5 for details). Statistical differences can be seen in table 6.5. LV, left ventricular; AVC, aortic valve closure; °, degrees.
Figure 6.5 Group mean data over one cardiac cycle as a percentage of systole and diastole for (a) LV apical rotation velocity (red lines), (b) LV basal rotation velocity (blue lines) and (c) LV twist velocity (black lines) in the intervention (left column) and control group (right column), at baseline (solid lines) and at 10 weeks (dashed lines). Peak values do not match those presented in table 6.5 due to normalisation of data for heart rate (see section 6.3.5 for details). Statistical differences can be seen in table 6.5. LV, left ventricular; AVC, aortic valve closure; °, degrees.
6.6 Discussion
The present study, in post-MI patients with mildly abnormal LVEF, evaluated the effects of 10 weeks of CR exercise training on LV functional remodelling using the measurement of LV mechanics. A number of significant findings were observed. Firstly, as in previous chapters, the 10-week CR exercise training intervention improved functional capacity, as indicated by increased VO$_{2\text{peak}}$, CPEX exercise time and workload. Secondly, as evidenced by reduced LVEDV, reduced LVESV and increased LVEF, the measurement of conventional echocardiographic parameters identified that 10 weeks of CR exercise training was successful in volumetrically and functionally reverse remodelling the LV. Thirdly, the study is unique in reporting reverse LV functional remodelling secondary to CR exercise training, as measured by LV mechanics. Ten weeks of CR exercise training resulted in a reduction in LV apical rotation, relatively unchanged basal rotation and a consequent reduction in LV twist. In contrast, the 10-week control period culminated in an increase in LV apical rotation and twist. Moreover, following the 10 week period, the velocity of LV apical rotation and twist was reduced in the exercise training intervention group whilst an increase in LV twist velocity was observed in the control group. Finally, whilst the time to peak indices of basal diastolic rotation velocity, peak basal radial strain and peak longitudinal diastolic SR were altered with exercise training, there were no changes to longitudinal, radial or circumferential strain or SR in either group.

6.6.1 The effect of cardiac rehabilitation exercise training on left ventricular volumetric remodelling
Completion of the 10-week CR exercise training programme resulted in improvements in all measurements of functional capacity in parallel with clear evidence of reverse volumetric LV remodelling. Whilst volumetric parameters remained unaltered in the control group, both LVEDV and LVESV were reduced (6% and 11% respectively) on completion of the exercise training intervention. These data are in keeping with the results reported in chapter five of this thesis, within which a full appraisal of their significance and their relation to previously published work was presented. In contrast to chapter five, however, a 5% increase in LVEF was
noted, in line with previous findings (Haykowsky et al., 2011), indicating the coexistence of volumetric and functional reverse LV remodelling in the present cohort.

6.6.2 The effect of cardiac rehabilitation exercise training on left ventricular mechanics

The most striking finding from the current study was the differential response of LV twist to 10 weeks of CR exercise training or the control period. Exercise training resulted in a 16% reduction in LV twist, whereas in the control group, an increase of 23% was observed. These changes, reported for the first time in a post-MI population, were the result of altered rotation at the LV apex, while rotation at the base remained unchanged. This is in agreement with findings of previous studies which identified the predominant influence of apical rather than basal mechanics in physiological LV adaptation (Zocalo et al., 2007, Nottin et al., 2008, Weiner et al., 2010). In the present study, a 14% decrease in apical rotation was evident following exercise training, in contrast to a 17% increase in the control group. Accordingly, LV twist was decreased following exercise training and increased following the control period, as was LV twist velocity.

6.6.2.1 Left ventricular mechanics following 10 weeks of CR exercise training

In the exercise training group the decrease in LV twist in combination with reverse volumetric remodelling and increased LVEF likely represents positive LV functional adaptation. Whilst the response of LV mechanics to exercise training has not previously been studied in post-MI patients, limited data from longitudinal and cross-sectional studies in healthy individuals has been published (Weiner et al., 2010, Zocalo et al., 2007, Nottin et al., 2008, Stohr et al., 2012, Aksakal et al., 2013). In a longitudinal study by Weiner and colleagues (2010), a group of healthy, untrained, 18 year old college students undertook a three month period of rowing training following baseline echocardiographic assessment. In direct contrast to the present study, LV apical rotation and LV twist increased following the exercise training intervention. Alongside eccentric hypertrophy and increased SV, the authors concluded that this change to
LV mechanics was representative of LV functional adaptation, further to endurance training. In cross sectional studies in chronically endurance trained athletes, however, (Zocalo et al., 2007, Nottin et al., 2008) and in individuals with high cardiovascular fitness (Stohr et al., 2012), reduced LV twist has been reported in comparison to untrained, matched controls. Therefore, the findings of the present study, whilst at odds with data from previous longitudinal studies, appear consistent with data from cross sectional studies.

Whilst data from previous longitudinal and cross-sectional studies in healthy individuals are relevant, the populations are markedly different from the present study in terms of subject demographics, training volume and VO$_{2peak}$. On this basis, the results of these studies are unlikely to aid understanding of the effects of exercise training on LV mechanics in post-MI patients. However, comparison of the longitudinal studies may indicate a differential response of LV mechanics to a period of exercise training in healthy individuals and patients with recent MI i.e. increased twist in the former and decreased twist in the latter. This novel finding complements the substantial body of work which has previously identified a differential response between these populations in relation to LV volumetric remodelling. Athletic populations commonly demonstrate physiological LV remodelling, characterised by increased LV volumes, in response to repeated and prolonged bouts of LV volume overload (Weiner and Baggish, 2012, Naylor et al., 2008, George et al., 2012). In contrast, post-MI and CHF populations demonstrate a reduction in LV volumes (Haykowsky et al., 2011, Haykowsky et al., 2007) further to the positive effects of training on neurohormonal overexpression, autonomic activation and maladaptive molecular signalling pathways (Gielen et al., 2010). Therefore, it is possible that the increase in LV twist following exercise training in healthy individuals relates to ‘athletic’ LV remodelling and the decrease in LV twist in post-MI patients is a response to reverse LV remodelling. However, this explanation is not confirmed by comparison between cross-sectional and longitudinal studies in healthy individuals. In contrast to the longitudinal study by Weiner and colleagues (2010), LV twist has been shown to be reduced in chronically trained individuals (Zocalo et al., 2007, Nottin et al., 2008).
To understand the seemingly different findings between current and previous studies, the fundamental principles of LV twist and its physiological determinants should be considered. Left ventricular twist is generated via the opposing contraction of obliquely orientated subendocardial and subepicardial myofibres (Nakatani, 2011). This unique motion has been shown to normalise myofibre stress across the LV wall, thus efficiently generating high intraventricular systolic pressures with minimal fibre shortening. As a result, myocardial $O_2$ consumption and energy expenditure are decreased (Bloechlinger et al., 2011, Vendelin et al., 2002). It is, therefore, possible that cross-sectional reports of preserved or enhanced systolic ejection, concomitant with reduced LV twist in endurance trained and high fit individuals, indicate an increased systolic efficiency. There may exist the potential for a greater ‘twist reserve’ i.e. a lower twist at rest may provide a greater ability to augment LV twist during periods of increased hemodynamic demand (Sengupta et al., 2008a, Beladan et al., 2013).

The concept of ‘twist reserve’ is at odds with findings from longitudinal training studies which have indicated an increased LV twist following three to six months of endurance training (Aksakal et al., 2013, Weiner et al., 2010). It has been proposed in previous studies (Weiner et al., 2010) that the differences between these cross sectional and longitudinal studies may be partly explained by the increase in blood volume at the onset of chronic training in previously untrained individuals (Green et al., 1991). As previous work has demonstrated the preload dependency of LV twist (Burns et al., 2009, Hodt et al., 2011), an increase in LV twist may occur to counteract and overcome vascular blood volume expansion (Weiner et al., 2010). Authors have hypothesised that this may be a ‘semi acute’ adaptation to relatively short term endurance training (Stohr et al., 2012). Chronic, high volume endurance training may ultimately lead to reduced LV twist, further to a prolonged period of adaptation, during which time macro-structural LV changes are known to occur (Levine, 2008, Morganroth et al., 1975). However, an increased blood volume is also likely in the present cohort given the prior sedentary nature of the participants. Therefore, reduced LV twist in this context must be alternatively explained by mechanisms unique to exercise induced reverse LV remodelling in post-MI patients. It is
possible that the effect of reverse LV remodelling on LV mechanics may be greater than the potential effect of blood volume expansion, thus reversing the acute increase in LV twist seen in healthy individuals.

**6.6.2.2 Left ventricular mechanics following the 10-week control period**

In the present study, LV twist and twist velocity were increased following the 10-week control period. Left ventricular volumetric parameters, which were within normal range at baseline, remained unchanged at 10 weeks, indicating the absence of adverse gross LV remodelling at this point in time. The increase in LV twist could be interpreted in one of two ways. Firstly, it could have negative connotations as a compensatory adaptation preceding adverse LV volumetric remodelling and subsequent functional decline. Indeed, increases in LV twist have been consistently reported in a number of pathologies such as aortic stenosis, hypertrophic obstructive cardiomyopathy and hypertension (Wang et al., 2013, Moravsky et al., 2013, Cameli et al., 2012). However, the stimulus for increased LV twist in each of these studies was likely pathologic LV hypertrophy and increased afterload, unlike the current cohort.

The increase in LV twist in the control group could be alternatively viewed as positive LV functional recovery in response to optimal pharmacological therapy and natural recovery. Compared to healthy age matched controls, a number of previous studies have described reduced LV twist in the days immediately following successful revascularisation for MI (Bertini et al., 2010, Bertini et al., 2009b, Jia et al., 2011, Han et al., 2008, Jang et al., 2010, Takeuchi et al., 2007a). The degree of reduction has been shown to be dependent upon the extent of LVEF impairment (Gjesdal et al., 2008, Takeuchi et al., 2007a). Subsequently, at six months and two years, LV twist has been reported to increase in patients without adverse LV remodelling, whilst continued suppression and/or deterioration of LV twist has been observed in pathological LV dilation (Jang et al., 2010, Zito et al., 2011). Essentially, those sustaining less severe MI, and thus absent of adverse remodelling at six months, were more likely to demonstrate an increase
in LV twist, secondary to medical therapy. Specifically, in the study by Jang and colleagues (2010), reduced LV twist was observed at three days post-MI in comparison to age matched controls. At six months, however, LV twist had increased to ‘normal’ levels in the presence of reverse LV remodelling (reduced LVEDV and increased LVEF) but remained impaired in the presence of adverse LV remodelling. It should be noted that in these previous studies, and in the current study, LV twist prior to MI was unknown and therefore it is not possible to confirm that LV twist had returned to ‘normal.’ Furthermore, despite a number of papers addressing the issue of what constitutes ‘normal’ LV twist in healthy and clinical populations, data is currently insufficient to determine a reference range (Weyman, 2007, Beladan et al., 2013).

6.6.2.3 Differential response of LV mechanics to 10 weeks of CR exercise training or the control period

Studies examining LV twist following MI may help to explain the differential response of LV twist to exercise training or the control period in the current study. The control group did not display any adverse or, indeed, reverse volumetric LV remodelling between the baseline and 10-week measurements. As such, it may be concluded that this population were medically stable from an LV remodelling perspective. In line with previous studies, therefore, the presently observed increase in LV twist may indicate improved systolic function, albeit not represented by an improved LVEF at the time of assessment. Previous work has shown positive correlation between LVEF and LV twist in the first few days following MI (Bertini et al., 2009b, Jia et al., 2011, Bertini et al., 2010), and that both measures increase concurrently at six months in the presence of reverse volumetric LV remodelling (Jang et al., 2010). However, the absence of any interim measurements (i.e. during the six months post-MI) in the available literature makes the understanding of this relationship in the recovering LV difficult. It is possible that in the six month period following MI, an increase in LV twist may occur first, as a precedent for subsequent beneficial LV remodelling and improved LVEF. Thus, the increased twist and unchanged volumetric parameters at 3-4 months in the current control group may signify a precursor to reverse volumetric LV remodelling and functional improvement.
Confirmation of this interpretation is required from more regular serial echocardiographic measurement in longitudinal follow-up studies.

On initial examination, the decrease in LV twist in the intervention group and the increase in the control group could be viewed as a positive adaptation in the former, and a negative adaptation in the latter. However, in relation to the above discussion, it could be alternatively proposed that both responses are equally representative of myocardial recovery. The differential response is most likely a product of the physiological, neurohormonal and biomolecular adaptation associated with CR exercise training (Gielen et al., 2010, Gademan et al., 2007, Kemi and Wisloff, 2010). Based on the previously documented absence of serial increases in LV twist in functionally impaired, adversely remodelled post-MI LV’s (Jang et al., 2010), the increase in LV twist in the current control group is likely to represent functional recovery in relatively preserved post-MI LV’s. Likewise, despite the uncertainty as to what constitutes a beneficial change in LV twist in clinical and athletic populations, the present study indicates a physiological reduction in LV twist in response to exercise training as opposed to the pathological reduction witnessed immediately post-MI.

The reduced LV twist with exercise training in the current study was paralleled with an increase in LVEF. Similarly, exercise training studies in healthy subjects have demonstrated unchanged LVEF in the context of increased LV twist (Aksakal et al., 2013, Weiner et al., 2010). In contrast, clinical studies have identified a positive correlation between impaired LV twist and LVEF, acutely and chronically post-MI (Bertini et al., 2009b, Jia et al., 2011, Bertini et al., 2010). These findings, once more, may serve to confirm the differential response of LV twist to a variety of physiological and pathological environments. Furthermore, these findings pose questions as to the mechanism(s) by which maintenance of LVEF is achieved despite a lesser contribution from LV twist mechanics. In the presence of reduced LV twist, Stohr and colleagues (2012) identified an increased radial stain in high versus low fitness individuals, as a potential compensatory mechanism for the maintenance of systolic ejection. Data from the
current study does not follow these findings as there were no apparent changes in measurements of LV strain and strain rate.

A number of speculative explanations may contribute to the phenomenon of increased LVEF with reduced LV twist. Firstly, in this small, heterogeneous sample of post-MI patients, subtle alterations in the timings of LV mechanics (i.e. decreased time to peak basal diastolic rotation velocity and decreased time to peak longitudinal strain) may have collectively contributed to enhancement of LVEF. It is possible that an increase in the speed with which peak diastolic or systolic rotation velocities or strains are achieved may ultimately aid systolic ejection. Secondly, as proposed in previous papers, molecular and cellular adaptation of the cardiac microstructure, such as altered titin isoform expression, and cardiac myofibre function and alignment may be responsible for a twist independent improvement in contractile efficiency (Weiner et al., 2010, Stohr et al., 2012). Finally, it is possible that, given the methodological inadequacies of LVEF (Feigenbaum et al., 2012) and its dissociation with exercise capacity (Franciosa et al., 1981, Higginbotham et al., 1983, Benge et al., 1980), improvement in LVEF may be misrepresentative of exercise induced LV functional adaptation. With LVEF essentially measuring the change in LV cavity size during systole rather than myocardial deformation and function per se, a disconnect between mechanical and volumetric remodelling may not be surprising, particularly during reverse remodelling in the post-MI LV. The mechanisms underpinning alterations in LV mechanics, therefore, are currently speculative and the underlying physiology of maintained or enhanced systolic ejection, despite the apparently lesser contribution of LV twist, requires continued investigation.

6.6.3 Clinical significance of findings

Further to recent MI, these novel data indicate LV functional adaptation following CR exercise training in patients with mildly abnormal LVEF. Currently, there is limited literature with which to clinically contextualise the significance of these findings. However, the reduction in LV twist
with CR exercise training occurs alongside reverse LV volumetric and functional remodelling, both of which have clear prognostic significance (Solomon et al., 2005, Konstam et al., 2011). This potentially highlights a previously unknown exercise induced LV adaptation which in itself may prove to be an independent predictor of improved mortality following MI. The systemic and myocardial specific adaptations known to result in reverse LV structural remodelling, following endurance training in cardiac populations, may also contribute to the reduction in LV twist. As such, the measurement of LV twist in post-MI populations may in the future help to explain the benefits of CR exercise training. As a specific measure of LV functional performance, LV twist may also serve as a more powerful indicator than conventional indices of improved outcome following CR exercise training. Indeed, this would fit with data showing LV twist to be a more accurate predictor of adverse LV remodelling than conventional echocardiographic measures (Spinelli et al., 2012). Finally, in support of the clinical significance of reduced NT-pro-BNP and reduced LV volumes proposed in chapters four and five, it is likely that these findings represent a further piece of the pathophysiological ‘jigsaw’ which dictates the mortality benefits associated with CR exercise training.

6.7 Hypotheses

1) Resting LV twist will increase in response to ten weeks of CR exercise training - REJECTED

2) Resting LV longitudinal, radial and circumferential strain will increase in response to ten weeks of CR exercise training - REJECTED

3) Resting LV longitudinal, radial and circumferential strain rate will increase in response to ten weeks of CR exercise training - REJECTED

6.8 Conclusion

In conclusion, completion of a 10-week CR exercise training programme resulted in a reduction in LV twist in combination with reverse volumetric and functional LV remodelling. Conversely,
LV twist was increased following a 10-week control period whilst LV volumetric parameters remained unchanged. Neither group displayed changes in LV strain or strain rate, although subtle changes in the timings of these measurements were evident. In patients with mildly abnormal LVEF following recent MI, this study is the first to describe specific LV mechanical adaptation to a period of CR exercise training. Moreover, these findings indicate a differential LV mechanical response in healthy and post-MI patients, commensurate with different patterns of LV remodelling. The measurement of LV mechanics likely has a future role as an indicator of the therapeutic benefit of CR exercise training.
CHAPTER 7

General discussion
7.1 Introduction

The overall purpose of this thesis was to examine the effects of a structured programme of CR exercise training on LV remodelling in post-MI patients. To do so, data from three experimental studies were presented. Firstly, in chapter four, the effect of CR exercise training on NT-pro-BNP (a neurohormonal marker of LV wall stress) was examined in order to establish the neurohormonal influence of the intervention and to indirectly evaluate reverse LV remodelling. Secondly, in chapter five, conventional echocardiographic techniques were employed to directly measure structural and functional reverse LV remodelling. Finally, in chapter six, STE was utilised to characterise the effects of CR exercise training on LV mechanics, with a view to further advancing our knowledge of reverse functional LV remodelling. The following chapter will present a summary of the main findings as a preface to discussing the overall physiological and clinical impact of CR exercise training in relation to LV remodelling. To conclude, the limitations relevant to the collection and analysis of data are described, prior to detailing potential future research directions.

7.2 Summary of main findings

The three experimental chapters in this thesis consistently demonstrated a positive therapeutic effect of CR exercise training in post-MI patients with mildly abnormal LVEF (~55%).

Functional capacity, as measured with VO_{2peak}, peak CPEX workload and CPEX exercise time was unequivocally improved following CR. After completion of the exercise training intervention, the key findings from chapter four were a 24% reduction in resting NT-pro-BNP and an attenuation of the post exercise NT-pro-BNP response. In chapter five, significant reverse volumetric remodelling was evidenced by a 5% and 9% reduction in LVEDV and LVESV respectively. Finally, in chapter six, an LV functional remodelling effect of CR exercise training was observed as indicated by an 18% reduction in LV twist in comparison to a 23% increase in controls. Collectively, these findings demonstrate a positive influence of CR exercise training on post-MI LV remodelling.
7.3 Effect of cardiac rehabilitation exercise training on left ventricular remodelling - an integrative approach

Further to MI, the combined effects of regional LV dysfunction, altered LV structure/geometry and neurohormonal overexpression result in adverse LV remodelling (Koitabashi and Kass, 2012, Bonow et al., 2012, Konstam et al., 2011). Immediately and progressively, functional capacity is impaired and prognosis affected (Solomon et al., 2005). Evidence from this thesis suggests that participation in CR exercise training following MI can lead to reverse LV remodelling. Figure 7.1 provides a summary of the coordinated, physiological and biomolecular mechanisms that may contribute to exercise induced reverse LV remodelling in the initial 3-4 months post-MI. While not exhaustive, this general overview provides sufficient detail to highlight the integrated process of reverse LV remodelling and informs discussion of the clinical significance of the results of this thesis and the potential utility of these measurements in CR exercise programmes.
Figure 7.1 Reverse left ventricular (LV) remodelling with cardiac rehabilitation (CR) exercise training. Following myocardial infarction (MI), structural and functional LV changes give rise to autonomic and neurohormonal over-expression. Whilst initially compensatory, these responses subsequently become cardio-destructive, contributing to further exacerbation of LV remodelling. Cardiac rehabilitation exercise, through its systemic influence, can result in beneficial structural and functional LV remodelling with improved functional capacity and prognosis. Both evidenced and speculative mechanisms are presented. Colour coding of text corresponds with colour coding in figures 3.1 and 3.2; blue, study 1; green, study 2; purple, study 3. ↑, altered; LVEF, LV ejection fraction.
Further to exercise training, a number of mechanisms are thought to contribute to reverse LV remodelling. Animal and human studies have previously identified structural and functional myocardial adaptation. In animals, a direct effect on the signalling pathways responsible for LV maladaptation has been reported, with resultant reduction in hypertrophy, fibrosis and apoptosis (Kemi and Wisloff, 2010, Schober and Knollmann, 2007, Kemi et al., 2007, McMullen et al., 2007). In humans, both an improvement in systemic neurohormonal and autonomic control (Gademan et al., 2007), and a decreased afterload in response to improved endothelial function are thought to contribute to positive myocardial adaptation (Gielen et al., 2010). While this thesis does not provide direct evidence of this altered cardiac physiology, the LV adaptation observed in this patient cohort is most likely the end product of the combined effect of these mechanisms.

The precise relationships between the various reverse LV remodelling effects reported in this thesis are difficult to describe due to structural, functional and neurohormonal adaptation likely occurring simultaneously. However, it is probable that improvements in the structural integrity of the myocardium are the catalyst for subsequent functional improvement. The observed reduction in LV volumes indicates improved structural integrity, which in turn likely facilitates an improvement in function. Modest changes in LVEF were observed, however, the poor association of LVEF with exercise capacity (Franciosa et al., 1981, Higginbotham et al., 1983, Benge et al., 1980) and the inherent limitations associated with the measurement of LVEF (Feigenbaum et al., 2012) may limit the value of this measure in the CR context. Evaluation of LV mechanics provides a far more detailed view of LV function by characterising three-dimensional LV deformation throughout the entire cardiac cycle, as opposed to simply changes in chamber volume at end systole and end diastole. In this thesis, the reduction in resting LV twist and twist velocity may better reflect the LV functional remodelling effect of CR exercise training. In addition, the more automated derivation of STE derived indices, in comparison to LVEF, may make it a more reliable tool for the serial assessment of exercise induced LV functional adaptation (Sjoli et al., 2011, Munk et al., 2012). The absence of change in any other
structural or functional parameters in this thesis further indicates the lack of sensitivity of conventional echocardiographic parameters for detecting exercise induced LV remodelling, and confirms the potential application of STE.

During the process of reverse LV remodelling, it is not known at which point LV mechanical adaptation occurs, relative to structural changes. As previously discussed, LV structural change likely precedes an improvement in LVEF. Likewise, improved structural integrity probably occurs prior to a reduction in LV twist. It has been proposed that changes in titin isoform expression and myofibre alignment may contribute to improved contractile efficiency following exercise training in healthy individuals (Stohr et al., 2012, Weiner et al., 2010), which may be responsible for changes in LV mechanics. In the current cohort, changes in titin isoform or myofibre alignment may have occurred in conjunction with reductions in hypertrophy, fibrosis and apoptosis. Accordingly, the reduction in LV twist observed following CR could, therefore, be a product of both structural change and an improved contractile efficiency.

The overall result of improved structural integrity following CR exercise training is an improvement in LV hemodynamics and efficiency (Haykowsky et al., 2011). In addition to improved LVEF and reduced LV twist in this thesis, the reduction in resting and exercise induced NT-pro-BNP is further evidence of positive adaptation. NT-pro-BNP is a measure of LV wall stress (Ruskoaho, 2003) which is abnormally elevated in the dysfunctional post-MI LV (Hall, 2005, Konstam et al., 2011). The current results indicate a reduction in LV wall stress, not only at rest, but also during increased hemodynamic demand. This would suggest that the beneficial changes to LV structure and function at rest are also evident during exercise, contributing to enhanced hemodynamics and potentially improved exercise capacity. An enhanced ‘LV twist reserve’ may further demonstrate an overall improvement in hemodynamics. A lower resting LV twist provides greater scope for increased LV functional performance during exercise. An increase in resting LV twist (i.e. a reduction in ‘LV twist reserve’) has also been reported with ageing (Beladan et al., 2013). It is thought that age
associated myocardial fibrosis may be responsible for this phenomenon (Burns et al., 2008).
Therefore, a loss of structural integrity with increasing age leads to an increase in LV twist at rest and, similarly, a reduction in fibrosis with exercise training (Wisloff et al., 2009) in the current study may be partly responsible for an increase in ‘LV twist reserve’ (i.e. reduced twist). The measurement of LV function during exercise is required to confirm enhanced exercise hemodynamics and the concept of ‘LV twist reserve’ in post-MI patients.

The changes to LV twist observed in this thesis are of particular interest in the context of reverse volumetric LV remodelling, not least as they are previously undocumented. In combination with results in healthy individuals (Aksakal et al., 2013, Weiner et al., 2010), the current findings support the hypothesis of a differential response of LV mechanics to different patterns of pathological and physiological LV remodelling. Increased LV twist, in response to a relatively acute three month exercise training programme, in healthy individuals has been observed in conjunction with an increase in LV volumes (Aksakal et al., 2013, Weiner et al., 2010). In the current study, reduced LV twist was noted with a reduction in LV volumes. This potential relationship requires further investigation, as does the response of LV twist to prolonged training in post-MI patients. Chronic training in athletes appears to result in a reduction in LV twist (as opposed to an increase following three months of training) and, therefore, the effects of a longer period of training in post-MI patients may provide further insight into the relationship between reverse LV structural remodelling and LV mechanics.

In contrast to the intervention group, control group patients in this thesis did not display any change in NT-pro-BNP or LV volumetric parameters. The only observed adaptation was an increase in LV twist and LV twist velocity. Whilst the lack of change in LV volumes and NT-pro-BNP indicated a stable post-MI cohort, the change in LV mechanics could be interpreted as a functional adaptation preceding adverse LV volumetric remodelling. However, previous data has shown an increase in LV twist three to six months post-MI in patients without LV remodelling (Jang et al., 2010, Zito et al., 2011). This may suggest that the increase in LV twist
in the control group represents functional improvement in response to normal recovery and pharmacological therapy. Irrespective, the differential response of increased LV twist and twist velocity in the intervention and control groups does, however, confirm a direct influence of CR exercise training on LV twist mechanics.

Completion of CR exercise training is known to confer significant clinical benefit, not only from the perspective of reduced mortality, but also with respect to improved, physical functioning, reduced morbidity, improved psychosocial status and reduced hospital readmission (Heran et al., 2011, Lawler et al., 2011, Valkeinen et al., 2010, Schwaab et al., 2011). While in isolation, the exact clinical benefit of each of the present LV remodelling findings is difficult to delineate, their collective influence may contribute to these impressive clinical outcomes. An improvement in functional capacity, which is strongly correlated with reduced mortality (Paffenbarger et al., 1993, Reibis et al., 2010), is reflective of a multitude of cardiovascular adaptations that occur with CR exercise training. Prior to completion of this thesis, little was known of the influence of cardiac structure and function on improved functional capacity in post-MI patients. It is likely that the reverse LV remodelling reported in chapters five and six, in combination with previously described adaptations (i.e. improved endothelial function), contribute to the overall reduction in mortality associated with CR exercise training.

In addition to observing reverse LV remodelling in this thesis, the potential clinical utility of serial NT-pro-BNP measurement in CR exercise training programmes was highlighted. Not only could this marker serve as a measure of overall neurohormonal status and clinical stability, but also as an indirect assessment of reverse LV volumetric remodelling. The finding of a moderate correlation between the reduction in NT-pro-BNP and the reduction in LVEDV suggests that NT-pro-BNP might be useful as a surrogate measure of exercise induced reverse LV remodelling. From the perspectives of health economics and patient compliance, a relatively inexpensive and rapid biochemical assessment of reverse LV remodelling would be useful for patient care and management. Furthermore, in addition to serial measurement of NT-pro-BNP,
examination of LV mechanics may prove more informative than the currently preferred indices of LV volumes and LVEF in the assessment of reverse LV remodelling.

Finally, it was not the initial intention of the present studies to compare the efficacy of the CR exercise training protocol adopted in this thesis with current CR guidelines. However, from the perspective of the clinical efficacy of CR, this is worthy of discussion. In line with current CR guidelines (AACVPR, 2003), patients were enrolled within six weeks of MI, completed >20 min of twice weekly cardiovascular exercise training for a period of 10 weeks, and conducted an appropriate warm-up, cool down and resistance training programme. However, considerable attention was paid to ensuring that exercise intensity was maintained at 80% VO\textsubscript{2peak}, as opposed to the recommended 40-65% VO\textsubscript{2peak}. This decision was based on literature demonstrating the greater efficacy and comparable safety of this approach in CR patients (Rognmo et al., 2012, Wisloff et al., 2009). It is possible that without this higher stimulus, the outcome of the intervention may have been different. Moreover, the novel observation of different NT-pro-BNP kinetics following maximal and submaximal exercise in chapter four of this thesis may support the argument for higher intensity training. Prior to the start of the CR exercise training programme, a similar peak NT-pro-BNP was achieved following the maximal and submaximal exercise tests. In addition, sustained elevation was evident with submaximal exercise suggesting that exercise duration rather than intensity may be more influential in the release of NT-pro-BNP release. On the basis of these results, and in the absence of cardiovascular complications, data from this thesis support the use of higher intensity CR exercise training. As such, an imperative may exist for a thorough guideline review to ensure patients’ achieve optimal clinical and therapeutic benefit from CR exercise programmes in this country.
7.4 Limitations
In the planning and execution of the three presented studies, great care was taken to ensure the highest possible methodological rigour and experimental accuracy. However, the completion of research in clinical populations is limited in a number of areas. The following section will outline the general and study specific limitations related to this thesis. Overall, the studies were limited by the non-randomised study design, the small control group sample sizes and the exclusively male population. Ethical approval was not sought for a randomised control trial on the grounds of the additional resource required in adopting this approach and the unlikely occurrence of a favourable ethical opinion. However, the inclusion of a control group, albeit not randomised, does provide additional scientific rigour, particularly when baseline characteristics are similar between the two groups. Naturally, following MI, the preference of the majority of study-eligible patients was to participate in the exercise intervention. Subsequently, recruitment to the control group was significantly slower resulting in a smaller population on completion of the time-limited enrolment period. However, for the statistical techniques employed, the control group was considered adequately powered for detection of change in the majority of measures. Future trials should aim to include females and randomise participants. Finally, although expected, the inability to collect a complete biochemical and echocardiographic dataset in all the participants was also a limitation.

7.4.1 Study 1 - specific limitations
In study one, it was not possible to collect SIES data in the control group due to the additional visits that would have been required for the participants. The lack of this data prevented direct between groups comparison of the effect of CR exercise training on the response of NT-pro-BNP to submaximal exercise.
7.4.2 Study 2 - specific limitations

Study two presented well matched intervention and control groups at baseline. However, despite no difference in absolute VO$_2$ peak between the intervention and control groups, a statistically higher VO$_2$ peak relative to body weight was identified in the intervention group. Whilst this is a limitation of the study, it does not detract from the significant improvement in VO$_2$ peak witnessed following the exercise training intervention and the concurrent reverse LV remodelling. Had both populations been subject to different exercise interventions, with the intention of evaluating the efficacy of one versus the other, this difference at baseline may have been considered problematic. However, with an unchanged VO$_2$ peak over the course of the control period, and the lack of change in any demographic, clinical or echocardiographic variables, the slightly lower baseline VO$_2$ peak in the control group was not considered to represent significant clinical or physiological difference between the two groups.

7.4.3 Study 3 – specific limitations

Study three was limited by a small number of baseline differences. In the control group, VO$_2$ peak relative to body weight, peak LV twist, peak LV twist velocity, peak apical rotation and peak apical rotation velocity were lower. There is, therefore, the potential that the differential response in LV twist and twist velocity over the 10-week period in the intervention and control groups was influenced by these differences at baseline. The effect of infarct territory (i.e. anterior, inferior, posterior etc.) is also a potential limitation of this study. Although infarct territory was not actively controlled, there was very little difference between the groups. Unfortunately, in this small, relatively heterogeneous sample (from the perspective of infarct territory), sub-group analysis of patients categorised according to the territory of infarct was not possible. Infarct territory may be of particular relevance when analysing rotational parameters. It is well known that apical rotation is the primary contributor to LV twist and that the contribution from LV basal rotation is comparatively small (Opdahl et al., 2008). When assessing MI with regional wall motion abnormalities, anterior MI’s are associated with apical dysfunction whilst inferior MI’s predominantly cause dysfunction at the LV base (Armstrong
and Ryan, 2009). As such, previous work has identified greater impairment of LV apical mechanics in patients with anterior MI’s when compared to those with inferior MI’s (Bansal et al., 2008). However, Park et al. (2012) reported equal impairment of LV twist in anterior and inferior MI as a result of a compensatory increase in LV basal rotation in the former. Therefore, whilst regional variation exists in rotational parameters, LV twist as a global measure appears unaffected by MI territory. However, it is possible that the effect of CR exercise training on LV twist may differ, dependant on the territory of the infarct and, as such, future studies should consider this issue.

7.5 Implications for practice

Data from this thesis provides insight into the effects of CR exercise training on LV remodelling. It is likely that the presented adaptations are important in the functional restoration of the LV and thus patient outcome. The delivery of an effective programme of exercise rehabilitation for patients with MI has been previously identified as a key component of holistic CR. However, studies, predominantly conducted in the U.S.A, do not include a representative sample of ‘real life’ CR patients. Furthermore, they are commonly conducted in a well controlled research environment which bears little resemblance to actual CR practice, particularly in the U.K. The current study demonstrates that there is the potential for reverse LV remodelling in a ‘true’ CR environment in a relatively ‘normal’ CR population. However, patients in the current study were exercised to a higher intensity than is currently recommended and it is possible that this additional stimulus was instrumental in facilitating adaptation. The results of this thesis have, therefore, provided the momentum to adopt a higher intensity of CR exercise training as standard practice in the University Hospital, Coventry CR programme.

Despite the overwhelming evidence of CR efficacy, a lack of resource and at times an insufficiently skilled workforce, prevents CR programmes in the U.K. from quantitatively measuring CR outcome. As such, there is still considerable apathy from the medical fraternity
and NHS commissioners as to the worth of CR exercise programmes. Through the relatively simple and inexpensive application of NT-pro-BNP measurement and echocardiography, the ability to demonstrate reverse LV remodelling, as a meaningful clinical outcome, is an attractive proposition for CR practitioners and service leads for whom the struggle to convince clinical commissioners to maintain programme funding is increasingly challenging. These measures, which with further work may translate to cost savings for the NHS, may provide substantive evidence of the clinical and financial worth of CR exercise training programmes and thus complement current qualitative data.

7.6 Future directions
The overall heterogeneity of the post MI population dictates that larger multi-centre trials will be required to confirm the findings of these studies. Future studies may wish to examine the LV remodelling response in patients specifically categorised according to the region of infarct. With STE, the ability to conduct regional LV analysis provides the tool with which the response of infarcted and non-infarcted territories may be characterised. The study of LV mechanics in this regard may provide valuable insight into the potential for CR exercise training to favourably influence dysfunctional myocardium. Furthermore, the mechanisms by which LV mechanics are altered following CR exercise training require more detailed examination. For example, the accurate assessment of LV hemodynamics and vascular blood volume may enhance understanding of the influence of LV mechanics. Whilst this area of research is technically challenging and may be limited by the invasive and costly nature of the measurements, the continued development of non-invasive technologies is likely to provide investigators with additional options in the future. The assessment of LV mechanics during exercise further to a period of exercise training would also extend the results of the present studies. The measurement of resting mechanics provided an insight into LV functional adaptation, but it may only be during exercise that the true extent of this phenomenon may be observed.
The current study employed a relatively conservative exercise training protocol. As is reflected in current research, there is a great desire to identify the most effective exercise prescription for both healthy and clinical populations. Currently, there are no publications that have specifically examined reverse LV remodelling in post-MI patients following exposure to different training protocols. An improved response to high versus low intensity interval training has been reported in limited CHF studies and this is, therefore, an area which future research may wish to explore in patients with relatively preserved LVEF.

7.7 Conclusion
In post-MI patients with mildly abnormal LVEF, results from this thesis provide evidence of reverse LV remodelling. Completion of a structured programme of CR exercise training was shown to be effective in attenuating the post-MI neurohormonal response, volumetrically reverse remodelling the LV and mechanically improving LV function. The evolution of LV remodelling following MI is undoubtedly an area of great physiological and biomolecular complexity. Understanding the reversal of this process with CR exercise training is equally challenging. Continued research in this area may ultimately provide the impetus for the routine assessment of LV remodelling within CR exercise programmes as a measure of therapeutic efficacy and an aid to future design of CR exercise training interventions and optimal post-MI treatment.
References
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Appendices
06 June 2008

Mr Gordon McGregor
Senior Clinical Exercise Physiologist
UHCW NHS Trust
Cardiac Rehab, Cardiac Services Office Suite
University Hospital
Clifford Bridge Rd, Coventry
CV22DX

Dear Mr McGregor

Full title of study: The effects of cardiac rehabilitation exercise training on cardiac biomarkers
REC reference number: 08/H1210/56

Thank you for your undated letter of responding to the Committee’s request for further information on the above research, subject to the conditions specified below.

The further information has been considered on behalf of the Committee by the Chairman.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA. There is no requirement for [other] Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.
Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

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<th>Document</th>
<th>Version</th>
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<td>28 April 2008</td>
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<td>28 April 2008</td>
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<td>Dr S Bradford Brunel University</td>
<td>15 April 2008</td>
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<td>Letter of invitation to participant</td>
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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.
We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

08/H1210/56 Please quote this number on all correspondence

With the Committee’s best wishes for the success of this project

Yours sincerely

Mr Stephen Keay  
Chairman

Email: pauline.pittaway@uhcw.nhs.uk

Enclosures: “After ethical review – guidance for researchers” SL- AR2

Copy to: Dr Rob Shave, Brunel University

R&D office for UHC&W NHS Trust
18th June 2008

Our Reference: GM12/0408
MREC number: 08/H1210/56

Mr Gordon McGregor
Senior Clinical Exercise Physiologist
Cardiac Rehab, Cardiac Services Office Suite
University Hospital
Coventry, CV2 2DX

Dear Gordon,

Study Title: The effects of cardiac rehabilitation exercise training on cardiac biomarkers.

Thank you for submitting the above study for consideration by the Research & Development Office. I am pleased to inform you that the study has been approved and your research is covered by NHS indemnity as set out in HSG(96)48. For reference, the approval number is: GM12/0408 and it would be appreciated if you could quote the R&D reference in all future correspondence.

May I take this opportunity to remind you that, as a researcher, you must ensure that your research is conducted in a way that protects the dignity, rights, safety and well-being of participants. Trust R&D Approval assumes that you have read and understand the Research Governance Framework and accept that your responsibilities as a researcher are to comply with it, the Data Protection and Health & Safety Acts.

Your project may be subject to ad hoc audit by our department to ensure these standards are being met.

The Trust wishes you every success with your project.

Yours sincerely

Professor Steve Thornton
Associate Medical Director of R&D

Cc: Mrs Ceri Jones, R&D Services Manager, University Hospital
Mr Gordon McGregor  
Senior Clinical Exercise Physiologist  
University Hospital  
Clifford Bridge Road  
Walsgrave  
Coventry CV2 2DX

7th October 2008

Dear Gordon,

RE89-07 - The effects of cardiac rehab exercise training on cardiac biomarkers

I am writing to confirm the Research Ethics Committee of the School of Sport and Education received your application connected to the above project. Your application has been independently reviewed and I am pleased to confirm your application complies with the research ethics guidelines issued by the University.

On behalf of the Research Ethics Committee, I wish you every success with your study.

Yours sincerely

Dr Simon Bradford  
Chair of Research Ethics Committee  
School of Sport and Education
Appendix II - patient consent form

University Hospitals
Coventry and Warwickshire
NHS Trust

Consent form

Title of Project: The Effects of Cardiac Rehabilitation Exercise Training on Cardiac Biomarkers.

Ethics code (08/H1210/56)

Research Team: Dr P Banerjee - Consultant Cardiologist, Gordon McGregor, Senior Clinical Exercise Physiologist, Dr R Shave – Reader, Brunel University, David Gaze – Cardiac Research Scientist

1. I confirm that I have read and understand the information sheet dated 19/03/09 (version 3) for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at anytime, without giving any reasons and without my medical care or legal rights being affected.

3. I give permission for my GP to be informed of my participation in this study

4. I understand that sections of any of my medical notes may be looked at by the researchers, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

5. I kindly agree to the donation of my blood samples as a gift to be stored and used for future research into cardiac biomarkers, even in the event of loss of capacity. I understand that any unused samples will be destroyed after 10 years.

6. I am willing to be contacted and give a blood sample after 6 months and 1 year

7. I agree to take part in the above study

Please initial box

Name of patient Date Signature

Name of person taking consent Date Signature

Researcher Date Signature

1 for patient, 1 for researcher, 1 to be kept with medical notes

CR Exercise and cardiac biomarkers Version 2 – 19.03.09
Appendix III – Conference abstracts

Evidence of reverse left ventricular remodelling following exercise training in post-myocardial infarction patients.

Gordon S. McGregor1,2, David C. Gaze3 and Rob E. Shave1
1Cardiff Metropolitan University, Cardiff, UK. 2University Hospital, Coventry, UK. 3St George’s Hospital, London, UK.

Raised serum NT-proBNP concentration is indicative of hemodynamic compromise following myocardial infarction (MI) and also in chronic heart failure (CHF). A reduction in NT-proBNP is evidence of successful treatment and may also indicate reverse left ventricular (LV) remodelling. Cardiac rehabilitation exercise training has been shown to reduce NT-proBNP in CHF, however, the effect of exercise training on resting and peak exercise NT-proBNP is less well characterised in post MI patients.

PURPOSE: To determine the effect of exercise training on resting and peak exercise NT-proBNP in post MI patients following successful percutaneous coronary intervention (PCI).

METHODS: Cardiopulmonary exercise testing (CPET) was undertaken in 31 male (56±10 yrs) clinically stable post MI (33±7 days) patients prior to (CPET1) and following (CPET 2) 10 weeks of exercise training. NT-proBNP measurements were determined from serum samples obtained at rest and at peak exercise via a peripheral venous cannula. Mixed modality (treadmill, cycle, rower, cross-trainer) supervised exercise training was conducted for 30-40 minutes twice weekly at 60-80% of VO2 peak.

RESULTS: VO2 peak significantly improved (3.1±2.63 ml.kg⁻¹.min⁻¹, P<0.0001) following 10 weeks of exercise training. Resting and peak NT-proBNP were significantly reduced by 178±419 ng/L (P<0.01) and 202±384 ng/L (P<0.001) respectively. NT-proBNP increased significantly (49.5±97.6 ng/L, P<0.001) from rest to peak exercise on CPET 1 but not on CPET 2 (25.3±77.0 ng/L, P>0.05) despite a greater exercise stimulus (147±26 vs 171±28 Watts, P<0.0001).

CONCLUSION: Consistent with findings in the HF population, exercise training improves VO2 peak and lowers resting plasma NT-proBNP concentration in post MI patients. Furthermore, peak exercise NT-proBNP concentration is reduced. These reductions may potentially indicate reverse LV remodelling secondary to exercise training. However confirmation of this is required.
Left ventricular twist mechanics following exercise training in post-myocardial infarction patients.

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¹Cardiff Metropolitan University, Cardiff, UK. ²University Hospital, Coventry, UK. ³University of Leeds, Leeds, UK

INTRODUCTION: Endurance exercise training has been shown to reduce left ventricular (LV) end diastolic and end systolic volumes in patients with myocardial infarction (MI). Whilst these structural changes are reasonably well characterised, the effects of exercise training on LV function are less well understood. The development of novel echocardiographic techniques such as speckle tracking imaging (STI) has enabled a more detailed study of global LV function. LV systolic twist, the net difference between basal and apical rotation, is a key component of efficient LV systolic contraction. The effect of exercise training on LV twist mechanics in post MI patients has not been previously reported.

PURPOSE: To determine the effect of exercise training on resting LV twist mechanics in post MI patients following successful percutaneous coronary intervention (PCI).

METHODS: Cardiopulmonary exercise testing (CPET) and resting echocardiography were performed on 33 male (56±9 yrs) clinically stable post MI patients at baseline (34±7 days post MI) and 10 weeks later. Patients were assigned to either supervised exercise training (n=21) or control (n=12). Supervised exercise training consisted of mixed modality (treadmill, cycle, rower, cross-trainer) exercise training for 30-40 minutes twice weekly at 60-80% of VO₂peak. Controls received standard general physical activity advice.

RESULTS: The exercise training group showed significant improvements in peak VO₂ (3.2±3.1 ml.kg⁻¹.min⁻¹, P<0.001) and ejection fraction (EF) (2.0±4.4%, P<0.05) and significant reductions in EDV (-6.1±6.7ml, P<0.001) and ESV (-4.3±5.6ml, P<0.001). In contrast, peak VO₂ (-0.6±3.4 ml.kg⁻¹.min⁻¹, P>0.05), EDV (0.4± 7.2ml, P>0.05), ESV (1.0±5.4ml, P>0.05) and EF (-1.0±4.7%, P>0.05) were unchanged in the control group. LV twist mechanics in the exercise training group were characterised by a reduction in apical rotation (-2.3±4.6°, P<0.05), unchanged basal rotation (-1.1±3.5°, P>0.05) and a resultant reduction in peak LV twist (-3.4±5.3° P<0.01). Conversely, controls demonstrated an increase in peak LV twist (4.1±4.2°, P<0.01) secondary to an increased basal rotation (2.0±2.5°, P<0.05) and unchanged apical rotation (1.6±3.2°, P>0.05).

CONCLUSION: Consistent with findings in previous studies, exercise training improves VO₂ peak and facilitates favourable change in EDV, ESV and EF in post MI patients. Furthermore, LV systolic twist mechanics appear to be influenced by exercise training in these patients. These data offer a valuable insight into the effects of exercise training on LV function in post MI patients.
## Appendix IV - Time to peak data

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Week 10</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Twist (°) - Time To Peak (ms)</strong></td>
<td>361 ± 84</td>
<td>361 ± 40</td>
</tr>
<tr>
<td><strong>Twist (°) - Time To Peak (%)</strong></td>
<td>94 ± 14</td>
<td>95 ± 11</td>
</tr>
<tr>
<td><strong>Sys Twist Velocity (°·sec⁻¹) - Time To Peak (ms)</strong></td>
<td>164 ± 51</td>
<td>179 ± 68</td>
</tr>
<tr>
<td><strong>Sys Twist Velocity (°·sec⁻¹) - Time To Peak (%)</strong></td>
<td>44 ± 15</td>
<td>47 ± 16</td>
</tr>
<tr>
<td><strong>Uwisting velocity (°·sec⁻¹) - Time To Peak (ms)</strong></td>
<td>680 ± 294</td>
<td>565 ± 227</td>
</tr>
<tr>
<td><strong>Uwisting velocity (°·sec⁻¹) - Time To Peak (%)</strong></td>
<td>143 ± 41</td>
<td>127 ± 29</td>
</tr>
<tr>
<td><strong>Basal Rot (°) - Time To Peak (ms)</strong></td>
<td>387 ± 131</td>
<td>376 ± 134</td>
</tr>
<tr>
<td><strong>Basal Rot (°) - Time To Peak (%)</strong></td>
<td>96 ± 25</td>
<td>95 ± 26</td>
</tr>
<tr>
<td><strong>Basal sys Rot Velocity (°·sec⁻¹) - Time To Peak (ms)</strong></td>
<td>199 ± 82</td>
<td>212 ± 82</td>
</tr>
<tr>
<td><strong>Basal sys Rot Velocity (°·sec⁻¹) - Time To Peak (%)</strong></td>
<td>52 ± 21</td>
<td>51 ± 21</td>
</tr>
<tr>
<td><strong>Basal diast Rot Velocity (°·sec⁻¹) - Time To Peak (ms)</strong></td>
<td>110 ± 11</td>
<td>108 ± 10</td>
</tr>
<tr>
<td><strong>Basal diast Rot Velocity (°·sec⁻¹) - Time To Peak (%)</strong></td>
<td>420 ± 74</td>
<td>442 ± 46</td>
</tr>
<tr>
<td><strong>Basal Rad Strain (%) - Time To Peak (ms)</strong></td>
<td>155 ± 47</td>
<td>150 ± 42</td>
</tr>
<tr>
<td><strong>Basal Rad Strain (%) - Time To Peak (%)</strong></td>
<td>40 ± 13</td>
<td>40 ± 13</td>
</tr>
<tr>
<td><strong>Basal diast Radial SR (/sec) - Time To Peak (ms)</strong></td>
<td>524 ± 73</td>
<td>542 ± 106</td>
</tr>
<tr>
<td><strong>Basal diast Radial SR (/sec) - Time To Peak (%)</strong></td>
<td>121 ± 19</td>
<td>123 ± 20</td>
</tr>
<tr>
<td><strong>Basal Rad Strain (%) - Time To Peak (%)</strong></td>
<td>357 ± 70</td>
<td>383 ± 53</td>
</tr>
<tr>
<td><strong>Apical Rot (°) - Time To Peak (ms)</strong></td>
<td>357 ± 70</td>
<td>383 ± 53</td>
</tr>
<tr>
<td><strong>Apical Rot (°) - Time To Peak (%)</strong></td>
<td>96 ± 14</td>
<td>102 ± 11</td>
</tr>
<tr>
<td><strong>Apical sys Radial SR (/sec) - Time To Peak (ms)</strong></td>
<td>500 ± 74</td>
<td>488 ± 57</td>
</tr>
<tr>
<td><strong>Apical sys Radial SR (/sec) - Time To Peak (%)</strong></td>
<td>120 ± 10</td>
<td>119 ± 11</td>
</tr>
<tr>
<td><strong>Apical Rad Strain (%) - Time To Peak (ms)</strong></td>
<td>400 ± 133</td>
<td>415 ± 93</td>
</tr>
<tr>
<td><strong>Apical Radial Strain (%) - Time To Peak (%)</strong></td>
<td>103 ± 28</td>
<td>107 ± 19</td>
</tr>
<tr>
<td><strong>Apical sys Radial SR (/sec) - Time To Peak (ms)</strong></td>
<td>199 ± 86</td>
<td>191 ± 97</td>
</tr>
<tr>
<td><strong>Apical sys Radial SR (/sec) - Time To Peak (%)</strong></td>
<td>56 ± 22</td>
<td>53 ± 27</td>
</tr>
<tr>
<td><strong>Apical diast Radial SR (/sec) - Time To Peak (ms)</strong></td>
<td>542 ± 65</td>
<td>533 ± 60</td>
</tr>
<tr>
<td><strong>Apical diast Radial SR (/sec) - Time To Peak (%)</strong></td>
<td>35 ± 19</td>
<td>40 ± 19</td>
</tr>
<tr>
<td><strong>Longitudinal Strain (%) - Time To Peak (ms)</strong></td>
<td>358 ± 46</td>
<td>362 ± 29</td>
</tr>
<tr>
<td><strong>Longitudinal Strain (%) - Time To Peak (%)</strong></td>
<td>99 ± 2</td>
<td>100 ± 1</td>
</tr>
<tr>
<td><strong>Longitudinal sys SR (/sec) - Time To Peak (ms)</strong></td>
<td>183 ± 41</td>
<td>181 ± 31</td>
</tr>
<tr>
<td><strong>Longitudinal sys SR (/sec) - Time To Peak (%)</strong></td>
<td>51 ± 11</td>
<td>50 ± 8</td>
</tr>
<tr>
<td><strong>Longitudinal diast SR (/sec) - Time To Peak (ms)</strong></td>
<td>541 ± 49</td>
<td>547 ± 50</td>
</tr>
<tr>
<td><strong>Longitudinal diast SR (/sec) - Time To Peak (%)</strong></td>
<td>126 ± 8</td>
<td>128 ± 9</td>
</tr>
<tr>
<td><strong>Longitudinal Strain (%) - Time To Peak (%)</strong></td>
<td>104 ± 6</td>
<td>100 ± 6</td>
</tr>
<tr>
<td><strong>Longitudinal sys SR (/sec) - Time To Peak (%)</strong></td>
<td>145 ± 36</td>
<td>167 ± 37</td>
</tr>
<tr>
<td><strong>Longitudinal sys SR (/sec) - Time To Peak (%)</strong></td>
<td>37 ± 13</td>
<td>45 ± 8</td>
</tr>
<tr>
<td><strong>Longitudinal diast SR (/sec) - Time To Peak (%)</strong></td>
<td>515 ± 44</td>
<td>534 ± 28</td>
</tr>
<tr>
<td><strong>Longitudinal diast SR (/sec) - Time To Peak (%)</strong></td>
<td>121 ± 5</td>
<td>125 ± 6</td>
</tr>
</tbody>
</table>

Data as mean ± SD. † P < 0.05 time effect (ANOVA), ‡ P < 0.05 group × time interaction effect (ANOVA), *P<0.05 vs. baseline, **P<0.01 vs. baseline. Sys, systolic; rot, rotation; diast, diastolic; rad, radial; circ, circumferential; SR, strain rate.