Echocardiographic Parameters of Dyssynchrony in Cardiac Resynchronisation Therapy

A thesis submitted to the University of Manchester for the degree of Doctor of Medicine (MD) in the Faculty of Medical and Human Sciences

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School of Medicine
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<td>2D</td>
<td>Two-dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three-dimensional</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ASE</td>
<td>American Society of Echocardiography</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under curve</td>
</tr>
<tr>
<td>AV</td>
<td>Atrio-ventricular</td>
</tr>
<tr>
<td>AVC</td>
<td>Aortic valve closure</td>
</tr>
<tr>
<td>AVO</td>
<td>Aortic valve opening</td>
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<tr>
<td>CFM</td>
<td>Colour flow mapping</td>
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<td>CRT</td>
<td>Cardiac resynchronisation therapy</td>
</tr>
<tr>
<td>CRT-D</td>
<td>Cardiac resynchronisation therapy – defibrillator</td>
</tr>
<tr>
<td>CW</td>
<td>Continuous wave (Doppler)</td>
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<tr>
<td>DFT</td>
<td>Diastolic filling time</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EROA</td>
<td>Effective regurgitant orifice area</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ICC</td>
<td>Intra-class correlation co-efficient</td>
</tr>
<tr>
<td>ICD</td>
<td>Implantable cardioverter-defibrillator</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior vena cava</td>
</tr>
<tr>
<td>IVFD</td>
<td>Inter-ventricular filling delay</td>
</tr>
<tr>
<td>IVMD</td>
<td>Inter-ventricular mechanical delay</td>
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<tr>
<td>LA</td>
<td>Left atrium / atrial</td>
</tr>
<tr>
<td>LBBB</td>
<td>Left bundle branch block</td>
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<tr>
<td>LV</td>
<td>Left ventricle / ventricular</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
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<td>LVOT</td>
<td>Left ventricular outflow tract</td>
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<td>MPI</td>
<td>Myocardial performance index</td>
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<tr>
<td>MR</td>
<td>Mitral regurgitation</td>
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<tr>
<td>MS</td>
<td>Milliseconds</td>
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<tr>
<td>NHS</td>
<td>National Health Service</td>
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<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>PA</td>
<td>Postero-anterior</td>
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<td>PCWP</td>
<td>Pulmonary capillary wedge pressure</td>
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<td>PEP</td>
<td>Pre-ejection period</td>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>PISA</td>
<td>Proximal isovelocity surface area</td>
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<td>PSMR</td>
<td>Pre-systolic mitral regurgitation</td>
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<tr>
<td>PW</td>
<td>Pulsed wave (Doppler)</td>
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<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RA</td>
<td>Right atrium / atrial</td>
</tr>
<tr>
<td>RBBB</td>
<td>Right bundle branch block</td>
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<tr>
<td>RegVol</td>
<td>Regurgitant volume</td>
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<tr>
<td>ROC</td>
<td>Receiver Operating Characteristic</td>
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<td>ROI</td>
<td>Region of interest</td>
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<tr>
<td>RV</td>
<td>Right ventricle / ventricular</td>
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<tr>
<td>RVOT</td>
<td>Right ventricular outflow tract</td>
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<td>SAECG</td>
<td>Signal-averaged electrocardiogram</td>
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<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SDI</td>
<td>Systolic dyssynchrony index</td>
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<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
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<td>SPWMD</td>
<td>Septal-posterior wall motion delay</td>
</tr>
<tr>
<td>SPWTD</td>
<td>Septal-posterior wall thickening delay</td>
</tr>
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<td>TAPSE</td>
<td>Tricuspid annular plane systolic excursion</td>
</tr>
<tr>
<td>TDI</td>
<td>Tissue Doppler imaging</td>
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<td>TSI</td>
<td>Tissue synchronisation imaging</td>
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<tr>
<td>VO₂</td>
<td>Volume oxygen consumption</td>
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<tr>
<td>VTI</td>
<td>Velocity time integral</td>
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<td>VV</td>
<td>Ventriculo-ventricular</td>
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Pacing mode abbreviations:

**DDD** – Sensing and pacing in atria and ventricle with triggering of ventricular pacing in response to sensed atrial activity to maintain AV synchrony

**VDD** – Sensing in both atria and ventricle but pacing only in the ventricle, atrio-ventricular synchrony is maintained when intrinsic atrial rate is above programmed base rate

**VVI** – Pacing and sensing only in the ventricle, generally used with a low base rate providing back-up only pacing in research settings to minimise pacing in a control group
Abstract

The University of Manchester

Matthew James Luckie

Doctor of Medicine

Echocardiographic Parameters in the Assessment of Response to Cardiac Resynchronisation Therapy

2012

Background:
Cardiac resynchronisation therapy (CRT) is a pacemaker-based therapy for patients with heart failure and dyssynchrony manifest as prolonged QRS duration. Approximately 30% fail to respond either symptomatically or echocardiographically. The role of several echocardiographic parameters to select patients and improve response rate has been studied. The utility of these parameters remains unclear. In particular recent advances in echocardiography with speckle tracking technology may provide more accurate assessment of dyssynchrony. This study aims to explore the role of echocardiography in prediction of CRT response and investigate mechanisms involved in response.

Methods:
Patients undergoing CRT according to national guidance were recruited. Baseline assessment included clinical examination, quality of life questionnaire, six minute walk test, electrocardiogram and detailed echocardiography. Follow-up assessment was performed six months after CRT. Response was defined as ≥15% reduction in left ventricular end-systolic volume. Baseline parameters of echocardiographic dyssynchrony were compared between responders and non-responders. Individual baseline and follow-up echocardiograms also were examined to assess mechanism of response.

Results:
51 patients were recruited and 40 patients completed six months follow-up. Echocardiographic response rate was 67.5%. Baseline parameters of dyssynchrony were not significantly different between responders and non-responders, and receiver operating characteristic (ROC) curve analysis suggested echocardiographic parameters have no role in prediction of response beyond QRS duration. Study of individual echocardiograms demonstrated several mechanisms of CRT response the relative importance of which vary between patients.

Conclusion:
Single echocardiographic dyssynchrony parameters appear to have no role in the prediction of CRT response. However, several mechanisms of response to CRT are identified, each of which may be identified echocardiographically, and echocardiography therefore continues to have an important role in pre-assessment of patients undergoing CRT.
Declaration

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Preface

I am a Specialist Registrar in Cardiology in the North West Deanery and developed an interest in echocardiography and cardiac pacing during the early stages of my training. The research leading to this thesis was performed at the Manchester Heart Centre within Manchester Royal Infirmary over a two year period of out of programme experience, following a fellowship in adult echocardiography at the same unit. I recruited all patients for the study, performed baseline and follow-up clinical assessment, and acquired and analysed all echocardiographic studies. I was also involved in device implantation, along with several other members of the cardiac pacing team at the Manchester Heart Centre.
Chapter 1

Introduction
1.1 Introduction

Heart failure is a clinical syndrome which may occur as a result of several underlying disease processes. Heart failure manifests with symptoms related to low cardiac output and salt and water retention, including breathlessness, fatigue, orthopnoea and oedema. In many cases heart failure is associated with a poor prognosis. Advances in pharmacological therapy in the past 20-25 years have brought about great improvements on both symptomatic and prognostic grounds, however despite this heart failure remains responsible for considerable morbidity and mortality.

Since the 1980s the role of pacemakers in the management of heart failure has been explored, and more recently biventricular pacemakers that pace both right and left ventricles developed. These devices aim to resynchronise cardiac function in patients with evidence of cardiac dyssynchrony, most commonly identified as a prolonged QRS complex on the electrocardiogram. In this specific group of heart failure patients marked improvement in symptoms and prognosis have been attributed to biventricular pacing, or cardiac resynchronisation therapy (CRT), in large clinical trials. A proportion of patients who undergo resynchronisation therapy fail to demonstrate improvement in either echocardiographic or clinical measures, so-called non-responders. Research has focussed upon identification of a more sensitive and specific marker than the duration of the QRS complex with which to select patients to receive CRT, with the aim of avoiding device implant in non-responders and to potentially identify other groups who may benefit from CRT but are not currently receiving it.

Several echocardiographic markers of dyssynchrony using Doppler echocardiography, M-mode imaging and tissue Doppler have been identified to be useful in this role, however promising results obtained in single centre studies were not been confirmed in a large multi-centre trial. More recently the role of a relatively new echocardiographic modality, speckle tracking, has been explored, which may have a role in this setting.
In addition to the focus upon identification of dyssynchrony, the mechanism of action of CRT has been questioned, and it remains unclear whether correction of dyssynchrony is the sole mechanism leading to response. It is likely that the precise mechanism of improvement in cardiac function and symptoms varies from patient to patient.

This thesis aims to further explore the role of echocardiographic parameters of dyssynchrony in the selection of candidates for CRT. The role of speckle tracking echocardiography and more established echocardiographic measures in the prediction of response to CRT will be studied, as well as an assessment of the relationship of speckle tracking parameters to other measures. The mechanism of response will also be assessed on an individual basis, to determine whether specific mechanisms of response can be identified.
Chapter 2

Background and Literature Review

2.1 Heart Failure
2.2 Pacemaker Therapy in Heart Failure
2.3 Non-Response to Cardiac Resynchronisation Therapy
2.4 Echocardiographic Parameters in Cardiac Resynchronisation Therapy
2.5 Echocardiographic Methods for Assessment of Mechanical Dyssynchrony
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2.12 The Mechanism of Response to Resynchronisation
2.13 Summary
2.1 Heart Failure

Heart failure is a clinical syndrome which manifests with symptoms including breathlessness, fatigue, orthopnoea, and oedema, along with specific clinical signs. Diagnostic terminology has varied, sometimes in an attempt to categorise heart failure with respect to the underlying pathology. Terms such as left heart failure, right heart failure and congestive cardiac failure are now used less commonly however, with the recognition that the presence of symptoms and signs traditionally described as right heart failure may occur just as commonly with underlying disease of the left heart, and vice versa.

2.1.1 Diagnosis and classification

The diagnosis of heart failure syndrome is made clinically based on the presence of specific symptoms (breathlessness, orthopnoea, and oedema) and clinical signs (pulmonary oedema, elevated venous pressure, and ascites) associated with salt and water retention. Heart failure syndrome is usually indicative of a significant reduction in cardiac output and occurs predominantly due to impairment of myocardial systolic function as a result of myocardial infarction, hypertension or valvular heart disease. Echocardiography is crucial in the further assessment of heart failure aetiology, and can accurately assess ejection fraction, presence of previous myocardial infarction, and valvular disease, although correlation between cardiac function and symptoms of heart failure is poor. Patients with severely impaired left ventricular (LV) function may exhibit no symptoms, and conversely heart failure syndrome may exist in the setting of apparently preserved cardiac function, so-called Heart Failure with Normal Ejection Fraction - this group of patients will not be discussed further in this thesis. Heart failure symptoms are traditionally classified according to the New York Heart Association classification.

NYHA Class

1. No symptoms and no limitation in ordinary physical activity
2. Mild symptoms and slight limitation during ordinary physical activity
3. Marked limitation with symptoms during less than ordinary activity
4. Symptoms at rest
2.1.2 Pathophysiology and treatment
Heart failure is associated with considerable neurohumoral disturbance, including activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system in response to reduced cardiac output and renal perfusion. Over time this neurohumoral response has adverse effects on the heart and vascular system which increase afterload and peripheral vasoconstriction and propagate the effects of impaired cardiac function. This understanding has lead to major advances in pharmacological therapy for heart failure over recent decades. The CONSENSUS study demonstrated significant improvement in symptoms and prognosis using the angiotensin-converting enzyme (ACE) inhibitor enalapril (1). CIBIS-II demonstrated marked reduction in mortality attributable to the beta-blocker bisoprolol (2), and more recently important improvements in symptoms and mortality have also been shown with angiotensin-II receptor antagonists (3) and aldosterone receptor antagonists (4). Despite these improvements however, considerable morbidity and mortality due to heart failure remains, and over the last decade or so the role of pacemakers in a particular subset of patients with heart failure syndrome and left ventricular systolic dysfunction has become established.

2.2 Pacemaker Therapy in Heart Failure
The first fully implantable pacemaker was implanted in 1958 and failed within a few hours (5). Pacemaker therapy has since evolved to become a routine treatment for brady-arrhythmia, with endocardial electrodes positioned transvenously in the right ventricle (RV) and/or right atrium (RA) as necessary and connected to single or dual channel pulse generators usually positioned subcutaneously in the pectoral area. Modern pacemakers sense intrinsic cardiac activity, and may be programmed to inhibit or trigger in one or other cardiac chamber as necessary at specific intervals, depending upon the needs of the patient, generally with the aim of promoting intrinsic cardiac rhythm where possible and maintaining atrio-ventricular synchrony.
2.2.1 Dual chamber pacemakers

The use of pacemakers as therapy for heart failure was first studied in detail in the late 1980s and early 1990s. It was noted that in patients with dilated cardiomyopathy and a prolonged atrio-ventricular (AV) conduction time, pre-systolic mitral regurgitation may occur which limited the duration of diastolic ventricular filling, further impairing cardiac output. Brecker et al studied 12 such patients (6), and reported that the use of conventional dual chamber (right atrial and right ventricular) pacemakers programmed with a short AV delay was associated with an immediate improvement in mitral regurgitation, ventricular filling time, cardiac output and exercise capacity, including peak oxygen consumption. Hochleitner et al reported upon a group of 16 patients with advanced heart failure, many of whom were under consideration for cardiac transplant or dependent upon intravenous inotropic agents. They demonstrated marked improvement in ejection fraction and NYHA class up to 14 days following dual chamber pacing (7). All patients on inotropic support were able to be weaned off. They hypothesised these benefits occurred because a short AV delay resulted in a reduction in pre-systolic mitral regurgitation (although this was not specifically demonstrated in all patients) and a consequent increase in left ventricular filling time, as well as optimisation of filling and preload by appropriate timing of atrial contraction at end-diastole.

Subsequent studies however reported no evidence of sustained improvement in either symptoms or cardiac function after dual chamber pacing. Linde reported that although short-term improvements in stroke volume and cardiac output were seen at 24 hours following pacing, follow-up at 3 and 6 months demonstrated no change in ejection fraction, stroke volume and NYHA class (8). A further study by Saxon et al reported that patients with pacemakers who were hospitalised for decompensated heart failure had a significantly increased risk (49% compared to 12% for those without a pacemaker) of future death due to progressive heart failure, or a need for cardiac transplantation over twelve months follow-up (9). The first randomised, controlled trial of short AV delay pacing in congestive heart failure was published in 1995 (10). This trial utilised a double-blind crossover design, recruiting 12 subjects with symptomatic heart failure despite appropriate medical therapy, who were implanted with dual chamber pacemakers. The participants were randomly assigned to receive either dual
chamber pacing with a short AV delay in VDD pacing mode, or backup pacing only (VVI mode) at a rate of 40 beats/min. After 4-6 weeks the subjects crossed over to the alternate pacing mode. There were no significant differences in invasive measures of cardiac output and pulmonary capillary wedge pressure immediately after pacing between the permanently paced and the backup-only pacing groups. In addition no change in ejection fraction or NYHA class was seen after 6 weeks of follow-up, suggesting the benefits seen in prior uncontrolled studies may have been due to placebo effect, and possible investigator bias.

Although a reduction in pre-systolic mitral regurgitation had been demonstrated previously (6) and was felt to be due to improved atrio-ventricular synchrony as a result of dual chamber pacing, this appeared to be offset by the deleterious effects of chronic right ventricular apical pacing upon cardiac electrical activation and contractile efficiency. Prinzen examined the haemodynamic effect of pacing from different sites in open-chested dogs, and demonstrated that pacing from the right ventricular outflow tract resulted in late activation of the anterior left ventricular wall, which was associated with significant falls in stroke volume and blood pressure compared to intrinsic activation (11). Prinzen concluded that asynchronous contraction of the left ventricular myocardium resulted in a reduction in global left ventricular systolic function, impairing cardiac output. Right ventricular apical pacing typically results in a left-bundle branch block (LBBB) pattern of cardiac activation with a wide QRS complex, due to slow intra-myocardial transit of the cardiac impulse. The resulting delay in electrical activation results in delayed contraction of the postero-lateral left ventricular wall (intra-ventricular dyssynchrony) and is associated with a reduction in stroke volume, and an increase in systolic mitral regurgitation (12). Incoordination of the normal interaction between left and right ventricles may also be seen (inter-ventricular dyssynchrony). Similar changes may be seen in left bundle branch block due to intrinsic conduction system disease (13). In patients with sinus node disease but normal intra-ventricular conduction and normal cardiac function, these adverse haemodynamic effects of long-term right ventricular pacing have been shown to result in an increased risk of atrial fibrillation and hospitalisation with heart failure (14).
It was hypothesised that in patients with heart failure the adverse haemodynamic effects of intrinsic or pacemaker-induced left bundle branch block could be offset by stimulation of ventricular activation from multiple pacing sites, resulting in synchronised activation and contraction of the right and left ventricles, and of the septum and posterolateral wall of the left ventricle.

2.2.2 Development of cardiac resynchronisation therapy
Multi-site ventricular pacing to resynchronise cardiac contraction and improve cardiac output and symptoms in patients with heart failure and LBBB was first reported in 1994 (15). Cazeau et al report a patient with end-stage heart failure and LBBB, who was resistant to standard medical therapy, and was not suitable for cardiac transplantation. Initially temporary pacing leads were positioned to each of the four cardiac chambers. Standard right atrial and right ventricular leads were used, the lead for pacing the left atrium was positioned in the coronary sinus, and the lead for left ventricular pacing was positioned retrogradely via the aorta. Haemodynamic measurements made during temporary left atrial and biventricular pacing (triggered by a sensed stimulus in the right atrium) confirmed an improvement in measured cardiac output, and a fall in pulmonary capillary wedge pressure. Subsequently a permanent pacing system was implanted using conventional right atrial and right ventricular leads, a coronary sinus lead for left atrial pacing, and a left ventricular lead surgically positioned on the epicardial surface over the LV free wall. The atrial and ventricular leads were both connected via Y-connectors to a standard dual chamber pacemaker. The clinical status of the patient was reported to improve substantially over six weeks following implantation, resulting in disappearance of previously intractable oedema, and improvement in symptoms from NYHA class IV to class II. Small case series of biventricular pacing soon followed, usually using a simplified three lead system. Standard right atrial and right ventricular leads continued to be used, with the left ventricular lead positioned either surgically on the epicardial surface, or later transvenously into a branch of the coronary sinus overlying the left ventricular free wall. Occasionally a left atrial lead would be positioned, in cases where prolonged inter-atrial conduction delay was identified. The ventricular leads were then connected to a standard dual chamber pacemaker using a Y-adaptor. Patients enrolled into these studies
had severe left ventricular systolic dysfunction and end-stage heart failure, in some cases requiring continuous inotropic support, and left bundle branch block with a wide QRS complex, either due to pre-existing right ventricular pacing, or more commonly due to intrinsic conduction system disease. These series confirmed improvements in ejection fraction, left ventricular filling time, and pulmonary capillary wedge pressure as well as reduction in mitral regurgitation. Inotropic support could be rapidly discontinued in those previously dependent upon it (16, 17). Subsequently, large scale randomised trials confirmed the benefits of biventricular pacing, or cardiac resynchronisation therapy (CRT). Dedicated CRT devices were developed by manufacturers, allowing separate programming of the right and left ventricular lead pacing output and adjustment and optimisation of timing of stimulation. Enrolled patients typically had left ventricular ejection fraction <35%, NYHA II-IV heart failure symptoms despite appropriate medical therapy, prolonged QRS duration >120-150 milliseconds (ms) and were in sinus rhythm. The demonstrated benefits included significant improvements in NYHA class, quality of life, 6 min walk distance, maximal oxygen consumption, left ventricular ejection fraction, left ventricular volumes, mitral regurgitation, and reduced rates of hospitalisation for decompensated heart failure (18-23). Selected trials are summarised below:

**VENTAK-CHF** (22) – non-significant mortality reduction attributable to CRT in patients also receiving implantable defibrillator (2000)

**MUSTIC** (20) – crossover study demonstrating improved quality of life and walk distance and reduced heart failure hospitalisations in CRT group (2001)

**MIRACLE** (23) – reduced hospitalisation and need for intravenous heart failure therapies, as well as improved walk distance, NYHA class and quality of life score (2002)

**MIRACLE-ICD** (18) – improvement in quality of life score and functional class with CRT in patients with NYHA class 3-4 heart failure, QRS duration >130ms and spontaneous or inducible ventricular arrhythmia (2003)
PATH-CHF (19, 21) – significant improvement in functional class and peak oxygen consumption maintained over 12 months follow-up by biventricular or left ventricular pacing in patients with NYHA 3-4 heart failure and QRS duration >150ms (2003)

Subsequently two landmark multi-centre studies confirmed a reduction in mortality attributable to CRT. The COMPANION study (24) reported significant reduction in a combined end-point of all-cause mortality and hospitalisation for heart failure with CRT, and significant reduction in all-cause mortality alone when CRT was combined with defibrillation capabilities (CRT-D). The CARE-HF study (25) advanced these findings further, reporting a significant reduction in mortality over 29 months of follow-up for CRT alone. This evidence base supporting the beneficial effects of CRT forms the basis for the National Institute for Health and Clinical Excellence (NICE) guidelines (26), which state that CRT should be considered in patients with NYHA III-IV heart failure, who are in sinus rhythm with an ejection fraction of <35% and QRS duration >120ms, and who are on optimal medical therapy. Based predominantly on the inclusion criteria for the CARE-HF study, the guidelines also state that those patients with QRS duration of 120-149ms should have further assessment for the presence of dyssynchrony by echocardiography before CRT is offered. As discussed later in this chapter there are several echocardiographic parameters of dyssynchrony which may be measured to achieve this, however no preferred method is specified in the guidance.

2.3 Non-Response to Cardiac Resynchronisation Therapy

Several measures have been used in published studies to determine response to CRT. Clinical or symptomatic improvement has been assessed by NYHA class, six-minute walk distance or quality-of-life questionnaire. Measurement of maximal oxygen consumption (peak VO₂) during cardiopulmonary exercise testing has also been used as a potentially more objective measure of symptomatic and metabolic improvement. Echocardiographic methods may be used to document changes in ejection fraction or left ventricular volumes
(remodelling). However, no single measure of response has been used consistently during studies of CRT and changes in measures of clinical, metabolic and echocardiographic response correlate poorly (27).

Despite the clearly demonstrated benefits of CRT, it has been consistently observed that a proportion of patients do not show evidence of improvement following CRT, either in terms of symptoms, metabolic parameters, or measures of cardiac structure and function. Typically this non-response rate is in the region of 30%, although varies depending on the measure of response used.

Having firmly established a beneficial effect related to CRT, studies began to focus upon identification of the most appropriate criteria to select patients to receive CRT, in order to reduce the rate of non-response to therapy. The primary trials which had demonstrated the efficacy of CRT relied upon the identification of dyssynchrony by electrical parameters, using prolongation of the QRS complex on the 12 lead electrocardiogram (ECG), usually in the form of LBBB. Prolongation of the QRS complex reflects delayed electrical activation of the myocardium, and this was felt to be co-existent with dyssynchronous mechanical contraction. LBBB is highly heterogeneous however, and the surface ECG appearance may not accurately reflect the pattern of electrical activation and consequent mechanical contraction. Auricchio used non-contact endocardial mapping to study activation patterns in patients with heart failure and LBBB (28). In one third of patients endocardial activation time was normal despite the presence of LBBB on the surface ECG. In the remaining patients there were varying sites of functional conduction block in the anterior, lateral or inferior walls, the varying sites of block not reflected in the surface ECG. Fung used a combination of non-contact mapping and echocardiographic tissue Doppler imaging to characterise LV activation in 7 patients with LBBB (29). This confirmed normal endocardial activation in one patient. In three patients a specific site of block was identified, and in the final three patients homogenously slow intra-myocardial conduction was seen. The surface ECG again failed to reflect the noted differences in LV activation sequence. Myocardial activation sequence as assessed by tissue Doppler imaging correlated well with the findings of electrical mapping. It was therefore hypothesised that direct identification of the presence of mechanical dyssynchrony using echocardiography, rather than
relying on the surface ECG, may improve selection of patients for CRT, and reduce the rate of non-response to therapy.

2.4 Echocardiographic Dyssynchrony and Cardiac Resynchronisation Therapy

The presence of mechanical dyssynchrony may be assessed using various techniques, including multiple echocardiographic parameters which will be described in detail below. Echocardiographic parameters may be broadly described as falling into three groups.

i. Intra-ventricular dyssynchrony
Parameters which aim to identify mechanical dyssynchrony within the left ventricle, usually differences between timing of activation and contraction of opposing segments such as the septum and posterior wall.

ii. Inter-ventricular dyssynchrony
Parameters which aim to identify dyssynchrony between right and left ventricles, usually due to late activation and contraction of the left ventricle compared to the right.

iii. Atrio-ventricular dyssynchrony
Parameters which aim to identify abnormality of the interaction between atrium and ventricle usually manifest as late ventricular activation and contraction in relation to atrial activity.

2.4.1 Prevalence of mechanical dyssynchrony assessed by echocardiography
Assessment of the prevalence of mechanical dyssynchrony by echocardiography confirms that mechanical dyssynchrony tends to become more common as QRS duration increases. However, a significant proportion of patients with LBBB do not have detectable mechanical dyssynchrony, perhaps reflecting normal electrical activation despite LBBB on the surface ECG as demonstrated by Auricchio and Fung (28, 29). Conversely, a proportion of patients with normal
QRS duration (<120ms) have evidence of dyssynchronous mechanical contraction. Table 2.1 (page 32, overleaf) summarises the studies which have examined the prevalence of mechanical dyssynchrony in relation to QRS duration in patients with heart failure and impaired left ventricular systolic function (30-34). These studies confirm the prevalence of both inter-ventricular and intra-ventricular dyssynchrony increases with increasing QRS duration. However, although the degree of measured inter-ventricular dyssynchrony appears to correlate with the QRS duration, the degree of intra-ventricular dyssynchrony does not consistently correlate with QRS width. Indeed, van Bommel measured intra-ventricular dyssynchrony in 248 patients and found no difference in the frequency of dyssynchrony between patients with normal QRS, left bundle branch block, right bundle branch block (RBBB), and right ventricular pacing (35). Zakhama reports no correlation between measures of intra-ventricular dyssynchrony and QRS width (36). Zhang also reports a high prevalence of intra-ventricular dyssynchrony measured in different echocardiographic planes in patients with narrow QRS (37). These findings suggest that non-response to therapy in patients with LBBB may be due to absence of mechanical dyssynchrony despite the presence of delayed electrical activation on the surface ECG, and additionally that there may be a subset of patients with narrow QRS complexes and mechanical dyssynchrony who may benefit from CRT.

2.5 Echocardiographic Methods for Assessment of Mechanical Dyssynchrony

Echocardiographic assessment of mechanical dyssynchrony focuses upon identification of delay in contraction between the right and left ventricles (inter-ventricular dyssynchrony), opposing segments of the left ventricle (intra-ventricular dyssynchrony) or abnormal interaction between atrium and ventricle (atrio-ventricular dyssynchrony). Initial studies of echocardiographic dyssynchrony focussed upon the use of i) M-mode echocardiography and ii) tissue Doppler imaging (TDI) to detect intra-ventricular dyssynchrony, and iii) pulsed-wave Doppler to detect inter-ventricular dyssynchrony.
<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Dyssynchrony</th>
<th>Narrow QRS (&lt;120ms)</th>
<th>Intermediate QRS (120-150ms)</th>
<th>Wide QRS (&gt;150ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haghjoo (30)</td>
<td>Inter-ventricular dyssynchrony</td>
<td>32%</td>
<td>51.5%</td>
<td>76.5%</td>
</tr>
<tr>
<td></td>
<td>Intra-ventricular dyssynchrony</td>
<td>36%</td>
<td>58%</td>
<td>79%</td>
</tr>
<tr>
<td>Ghio (31)</td>
<td>Inter-ventricular dyssynchrony</td>
<td>12.5%</td>
<td>52.4%</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>Intra-ventricular dyssynchrony</td>
<td>29.5%</td>
<td>57.1%</td>
<td>71%</td>
</tr>
<tr>
<td>Bleeker (32)</td>
<td>Intra-ventricular dyssynchrony</td>
<td>27%</td>
<td>60%</td>
<td>70%</td>
</tr>
<tr>
<td>Badano (33)</td>
<td>Intra-ventricular dyssynchrony</td>
<td>39%</td>
<td>36%</td>
<td>60%</td>
</tr>
<tr>
<td>Yu (34)</td>
<td>Intra-ventricular dyssynchrony</td>
<td>51%</td>
<td>73%</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.1: Studies investigating the prevalence of echocardiographic dyssynchrony parameters
2.5.1 Septal – posterior wall M-mode delay

M-mode echocardiography is acquired from a short axis parasternal view through the left ventricle, transecting the mid-segment of the anterior ventricular septum and the mid-posterior wall. The timing of peak systolic motion of the septum and posterior wall can be identified, and any temporal delay between the two measured (Figure 2.1).

Xaio published early work demonstrating that in patients with dilated cardiomyopathy and prolonged QRS complex, delayed onset of left ventricular free wall contraction was seen using this method (38). Pitzalis first reported in 2002 that assessment of dyssynchrony by M-mode echocardiography could be used to predict response to CRT (39). Pitzalis assessed septal – posterior wall motion delay (SPWMD) in 20 patients with heart failure and LBBB prior to CRT. Response to CRT was defined as a 15% reduction in left ventricular systolic volume index (ie. reverse remodelling) one month following CRT. Analysis of SPWMD was said to be highly reproducible, with an inter-observer coefficient of 0.91. SPWMD >130ms was reported to predict echocardiographic response to CRT with a specificity of 63% and positive predictive value of 80%.

**Figure 2.1:** M-mode echocardiogram through the left ventricular cavity demonstrating measurement of the septal – posterior wall M-mode delay. In this case the delay is 130ms, which is the cut-off for prediction of CRT response proposed by Pitzalis et al.
A further report by Pitzalis in 2005 confirmed similar findings in 60 patients (40). The findings of Pitzalis have subsequently been disputed however, in particular by Marcus et al who reported poor feasibility and reproducibility for the measurement of SPWMD (41). Analysis in this study was only possible in 45% of patients, mainly due to limited image quality and akinesia of one or other walls, making accurate determination of the timing of peak motion difficult. This perhaps reflects the fact that Pitzalis’ study recruited predominantly patients with non-ischaemic cardiomyopathy, whereas Marcus’ study included 72% with ischaemic cardiomyopathy, and therefore greater likelihood of thinned and akinetic myocardial segments with unclear patterns of motion on M-mode echocardiography. Marcus also noted wide inter-observer variability, and in this study of 79 patients SPWMD failed to predict improvement in echocardiographic parameters. The poor feasibility of SPWMD and failure of this parameter to predict response has been confirmed in subsequent reports (42). A variation on the measurement of SPWMD which related the timing of posterior wall motion by M-mode to trans-mitral diastolic flow was one of three echocardiographic parameters used to select a subset of patients for the landmark CARE-HF study (43).

A further variation on SPWMD, the septal-to-posterior wall thickening delay (SPWTD) has also been proposed (44). The authors of this paper measured delay in septal and posterior wall thickening rather than motion, and in a study of 37 patients conclude that SPWTD predicts echocardiographic response to CRT more reliably than SPWMD. Practically however, this method appears to retain the main pitfalls of the SPWMD method, particularly the likelihood of poor feasibility and reproducibility due to either image quality or akinesia of one or other walls. This method also suffers from an inability to reliably differentiate between active wall thickening and passive wall motion, particularly in the septum where complex patterns of septal movement may be seen due to interaction with right ventricular filling and contraction.

More recently M-mode echocardiography combined with colour tissue Doppler imaging has been suggested as a way of identifying the early septal activation seen in LBBB, termed the ‘septal flash’ by some authors (45). The use of colour-coded velocity data to generate an M-mode image appears to minimise the pitfalls associated with grey-scale imaging outlined above, often providing a
much clearer delineation of the peak wall motion. Inter-observer variability is reported to be significantly lower for colour tissue Doppler M-mode than conventional SPWMD imaging (46). The use of colour TDI M-mode to identify early septal activation in LBBB (the “septal flash”) has been shown to predict reverse remodelling and increase in left ventricular dP/dt in a small number of patients (47). The abnormal septal activation pattern resolved with pacing in all patients.

2.5.2 Tissue Doppler imaging

Tissue Doppler imaging (TDI) is used to measure the velocity of motion of a chosen region of interest in a segment of myocardial tissue. Changes in regional myocardial velocity over the course of the cardiac cycle may be plotted graphically in real-time or during off-line analysis. Tissue Doppler may be acquired in pulsed-wave or colour TDI modes. Garrigue et al used pulsed-wave TDI to examine the effects of CRT in patients with right bundle branch block (RBBB) (48). They measured time to peak velocity in the basal septal and lateral segments, noting that in patients with RBBB only those with significant intra-ventricular delay showed improvement in functional class and left ventricular volumes. Pulsed wave TDI has the disadvantage of interrogating only one myocardial segment per acquisition, such that opposing segments may not be compared during the same cardiac cycle.

Colour TDI allows acquisition and analysis of velocity information from multiple myocardial segments simultaneously, and comparison of the graphical representation of the velocity profile for each segment allows temporal differences in the time to maximal velocity between opposing segments to be quantified during a single cardiac cycle. The time to peak myocardial velocity acts as a surrogate for the timing of mechanical activation in each segment. This technique is now widely described using between 2 and 12 myocardial segments to produce a measure of dyssynchrony.

The use of colour TDI-based methods to predict response to CRT has been studied by multiple research groups. The two main proponents of this method are Bax in Leiden, Netherlands, and Yu in Hong Kong. Yu published data in 2002 demonstrating significant improvement in tissue Doppler measures of dyssynchrony following CRT (49). In 2003 his group conducted pre-implant
echocardiography in 30 patients undergoing CRT (50), and calculated a systolic dysynchrony index representing the standard deviation of the measured time to peak systolic velocity in 12 myocardial segments (the basal and mid-segments of the anteroseptal, posterior, anterior, inferior, inferoseptal and lateral walls). Reverse remodelling of the left ventricle (> 15% reduction in end-systolic volume) was used as the measure of response. A dyssynchrony index of >32.6ms was able to completely differentiate responders from non-responders.

Bax reported in 2003 that delay in time to peak velocity between the basal septal and basal lateral segments in the apical 4 chamber view reduced significantly following CRT, and that this improvement appeared to correlate with the degree of reverse remodelling (51, 52). In 2004 Bax et al reported that the septal-lateral delay could also predict response to CRT (53) (Figure 2.2).

![Figure 2.2: Tissue Doppler velocity imaging demonstrating septal – lateral delay. The velocity profile of the basal septal segment is shown in yellow, and the basal lateral segment in green. Only peaks in the ejection period between aortic valve opening (AVO) and closure (AVC) are measured (marked with vertical lines). The delay between the septal and lateral systolic velocity peaks is 140ms, exceeding the cut-off for predicting remodelling of 65ms proposed by Bax et al.](image)

A delay of 65ms or more was able to predict clinical response (improvement by 1 or more NYHA classes and >25% improvement in 6 minute walk distance) with a sensitivity and specificity of 80%, and reverse remodelling with a sensitivity.
and specificity of 92%. In studies by both Yu and Bax it is noted that the respective TDI measures are the only independent predictive parameter of reverse remodelling.

Several subsequent non-randomised and single centre studies have also reported that detection of mechanical dyssynchrony by TDI is helpful in the prediction of response to CRT (54-58), some of which are summarised below.

**Ansalone et al 2001** (59) Intra-ventricular dyssynchrony was assessed by pulsed wave TDI of 5 basal left ventricular segments. Improved synchrony immediately following CRT predicted future reverse remodelling and improvement in functional class.

**Penicka et al 2004** (58) Intra-ventricular dyssynchrony was assessed as the longest delay between basal septal, lateral and posterior segments, and inter-ventricular dyssynchrony by delay between peak RV free wall velocity and latest LV segment. A combined index of inter- and intra-ventricular dyssynchrony was also produced. Intra- and inter-ventricular dyssynchrony predicted response to a greater extent than QRS duration, optimal predictive value was obtained by the combined index.

**Gorcsan et al 2004** (56) Studied the use of tissue synchronisation imaging (TSI), a tissue Doppler derived modality using additional software to automatically determine time to peak systolic velocity and overlay a colour coded velocity map corresponding to the measured time. A delay of >65ms between anterior septum and posterior wall in the apical 3 chamber view was associated with reverse remodelling with a sensitivity of 87% and specificity 100%.

**Yuan et al 2007** (60) Examined 6 basal left ventricular segments, reporting that the maximal delay between any two segments >179ms predicted reverse remodelling with a sensitivity of 86%.

### 2.5.3 Inter-ventricular dyssynchrony
Inter-ventricular dyssynchrony is typically manifest by delayed activation and contraction of the left ventricle with respect to the right. This may be quantified
echocardiographically using pulsed wave Doppler to detect the onset of ejection of blood by the ventricles in both the right and left ventricular outflow tracts. The time from onset of the QRS complex to the onset of ejection for both the left and right ventricles is measured (pre-ejection period, PEP - Figure 2.3), and the values subtracted from each other to generate the inter-ventricular mechanical delay (IVMD).

![Figure 2.3: Pulsed wave Doppler trace acquired from the left ventricular outflow tract (LVOT) demonstrating measurement of the pre-ejection period (time from onset of QRS complex to onset of forward flow in the LVOT). In this case the PEP is 196ms, which exceeds the cut-off of 140ms used as criteria for entry of a subgroup of patients into the landmark CARE-HF trial.](image)

An inter-ventricular mechanical delay >40ms, and a left ventricular PEP of >140ms, were two of the three echocardiographic criteria for entry of a subset of patients into the CARE-HF study. The majority of patients selected by echocardiographic criteria were entered based on these two parameters (43). Aksoy recently reported that of five measured parameters of dyssynchrony, only left ventricular pre-ejection period was able to predict response to CRT (61). In this study a cut-off value of 180.5ms was used, with a reported sensitivity of 93%, but a disappointing specificity of 42%.
Other methods for the assessment of inter-ventricular dyssynchrony have also been proposed. Wiesbauer et al measured inter-ventricular dyssynchrony in terms of ventricular filling, analysing the time interval from onset of QRS complex to onset of the transmitral E wave (Q to E delay), which represents the initial phase of left ventricular filling (62). They report that both IVMD (using a cut-off value of 60ms rather than 40ms), left ventricular PEP >140ms and QED >550ms predict reverse remodelling following CRT. Bax et al utilised TDI to measure inter-ventricular dyssynchrony, by comparing the difference in time to peak systolic velocity between the right ventricular free wall and the left ventricular lateral wall (53), however this parameter failed to predict response to CRT. In contrast Penicka et al reported that inter-ventricular dyssynchrony assessed by calculating the delay in systolic velocities between the right ventricular free wall and the most delayed basal left ventricular segment was predictive of CRT response assessed by improvement in ejection fraction >25% (58).

2.6 The Predictors of Response to Cardiac Resynchronisation Therapy (PROSPECT) Trial

The PROSPECT trial was conceived to determine which of the several reported echocardiographic methods for measurement of mechanical dyssynchrony was most predictive of response to CRT. The study was performed across 53 centres, enrolling a total of 498 patients who underwent CRT. Twelve parameters of dyssynchrony were measured before CRT, and positive response defined as reduction in left ventricular end-systolic volume >15%, and improved composite clinical score (scored blindly as worsened, unchanged or improved by the investigating team). Despite hopes that the study would define the most appropriate measures of dyssynchrony for prediction of response, the results were a disappointment. Although modest associations between several parameters and positive clinical and echocardiographic response were demonstrated, no single measure of dyssynchrony was associated with accurate prediction of response to CRT (63). Core training for echocardiographic acquisition and analysis was provided for the study, but duration of training was limited, and echocardiographic data was troubled by high rates of poor quality
imaging studies which could not be analysed, and by wide inter-observer variability. Co-efficients of variation up to 33.7% for tissue Doppler data, and as high as 72.1% for SPWMD were reported, despite echocardiographic analysis taking place in three core laboratories, suggesting that variability in the analysis of these parameters may be even higher in “real-world” situations. Tissue Doppler velocity data in particular is prone to variability in both acquisition and analysis. The accuracy of velocity data derived from Doppler ultrasound is highly dependent upon the angle of interception of the ultrasound beam and the tissue or blood flow to be studied. Inter-operator variation in the acquisition of images may therefore introduce significant variation in velocity measurements. Additionally, motion of cardiac tissue not directly related to cardiac contraction, for example respiratory movement, may also introduce error into acquired velocity data. Furthermore, graphical representation of segmental myocardial velocities may contain one, two, or more velocity peaks and choosing which peak to measure introduces a further potential variation in analysis between observers.

2.7 Advanced Echocardiographic Assessment of Dyssynchrony

The PROSPECT trial identified several deficiencies in the detection of mechanical dyssynchrony and identification of non-responders to CRT by echocardiographic methods. Refinement of this selection process would therefore require greater standardisation in both acquisition and analysis of echocardiographic data, and additionally research groups began to focus on the use of alternative echocardiographic methods which may be less prone to variability in acquisition and interpretation.

2.7.1 Doppler strain rate and strain

Tissue Doppler velocity imaging showed initial promise in the identification of non-responders to CRT in small single centre studies, however its usefulness was demonstrated to be limited in a multi-centre prospective study by high rates of non-analysable data, and wide inter-observer variability. TDI velocity data may also be limited because it represents only the velocity of myocardial motion,
rather than specifically myocardial contraction. Motion of non-contracting, infarcted myocardium may therefore be displayed due to the tethering of non-contracting and contracting segments, potentially giving a false impression of the pattern of mechanical activation. Myocardial strain rate analysis removes this limitation. Standard tissue Doppler images are acquired, and processed using a software algorithm to analyse the gradient in velocity profiles between adjacent points within the myocardium. This gradient represents strain rate, a measure of myocardial deformation (ie. myocardial thickening and contraction), rather than purely of motion. Integration of this parameter over time generates strain, expressed as %.

Breidhart et al examined the changes in septal and lateral wall strain before and after CRT, as well as studying how strain measures relate to velocity data (64). They report a strong disassociation between parameters of velocity and deformation, such that peak septal velocity preceded peak deformation by almost 100ms, although in some patients this relationship was reversed. A similar delay was also noted in the lateral wall and was particularly pronounced in patients with ischaemic left ventricular dysfunction. They concluded that velocity imaging did not accurately reflect timing of myocardial contraction and therefore degree of dyssynchrony present, and that measures of deformation should be the preferred imaging method to detect dyssynchrony.

Sogaard reported that the extent of dyssynchrony displayed in basal segments of the left ventricle using Doppler deformation imaging was able to predict response to CRT in 20 patients (65). Mele et al report that in 37 patients the standard deviation of time to peak longitudinal strain in twelve segments predicted reverse remodelling, whereas SPWMD did not (44). In a further report on 60 patients, time to peak strain in 12 segments predicted reverse remodelling with greater power than 12 segment TDI (66). Miyazaki reports that in 47 patients 12 segment strain predicts reverse remodelling and demonstrates improved synchrony following CRT, whereas TDI parameters failed to predict response and remained unchanged following device implant (67). Dohi et al used Doppler strain to assess radial dyssynchrony in the short axis view, in a method akin to SPWMD (68). They report that delay in time to peak radial strain of >130ms between the septum and posterior wall was highly predictive of an acute increase in left ventricular stroke volume following CRT.
However Yu has reported, including one multi-centre study of 256 patients, that velocity imaging provided superior predictive power of response to CRT (in terms of echocardiographic remodelling) than Doppler-derived strain imaging (69). Yu hypothesised temporal differences in deformation parameters may occur due to localised myocardial disease or ischaemia, rather than being representative of true dyssynchrony due to conduction delay, and as such would not predict response to CRT. Zhang also reports that baseline dyssynchrony assessed by longitudinal strain fails to predict adverse events following CRT, and that the presence of baseline dyssynchrony by velocity imaging conferred a lower risk of adverse events following resynchronisation (70).

Like TDI velocity imaging, deformation parameters derived by tissue Doppler are subject to the same limitations of angle-dependency and variability in image acquisition techniques. These issues are particularly evident in heart failure patients with dilated spherical ventricles, where alignment of the ultrasound beam with the vector of cardiac contraction may prove impossible. Additionally, strain rate analysis tends to be associated with a high signal-to-noise ratio (71), rendering accurate analysis of deformation curves difficult. For these reasons Doppler deformation parameters have not been widely accepted.

Scheffer et al published in 2010, again reporting superior predictive power of Doppler strain over tissue Doppler velocity imaging (72), however in general the limitations and difficulties in acquisition and analysis have led to a loss of interest in this parameter by most research groups.

### 2.7.2 Two-dimensional strain imaging by speckle tracking

The limitations of Doppler-derived strain parameters described above led to the development of strain parameters derived from two-dimensional (2D) echocardiographic images. Interaction of the ultrasound beam with myocardial tissue produces speckles within the 2D image which occur throughout the myocardium and remain stable from frame to frame, allowing these speckles to act as natural acoustic markers within tissue. Tracking the pattern of speckles between image frames allows the movement of individual markers and their relationship to each other to be recorded, the geometric movement of each speckle representing local tissue movement (73). Tissue velocity can therefore be derived by differentiating each individual marker’s change in position over the
time between image frames. Strain and strain rate parameters may be derived from relative changes in distance and velocity between neighbouring markers. This technique is independent of the angle of intersection of the ultrasound beam with tissue, unlike Doppler parameters, however shares the advantage of Doppler-derived strain in demonstrating myocardial deformation rather than simply motion.

The technique was first demonstrated to be useful in assessment of myocardial systolic function (74, 75), and was shown to accurately delineate regional changes in cardiac function in patients with ischaemic heart disease and myocardial infarction. Global circumferential strain derived by speckle tracking echocardiography has been shown to predict cardiac events in heart failure patients with greater accuracy than ejection fraction (76). Subsequently the use of 2D strain by speckle-tracking has been studied for the assessment of mechanical dyssynchrony. Four parameters of 2D strain may be measured, of these radial and longitudinal strain are the most widely studied to date.

i. **Radial strain** – deformation by systolic myocardial thickening measured in the parasternal short axis view

ii. **Circumferential strain** – deformation by circular myocardial shortening measured in the parasternal short axis view

iii. **Longitudinal strain** – deformation by myocardial shortening in the longitudinal (base to apex) direction measured from apical views

iv. **Transverse strain** – deformation by myocardial thickening measured in longitudinal views

**i. Radial strain dyssynchrony**

Suffoletto et al reported the first use of 2D strain to measure dyssynchrony and predict response to CRT (77). Using the parasternal short axis view (Figure 2.4, overleaf) they measured radial strain in 6 myocardial segments, defining dyssynchrony as a delay in the time to peak strain between the anteroseptal and posterior segments of >130ms. This measure predicted an acute increase in stroke volume with sensitivity 91% and specificity 75%. A combined approach where dyssynchrony was defined as the presence of either radial delay by speckle
tracking or longitudinal delay by tissue Doppler imaging increased sensitivity further to 97%, although reduced specificity to 67%.

Gorcsan reports similar findings with a combination of radial strain dyssynchrony and longitudinal velocity imaging by TDI (78). When both radial and longitudinal dyssynchrony were present, 95% of patients experienced an echocardiographic response, when both were negative, the response rate reduced to 21%.

Delgado also confirmed the predictive value of radial strain assessment for response to CRT, using a cut-off value for the delay between anteroseptal and posterior segments of 130 ms, and also for the standard deviation of time to peak strain in all 6 short-axis segments using a cut-off value of 76 ms (79). This cut-off value of 130 ms was also later reported to independently predict greater long-term survival following CRT (80). Tatsumi et al report that a radial strain dyssynchrony index, derived from the average difference between peak and end systolic strain in all six short axis segments, predicts reverse remodelling with a specificity of 81% (81).

**Figure 2.4:** 2D radial strain analysis of the parasternal short axis view of the left ventricle. The myocardium is divided into six segments for analysis, radial strain curves are then generated by the speckle tracking algorithm for each segment, and displayed in a colour-coded fashion. Any temporal delay in time-to-peak strain between the anteroseptal (yellow curve) and posterior (purple curve) segments, or the standard deviation in time-to-peak strain for all segments, may be measured.
Tanaka et al published data from the Speckle Tracking and Resynchronization (STAR) study in 2010 (82), reporting that septal-posterior wall delay >130ms by radial strain predicted improvement in ejection fraction with a sensitivity of 86%, and additionally that those with absent dyssynchrony at baseline were three times more likely to suffer either death, need for cardiac transplant or need for LV assist device following CRT.

**ii. Circumferential strain dyssynchrony**

Delgado reported that circumferential strain was unable to predict response to CRT (79). Tatsumi et al report circumferential strain to predict reverse remodelling, but to a lesser extent than radial strain (81). Tatsumi et al also report that where radial, circumferential, and longitudinal dyssynchrony are all present at the proposed cut-off values, reverse remodelling occurs in 100% of patients. More recently Artis et al reported that the standard deviation of time to peak circumferential strain between 6 short axis segments is able to predict reverse remodelling, specifically the time difference between peak strain in the anterior and inferior walls providing the greatest predictive value (83).

**iii. Longitudinal strain dyssynchrony**

Knebel et al report that both longitudinal and radial dyssynchrony were reduced following CRT in echocardiographic responders, although the predictive value of these parameters in this study was unhelpful, and inferior to longitudinal velocity delay assessed by TDI (55). Delgado also found longitudinal strain unhelpful in the prediction of response to CRT, in particular suffering from a high proportion of non-analysable segments (79). The apical segments were particularly prone to poor tracking by analysis software, probably exacerbated by the use of a 12 segment model derived by using basal, mid and apical segments from the 4 and 2 chamber apical views, rather than the conventional use of basal and mid segments in the 4, 2 and 3 chamber views. Using these basal and mid-segments for analysis, Shi et al report that the standard deviation of time-to-peak longitudinal strain in 12 segments showed a greater predictive value than velocity imaging for echocardiographic response (84).
The ability of speckle-tracking to assess not only timing, but also the degree of myocardial deformation has also been utilised. Inden et al hypothesised that the degree of deformation was indicative of myocardial viability and contractility, and that dyssynchronous but contractile myocardial segments were more likely to be associated with response to CRT than those which were dyssynchronous but non-contractile (85). They propose an index (i-index) produced from the product of the standard deviation of time to peak systolic strain in six short axis segments and the mean radial thickening in the same six segments. This index was able to predict echocardiographic reverse remodelling in response to CRT with a sensitivity of 95% and specificity 80%. Knappe et al studied echocardiographic parameters of 1077 patients enrolled in the multi-centre MADIT-CRT trial, and report that greater baseline contractile function assessed by 2D strain in addition to moderate dyssynchrony predicts beneficial effect upon mortality or hospitalisation due to heart failure (86). Pouleur et al studied data from the same trial (87), reporting that reduction in dyssynchrony measured by transverse strain following CRT is proportional to outcome, such that each 20ms reduction in dyssynchrony corresponds to a 7% reduction in primary outcome of death or heart failure hospitalisation.

Data available to date therefore suggests that assessment of dyssynchrony by speckle tracking in radial, circumferential, longitudinal and transverse planes may be helpful in the prediction of response to CRT. However, Miyazaki et al recently reported that multiple parameters of dyssynchrony by speckle tracking in the radial, circumferential and longitudinal planes have no value in the prediction of reverse remodelling (88). The current role of strain-based dyssynchrony parameters measured by speckle tracking therefore remains unclear.

2.7.3 Three-dimensional echocardiography
Advances in echocardiographic transducer technology and image processing capability led to the development of three-dimensional (3D) echocardiography. Early 3D acquisition allowed a limited field of the heart to be examined by 3D echocardiography in real time, and a complete image of the heart (full-volume acquisition) to be acquired over 4-7 cardiac cycles. More recent systems allow
single-beat full volume acquisition. 3D echo provides more accurate and reproducible assessment of left ventricular volume and function than 2D echocardiography (89). During analysis of left ventricular volume and function the time to minimum volume for each of 16 or 17 myocardial segments may also be measured, and a measure of dyssynchrony produced. This method has the advantage of reliably measuring all myocardial segments simultaneously. Kapetanakis et al first reported the use of 3D echocardiography to assess mechanical dyssynchrony (90). 3D echocardiography was performed in healthy volunteers, and in patients referred for routine echocardiography to assess left ventricular systolic function. A systolic dyssynchrony index (SDI) was generated as the standard deviation of time to minimum systolic volume for all myocardial segments. This is expressed as a percentage of the cardiac cycle rather than in absolute values, in order to allow comparison of values between studies with differing heart rates. The degree of systolic dysfunction was positively associated with the value of SDI. Soliman et al (91) confirmed that patients with heart failure and systolic dysfunction tended to have a higher SDI than healthy volunteers, but noted only a weak correlation between the SDI and QRS duration. They also found that the inter-observer variability of SDI measurement was dependent upon image quality, with low variability when image quality was good. In a small sub-study of 39 patients, they report that an SDI >10% predicted left ventricular reverse remodelling following CRT with a sensitivity of 93% and specificity of 91%. Liodakis confirmed the feasibility of 3D dyssynchrony assessment, noting a weak correlation between SDI and QRS duration, and that SDI tended to increase with worsening left ventricular systolic function (92). In a control group of healthy volunteers they found a mean SDI of 9.8%. Several further studies have assessed the ability of SDI to predict response to CRT. Van Dijk et al (93) and Marsan et al (94) both examined the role of SDI in the prediction of acute response to CRT. Van Dijk assessed acute response by change in invasively measured dP/dt, noting a high degree of correlation between SDI and percentage increase in dP/dt. Marsan assessed acute response echocardiographically, defining response as >15% reduction in end-systolic volume within 48 hours of CRT. They report that a cut-off value of 5.6% for SDI predicted acute response with a sensitivity of 88% and specificity of 86%.
Deplagne et al report a significant difference in SDI between echocardiographic responders and non-responders, although do not quote a specific cut-off value as predictive of response (95). They also report a high degree of correlation between reduction in dyssynchrony following CRT and improvement in echocardiographic parameters. Soliman et al report further data regarding the utility of 3D echo to predict long-term response to CRT (96). Response was defined by reverse remodelling, assessed by 3D echocardiography before and 12 months after CRT. They report that an SDI cut-off of 10% predicted long-term CRT response with a sensitivity of 96% and specificity of 88%. More recently Tani et al report a sensitivity of 90% and specificity of 75% to predict reverse remodelling using a cut-off value for SDI of 11.9% (97), and Lau et al report that a cut-off value of 10% is associated with a negative predictive value of 100% (98). Additionally Lau et al report in the same study that in those with a baseline SDI >10%, and an acute reduction in SDI of more than 5% at 24 hours following CRT, reverse remodelling is predicted with a positive predictive value of 83% at 6-12 month follow-up. Conversely, Kuppahally et al report no significant predictive value for reverse remodelling by 3D SDI (99).

There remains a clear disparity in the reported cut-off values, and in particular the cut-off of 5.6% reported by Marsan et al value seems low compared to other studies, being substantially lower than the control value of the Liodakis study, and within one standard deviation of the mean value for healthy volunteers from the study by Soliman (91). Marsan reports that higher values increase sensitivity, but with an unacceptable drop in specificity, with a reported sensitivity and specificity of 100% and 46% respectively for a cut-off value of 8.3%. The noted differences in normal and abnormal values may stem from the use of different analysis software for the 3D data set, the two most widely used being Philips Medical Systems QLab and TomTec. Further clarification of normal values and differences between software algorithms is clearly necessary before the optimum method and cut-off value may be determined.

Recently Tanaka et al report the use of a 3-dimensional speckle tracking algorithm developed by Toshiba Medical Systems (100). The algorithm robustly differentiated between healthy controls and patients with heart failure, and demonstrated a large reduction in measured dyssynchrony following CRT. The
values for 3D speckle tracking correlated well with conventional 3D SDI and radial strain dyssynchrony by 2D speckle tracking. Tatsumi et al subsequently reported that the Area Strain Dyssynchrony Index >3.8%, derived using the 3D speckle tracking algorithm, is able to predict reverse remodelling with a sensitivity of 78% and specificity of 100%, in this study proving more useful than 2D strain and tissue Doppler measures (101).

2.8 Alternative Methods of Dyssynchrony Assessment

This section will briefly examine various alternative methods which have been proposed for assessment of dyssynchrony, from simple visual assessment, to complex indices incorporating several echocardiographic parameters.

2.8.1 Visual assessment of left ventricular motion

The complexity of numerous echocardiographic measures of dyssynchrony has lead some investigators to question whether a simple visual assessment of dyssynchronous contraction based on standard 2D imaging would reliably predict CRT response (102). Jansen et al recorded a visual assessment of dyssynchrony by five independent observers in 53 patients undergoing CRT (103). They report that visual assessment showed a high level of agreement with dyssynchrony assessed by tissue Doppler imaging, and predicted response to CRT with a sensitivity of up to 92%.

Szulik et al examine the phenomenon of apical rocking, a transverse motion of the ventricular apex associated with regional abnormalities of function and timing of activation (104). This may be quantified by tissue Doppler interrogation of the apical segments, or assessed visually. They report that both visual and quantitative assessments of this parameter are more predictive of reverse remodelling than conventional tissue Doppler parameters.

2.8.2 Diastolic parameters of dyssynchrony

Echocardiographic assessment of dyssynchrony has tended to focus upon the systolic phase of the cardiac cycle, however systolic function is also dependent upon optimal diastolic filling.
Agacdkiken et al reported that CRT improved echocardiographic parameters of diastolic function in both responders and non-responders (105), however Waggoner et al state that improvement in diastolic function is only seen in those patients who also demonstrated an improvement in systolic function (106). Diastolic dyssynchrony manifest by timing differences in the relaxation of opposing myocardial segments may be assessed using similar methods to those described for systolic dyssynchrony. The Bax group suggest that improvement in diastolic synchrony assessed by tissue Doppler imaging between 4 basal segments is only seen in those who demonstrate reverse remodelling (107). Schuster et al report that both inter-ventricular and intra-ventricular diastolic dyssynchrony is common in heart failure patients when measured using TDI, and in general improves less than systolic parameters following CRT (108). They hypothesise that this lack of improvement may be a factor in non-response. Yu noted no significant change in diastolic parameters of dyssynchrony following CRT, and that diastolic dyssynchrony had no role in the prediction of reverse remodelling (109).

2.8.3 Multi-parametric strategies for prediction of response to CRT
Several parameters for the assessment of myocardial dyssynchrony have been studied, and some researchers have investigated the use of multiple combined parameters in an attempt to improve the sensitivity and specificity of the prediction of response to CRT. Lafitte evaluated the use of eight parameters based on conventional and tissue Doppler imaging and M-mode echocardiography (110). In this population of patients with QRS duration >120ms, the majority of patients had several positive parameters of dyssynchrony, and echocardiographic response rate to CRT increased in line with the number of positive parameters. Where more than three parameters were positive, regardless of which parameters, the specificity for predicting CRT response was 90%, with a positive predictive value of 65%.
Knebel measured seven M-mode, conventional Doppler and tissue Doppler parameters in patients with QRS duration >120ms (111), and prospectively selected patients for CRT based on the presence of at least two out of seven positive parameters. A mean of 4.1 positive parameters were found in the study population. They conclude that selection using this method significantly
increases the echocardiographic response rate compared to a control group of historical CRT patients who had not been selected based on echocardiographic dyssynchrony measures.

Seo et al also studied seven dyssynchrony parameters in 217 patients undergoing CRT (112). They report limited predictive value of individual variables, however a combination of SPWMD >130ms and septal-lateral delay by TDI of >65ms independently predicted volume response in multivariate analysis. Diab et al report a novel method of determining the presence of significant dyssynchrony (113). In this study patients with ejection fraction <35% and QRS duration >120ms undergoing implantable defibrillator were allocated to receive CRT on the basis of Doppler and tissue Doppler parameters. Dyssynchrony was said to be present if two major, or one major and three minor, or four minor criteria were present.

Major criteria
- Increased intra-ventricular dispersion of mechanical contraction >55ms by TDI
- Sum of intra-ventricular and inter-ventricular dispersion of mechanical contraction >100ms by TDI

Minor criteria
- Increased intra-ventricular dispersion of mechanical contraction >40ms by TDI (if not used for major criterion)
- Increased inter-ventricular dispersion of mechanical contraction >40ms by TDI (if not used as a major criterion)
- Inter-ventricular mechanical delay >40ms
- Prolonged aortic pre-ejection interval >140ms
- Left ventricular filling time <40% of cardiac cycle
- QRS duration >130ms

All those with dyssynchrony by these criteria received CRT, and additionally those without dyssynchrony were randomised to receive CRT or ICD only. Those with dyssynchrony showed significant improvement in peak oxygen
consumption, NYHA class and ejection fraction. Those without dyssynchrony also showed improvement in NYHA class following CRT, although no change in peak oxygen consumption or ejection fraction. Those with no dyssynchrony who did not receive CRT showed a significant deterioration in peak oxygen consumption over 6 months follow-up, suggesting that CRT may help prevent deterioration in functional parameters even in those with no baseline dyssynchrony.

The use of multiple parameters to predict response to CRT may provide a further benefit beyond any single parameter, particularly as the mechanism of response to CRT may not be identical in all responders. The combination of parameters is clearly important, and as yet an optimal multi-parametric strategy has yet to be defined.

2.9 The Relationship Between Dyssynchrony Parameters

Multiple parameters for echocardiographic assessment of myocardial dyssynchrony have been proposed, with data suggesting they provide additive information beyond QRS duration in the prediction of response to CRT. There is little data available concerning how these parameters relate to each other however, and whether a patient with one positive dyssynchrony parameter would have multiple positive parameters. In the two multi-parametric studies discussed above (110, 111), Knebel found a mean prevalence of 4.1 positive parameters from the seven measured, and Lafitte found that 53% of patients had 3 or 4 positive parameters from the seven measured.

Burri et al demonstrated poor agreement between the Doppler and M-mode parameters used in the CARE-HF study, and dyssynchrony measured using tissue Doppler (114). However, in this study an unconventional protocol incorporating 4 basal left ventricular segments and the right ventricular free wall was used. Additionally pulsed-wave tissue Doppler rather than the more conventional colour tissue Doppler was used for TDI measurements and this study therefore provides little information about the relationship between CARE-HF parameters and standard TDI measures.
Miyazaki compared TDI and Doppler strain parameters in patients with and without systolic dysfunction and with and without LBBB (115). They demonstrated considerable overlap between these groups in parameters of dyssynchrony derived by TDI, and showed a substantial proportion of normal patients who fulfilled published criteria for dyssynchrony. Dyssynchrony measured by Doppler strain more reliably distinguished between the groups. Mele also reported only a modest correlation between 12 segment tissue Doppler velocity imaging and 12 segment longitudinal Doppler strain measures (66).

Ng compared 12 segment TDI with 12 segment longitudinal strain by speckle tracking in patients following non-ST elevation myocardial infarction and healthy volunteers (116). The values correlated moderately well, although were not directly comparable, TDI values measuring consistently higher levels of dyssynchrony.

Conflicting studies have compared dyssynchrony analysis by tissue Doppler velocity imaging and 3D echocardiography. Vieira et al compared 3D echocardiography with pulsed-wave tissue Doppler analysis of the basal LV segments only (117). They report a high level of correlation between these two measures in a group of 32 patients with dilated cardiomyopathy. Conversely, Burgess et al report poor agreement between 3D echocardiography and the 12 segment TDI model in patients with ischaemic left ventricular dysfunction (118). They hypothesise that non-concordance between these methods occurs because each assesses a different component of myocardial function. Peak systolic velocity is an early systolic event which occurs at the time of peak left ventricular pressure, however time to minimal volume by 3D echocardiography is a late systolic event which occurs when LV pressure is falling. Kuppahally et al also compared tissue Doppler indices with 3D SDI in 12 and 16 segments (99). They report that both tissue Doppler measures and 3D SDI not surprisingly correlate well within modalities, and a modest correlation between TDI measures and QRS duration, however there was no correlation between TDI and 3D measurements. Similar findings are also reported by Tani et al (97).

The modest correlations between different modalities may reflect the different aspects of myocardial function that these parameters assess. It remains unclear which of these parameters provides the most appropriate assessment of dyssynchrony for the prediction of response to CRT.
2.10 Cardiac Resynchronisation in Heart Failure with a Narrow QRS Complex

The presence of detectable dyssynchrony in patients with normal QRS duration suggests there may be a group of patients with narrow QRS who would benefit from CRT. The mechanism of mechanical dyssynchrony in this group may be related to local wall motion abnormalities rather than conduction delays. Klemm evaluated the link between conduction and contraction in patients with narrow QRS complex, ischaemic cardiomyopathy, and significant intra-ventricular dyssynchrony using an electromechanical mapping system (119). They noted that conduction velocities were normal, and that dyssynchronous mechanical contraction was due to slow wall motion and ischaemia induced hypokinesia of the affected wall segment rather than delays in electrical activation. Given that electrical activation was normal in this group, CRT would not necessarily be expected to eliminate mechanical dyssynchrony in this setting. Conversely, Turner et al demonstrated that in patients with both narrow and wide QRS complexes, and evidence of dyssynchrony by TDI, that biventricular pacing improved the degree of dyssynchrony measured (120).

Achilli et al subsequently reported that improvements in ejection fraction, left ventricular volumes, NYHA class and six minute walk distance in a group of patients with narrow QRS and echocardiographic dyssynchrony were similar to improvements seen in a group of wide QRS patients (121). Echocardiographic dyssynchrony was defined as an inter-ventricular mechanical delay of >20ms, or delayed activation of the lateral wall on M-mode. Gasparini et al also reported similar improvements in clinical and echocardiographic parameters in narrow versus wide QRS complex patients without the use of echocardiographic pre-selection criteria (122). This study defines narrow QRS as <150ms, however included a subgroup of patients with QRS <120ms, with similar improvements (123). Gasparini subsequently published long-term follow-up data for a group of 45 patients with QRS <120ms, reporting similar improvements in echocardiographic parameters and walk distance to patients with standard indications for CRT (124).

Bleeker and Yu also report that in patients with QRS <120ms and echocardiographic dyssynchrony, similar improvements to those seen in wide
QRS complex patients are seen (125, 126). Both these studies utilised TDI parameters of dyssynchrony to select narrow QRS patients to receive CRT. Cazeau et al report that simple echocardiographic indices were able to predict response in 60 patients with a mean QRS duration of 120ms, however the response rate in the dyssynchrony positive group was only 70% (127). Oyenuga reports that IVMD and septal-lateral delay were able to predict response in a wide QRS but not narrow QRS group, however septal-posterior wall delay >130ms by radial 2D strain was able to predict reverse remodelling in both narrow and wide QRS groups (128). Van Bommel et al also note that septal-posterior wall delay by radial strain can be predictive of response in patients with narrow complex QRS, but suggest that a more stringent cut-off of 107ms is necessary in this setting, resulting in sensitivity of 70.9% and specificity of 75% (129).

Van Bommel et al also report on a subgroup of patients enrolled into the PROSPECT study with a narrow (<130ms) QRS complex, but mechanical dyssynchrony present on one or more of the seven echocardiographic parameters noted in the study (130). Small but significant reductions in left ventricular dimensions are reported, in association with improvements in 6 minute walk distance and quality of life score. Overall clinical response was seen in 63.8% of patients.

Conversely, the ESTEEM-CRT study reported no significant improvement in echocardiographic parameters, NYHA class and peak VO$_2$ in 68 patients with narrow QRS and dyssynchrony by 12 segment TDI (131). In addition the only randomised trial of CRT in narrow complex QRS patients, the RE-thinQ study (132), demonstrated no improvement in oxygen consumption or echocardiographic parameters in patients with QRS <120ms, however did report a significant improvement in peak oxygen consumption and NYHA class in a subgroup of patients with QRS duration of 120-130ms. This study enrolled patients with QRS <130ms, and echocardiographic dyssynchrony evidenced by either SPWMD >130ms, or opposing wall delay between either the anterior septum and posterior wall or the inferior septum and lateral wall of >65ms. A meta-analysis of narrow QRS trials published in 2008 concluded that CRT significantly improved NYHA class, ejection fraction and six minute walk distance in this group of patients (133). The meta-analysis included only three
non-randomised trials however, and did not include either the ESTEEM-CRT or RE-thinQ study.

It therefore remains unclear whether CRT has a role in patients with narrow QRS complex. CRT in this setting is not included with any recognised guidance, and any potential role requires clarification by further research.

2.11 Additional Factors Influencing Response to Resynchronisation

Factors beyond the presence or absence of dyssynchrony have also been identified which affect the response to resynchronisation therapy.

2.11.1 Left ventricular lead position

The left ventricular lead is conventionally placed in a branch of the coronary sinus, and the location of lead placement is dictated to a certain extent by individual patient anatomy. Coronary sinus anatomy is highly variable, and in some cases only one target vein for lead placement may be available, however frequently two or more branches exist and the degree of resynchronisation and subsequent response provided by CRT may be influenced by the anatomical pacing site chosen.

Early in the evolution of CRT Butter et al suggested that pacing from the left ventricular free wall versus an anterior pacing site was associated with greater improvement in acute haemodynamic measurements (134). Rossillo et al also reported that placement of the lead in a posterolateral rather than anterior position was associated with greater increase in ejection fraction and reduction in NYHA class (135). In a further study Wilton et al report that not only is clinical response significantly poorer from an anterior rather than lateral or posterior lead position, but that over 30 months of follow-up those with anterior leads were more likely to suffer cardiovascular death or require heart transplantation (136). Conversely, Gasparini et al report similar improvement in left ventricular function and NYHA class between those with anterior or septal left ventricular leads and patients with lateral lead positions (137). Derval et al examined multiple pacing sites including various endocardial pacing positions using a deflectable mapping catheter via trans-septal puncture. In this study they found
wide variation in the inter-individual response to pacing site, with no single position associated with consistent haemodynamic response (138).

In an attempt to individualise the chosen pacing sites, several researchers have examined the use of pre-implant echocardiography to identify the site of latest activation within the LV, and target this area to position the LV lead. Becker et al used circumferential strain analysis by speckle tracking to identify the segment of myocardium with latest activation (139). LV lead position concordant with the echocardiographically targeted site could only be achieved in 53% of patients. In those with optimal lead position ejection fraction and peak oxygen consumption increased significantly more than in those with non-optimal pacing sites. Ypenburg et al also reported that targeting lead position to site of latest activation by radial speckle tracking strain was associated with greater reverse remodelling and lower rates of heart failure hospitalisation (140), whereas Fung et al reported similar decrease in left ventricular volume between those with lead positions concordant with latest activation site identified by tissue Doppler and those without (141).

Distance between the left and right ventricular leads and the delay in electrogram sensed by the left ventricular lead may also be important factors determining degree of resynchronisation achieved following pacing. These factors were assessed by Merchant et al (142), who report that in patients where both these factors were greatest the degree of reverse remodelling following CRT was maximised.

Left ventricular lead position is clearly an important factor in determining response to CRT, although not one that an implanter can always influence. Final position of the left ventricular lead is a compromise based on venous anatomy, lead deliverability, lead stability, pacing parameters and absence of diaphragmatic stimulation.

2.11.2 Presence of myocardial scar

The presence of extensive myocardial scarring due to underlying coronary artery disease and previous myocardial infarction may influence response to CRT, perhaps simply because extensive scar indicates insufficient viable myocardium to respond to resynchronisation with a significant increase in overall cardiac function.
Scar may be visualised using several cardiac imaging modalities. Orlov et al reported the use of myocardial perfusion imaging by single photon emission computed tomography (SPECT) to assess scar burden (143). They report a close correlation between the extent of myocardial scar and reverse remodelling, with no echocardiographic response seen in those classified as having extensive scar. Adelstein et al report a similar absence of echocardiographic response in those with extensive scar on SPECT imaging, and additionally that extensive scar is associated with reduced survival following CRT (144). Taylor et al report that extensive transmural scar detected by magnetic resonance imaging is also associated with non-response to CRT (145). Ypenburg et al also confirm that scar extent by SPECT correlates with non-response and in particular the presence of scar in the lateral wall at the conventional left ventricular pacing site seemed to preclude echocardiographic response to CRT (143).

Birnie et al report that extent of lateral scar detected by positron emission tomography (PET) imaging is significantly less in responders than non-responders, although global scar burden was not significantly different (146). Combes et al suggest that slow conduction of the LV pacing impulse from within an area of lateral scar may be responsible for lack of response in this setting, although that perhaps optimisation of pacemaker timing intervals may overcome this (147).

In contrast, reports by both Arzola-Castaner et al and Riedlbauchova et al suggest that response to CRT may occur despite the extent of scar detected by PET imaging, and that pacing in an akinetic or scarred segment does not preclude CRT response (148, 149).

The role of scar in response therefore seems unresolved. Intuitively one would expect that the presence of extensive myocardial scar would be associated with a reduced tendency for remodelling and improved cardiac output, but the presence of scar is certainly not a reason to withhold CRT based on the evidence available to date.
2.12 The Mechanism of Response to Resynchronisation

The predominant focus in assessing response to CRT has been on the detection and elimination of intra-ventricular dyssynchrony. The numerous studies of echocardiographic dyssynchrony discussed earlier strongly support the hypothesis that the presence of baseline dyssynchrony is an important factor in response, indeed Bleeker et al suggest that reduction in intra-ventricular dyssynchrony is mandatory for response to CRT (150). Celikyurt et al also demonstrate more marked reduction in dyssynchrony in responders than non-responders, although suggest the relative difference in dyssynchrony changes is insufficient to fully explain differences in remodelling (151).

It remains unclear to what extent changes in inter-ventricular and atrio-ventricular synchrony, and perhaps other factors, play a role in improvement in cardiac function and clinical outcome following CRT. Cleland et al examine the relative role of these factors in a systematic review, suggesting that resynchronisation is only part of CRT response and that the term ‘atrio-biventricular pacing’ rather then CRT may better describe this therapy (152).

Parsai et al examined the individual mechanism of response to CRT, suggesting four predominant mechanisms of response (45). They describe a high rate of response in patients with intra-ventricular dyssynchrony manifest as the typical early septal activation of LBBB, termed the ‘septal flash’, detected by 2D or M-mode imaging and confirmed by radial velocity analysis. Where septal flash was eliminated after CRT, echocardiographic response rate was 100%. Response also occurred in groups with atrio-ventricular dyssynchrony where diastolic filling is impaired by an atrio-ventricular delay which is either too short or too long, and in those patients with evidence of abnormal right and left ventricular interaction and significant inter-ventricular mechanical delay. Those with abnormal AV synchrony all showed evidence of reverse remodelling when AV synchrony was corrected following CRT and the group with abnormal inter-ventricular interaction demonstrated a high rate of clinical improvement, although not always associated with reverse remodelling. None of the patients in whom none of these four abnormalities could be demonstrated at baseline showed improvement following CRT. This study suggests that the relative importance of
intra-ventricular versus atrio-ventricular and inter-ventricular dyssynchrony varies from patient to patient.

Atrio-ventricular interaction clearly plays an important role in maximising ventricular filling, and disruption of the relationship between atrial and ventricular contraction can impair cardiac function. Atrio-ventricular conduction delay (first degree heart block) is common in heart failure patients and results in an early atrial systole finishing before the onset of a relatively delayed ventricular systole. This may cause pre-systolic mitral regurgitation and has a marked deleterious effect on left ventricular filling, reducing the proportion of the cardiac cycle during which filling may occur, often resulting in fusion of the E and A waves of transmitral flow (153). Atrial synchronized CRT has the potential to correct these abnormalities by shortening the AV delay and eliminating diastolic mitral regurgitation, as well as shortening left ventricular systole, maximising filling time.

Tournoux et al examined the role of left ventricular filling time as a parameter of atrio-ventricular dyssynchrony in predicting response to CRT (154). They report that a filling time <39% of cardiac cycle predicts response with a specificity of 100%, but sensitivity of only 40%. Responders demonstrated a significant increase in diastolic filling time, but no change in filling time was seen in non-responders.

Kyriacou et al propose that electrical atrio-ventricular dyssynchrony evidence by prolonged PR interval on the ECG may be as important as QRS duration in predicting response to CRT, on the basis of a systematic review of available studies (155).

Ventricular interaction describes the relationship between right and left ventricular filling and ejection and is a further factor which may be altered in an advantageous way to produce response to CRT. Munclinger et al demonstrate favourable echocardiographic changes following CRT in a group of patients selected on the basis of inter-ventricular dyssynchrony. They hypothesise that CRT resynchronises electro-mechanical coupling between the ventricles, improving both systolic and diastolic function due to improved ventricular interaction (156). Morris-Thurgood et al also report improved ventricular
interaction, using only left ventricular pacing (157). In patients with a high pulmonary capillary wedge pressure (PCWP), pacing improved left ventricular filling and resulted in a reduction in PCWP. They hypothesise that in the presence of high PCWP, left ventricular filling is impeded by right ventricular and pericardial constraint.

Williams et al demonstrated that CRT in patients with narrow QRS complex and no echocardiographic intra-ventricular dyssynchrony resulted in significant increases in invasively measured cardiac output and dP/dt immediately upon commencement of pacing, and hypothesise that CRT acts in this group by delaying right ventricular filling and therefore reducing pericardial constraint to left ventricular filling (158). No specific echocardiographic measures of changes in the timing of ventricular filling were reported in this study, although the reduction in pericardial constraint was confirmed in 15 of the 30 patients by invasive haemodynamic measures. The authors hypothesise that the documented beneficial response in the remaining patients may have been due to ‘occult dyssynchrony’ missed by the combination of parameters used to exclude mechanical dyssynchrony in the study.

Reduction in mitral regurgitation may be a further mechanism which contributes to CRT response. Nazeri et al report significant improvement in several echocardiographic parameters a mean of 4.6 months following CRT in 6 patients with QRS duration <110ms and no dyssynchrony based on tissue Doppler imaging (159). They hypothesise that the benefits were predominantly seen due to a reduction in mitral regurgitation after CRT, although 2 of the patients had prolonged AV conduction and correction of atrio-ventricular synchrony may also have contributed to echocardiographic improvement.

2.13 Summary

Cardiac resynchronisation therapy has been shown to produce significant improvement in clinical and echocardiographic parameters in large multi-centre studies, however a non-response rate to CRT of approximately 30% remains problematic. Refinement of selection criteria to minimise non-response has been
extensively studied, and many methods for the assessment of mechanical
dyssynchrony by echocardiography have been proposed. Although data to date
suggest that several may have a role in the prediction of response to CRT, and
therefore the potential to identify non-responders, their exact role is yet to be
clearly defined. In particular the role of dyssynchrony measured by myocardial
strain parameters derived from speckle tracking echocardiography requires
further investigation.
In addition the relationships between the various echocardiographic parameters
and the relative importance of atrio-ventricular, inter-ventricular and intra-
ventricular dyssynchrony in the mechanism of response to resynchronisation at
the individual patient level remain unclear.
The present study aims to provide further information with regard to these
unknowns, and therefore contribute to the wider field of research aiming to
identify patients most likely to benefit from CRT, in order to allow this therapy
to be better understood and more appropriately targeted.
Chapter 3

Study Aims

3.1 Role of speckle tracking echocardiography in patients undergoing cardiac resynchronisation therapy

3.2 Echocardiographic assessment of method of response to cardiac resynchronisation therapy
This study aims to further evaluate the role of specific echocardiographic parameters in the assessment of response to cardiac resynchronisation therapy, and to examine echocardiographic changes which may provide further insight into potential mechanisms of response to CRT.

### 3.1 Role of Speckle Tracking Echocardiography in Patients Undergoing Cardiac Resynchronisation Therapy

Non-response to cardiac resynchronisation therapy remains a clinical problem despite study of several echocardiographic parameters aimed at refining the prediction of response to resynchronisation. Speckle tracking echocardiography has been proposed as a modality for the assessment of dyssynchrony relatively recently, and the role of speckle tracking parameters in the assessment of patients undergoing cardiac resynchronisation therapy currently remains unclear.

This study aims to further assess the role of speckle tracking dyssynchrony parameters in cardiac resynchronisation therapy. Study aims are therefore:

i. To study the role of radial, circumferential and longitudinal myocardial strain parameters in the assessment of baseline dyssynchrony and the prediction of subsequent response to cardiac resynchronisation.

ii. To examine how parameters of dyssynchrony and other measures of cardiac function derived by speckle tracking change following resynchronisation, to provide a greater mechanistic insight into the means by which response to CRT occurs.

iii. To assess how speckle tracking dyssynchrony parameters relate to more established echocardiographic dyssynchrony measures and to electrical measures of cardiac dyssynchrony.
3.2 Echocardiographic Assessment of Mechanisms of Response to Resynchronisation Therapy

Correction of intra-ventricular dyssynchrony is felt to be the predominant mechanism by which response to resynchronisation therapy occurs, however alternative mechanisms by which response to resynchronisation may occur have been proposed.

In addition to acquisition of multiple dyssynchrony parameters, several echocardiographic parameters assessing detailed aspects of myocardial systolic and diastolic function will be recorded both before and after CRT. This will allow potential mechanisms of response to CRT beyond the correction of intra-ventricular dyssynchrony to be explored. In particular, in addition to parameters of intra-ventricular dyssynchrony, we will focus upon the role of CRT in optimisation of atrio-ventricular interaction and ventricular filling, and in changes in inter-ventricular synchrony and ventricular interaction. In addition to conventional measures of inter-ventricular dyssynchrony, ventricular interaction will also be assessed by measures of the relative timing of left and right ventricular filling, in order to further expand on previous studies.
Chapter 4

Research Methods and Data Collection

4.1 Study Population
4.2 Study Design
4.3 Ethical Approval
4.4 Outcome Measures and Assessment of Response to CRT
4.5 Inclusion and Exclusion Criteria
4.6 Participant Identification and Recruitment
4.7 Baseline Assessment
4.8 Cardiac Resynchronisation Therapy Device Implant
4.9 Optimisation of Resynchronisation Therapy Parameters Post-Implant
4.10 Follow-Up Assessment
4.1 Study Population

The study consisted of patients planned to undergo cardiac resynchronisation therapy in accordance with NICE guidelines. Patients therefore suffered symptomatic heart failure with NYHA class III or IV symptoms. All patients were in sinus rhythm, with a prolonged QRS duration ≥120ms, left ventricular ejection fraction <35% and were on maximally tolerated appropriate medical therapy.

4.2 Study Design

The study was a prospective cohort follow-up study recruiting appropriate patients with symptomatic heart failure in whom resynchronisation therapy was planned. All study procedures were carried out within the Central Manchester University Hospitals National Health Service (NHS) Foundation Trust site, specifically within the Manchester Heart Centre. The Central Manchester University Hospitals NHS Foundation Trust acted as sponsor for the study. The study design consisted of a baseline assessment prior to resynchronisation therapy including detailed clinical and echocardiographic evaluation. Patients then underwent resynchronisation therapy, and a further follow-up assessment was performed six months following resynchronisation to determine the presence or absence of pre-defined criteria for response.

4.3 Ethical Approval

A completed application for ethical approval was submitted to the Stockport Ethics Committee on 16th January 2009, and reviewed at the next committee meeting on 2nd February 2009. The meeting was attended by the author as study representative. Further information and clarification was requested by the committee after the meeting, and following submission of the requested information final ethical approval was granted by the committee on 18th February 2009. Approval of the Research and Development department of Central
Manchester University Hospitals NHS Foundation Trust was given on 16th March 2009.

4.4 Outcome Measures and Assessment of Response to CRT

The primary end-point was echocardiographic response to resynchronisation therapy based upon the presence of reverse left ventricular remodelling. Participants were defined as echocardiographic responders based on a ≥15% reduction in left ventricular end-systolic volume between baseline and follow-up studies. Secondary echocardiographic measures included changes in other parameters of left ventricular systolic function (ejection fraction, fractional shortening, global peak strain, and systolic velocities), mitral regurgitation, diastolic function and changes in dyssynchrony parameters.

Clinical response was assessed on the basis NYHA class, and changes in six minute walk distance and quality of life questionnaire score. A positive clinical response was defined as two or more of:

- Improvement ≥1 NYHA functional class
- Improvement ≥20% in six minute walk distance
- Reduction ≥20% in Minnesota Living With Heart Failure quality of life score

Secondary end-points for clinical response are individual changes in NYHA functional class, six minute walk distance, total quality of life questionnaire score and physical and mental quality of life sub-scores.
4.5 Inclusion and Exclusion Criteria

Inclusion criteria
1. Individuals with chronic heart failure
2. Left ventricular ejection fraction (LVEF) <35% measured by echocardiography using the Modified Simpsons rule
3. NYHA class III-IV heart failure symptoms
   - NYHA Class III - marked limitation of physical activity, comfortable at rest
   - NYHA Class IV - profound breathlessness with symptoms occurring at rest
4. Euvolaemia and on maximal tolerated medical therapy for heart failure
5. Male or female, age at least 18 years and less than 85 years
6. Provision of signed consent form
7. Females of child-bearing potential (ie. those who are not chemically or surgically sterilized or females who are not post-menopausal) should have a negative pregnancy test at enrolment into the study

Exclusion criteria
1. Age <18 years or >85 years
2. Atrial fibrillation or other continuous or uncontrolled atrial arrhythmia
3. Recent (<3 months) myocardial infarction
4. Heart failure requiring continuous intravenous diuretic or inotropic therapy
5. Right-sided mechanical heart valve
6. Evidence of alcohol dependence or alcohol abuse based on standard diagnostic criteria (160)
7. Severe respiratory disease
8. Severe peripheral vascular disease which would limit exercise capacity
9. Inadequate echocardiographic images
10. Previous enrolment of the patient in the present study
11. Involvement in another investigational or interventional study in the preceding 30 days
12. Pregnant women
4.6 Participant Identification and Recruitment

Patients fulfilling the appropriate inclusion and exclusion criteria were recruited from within the Manchester Heart Centre. The Heart Centre consists of a cardiology in-patient ward, coronary care unit, and a day-case ward, as well as numerous out-patient clinics including specialist heart failure, electrophysiology and cardiac device clinics.

Appropriate patients were approached and invited to participate in the study. A participant information leaflet was given to the patient at least 24 hours prior to the planned visit for consent and baseline assessment. The participant information leaflet is shown in Appendix 1, participant consent form in Appendix 2, and letter informing the patient’s General Practitioner of involvement in the study in Appendix 3.

Recruitment took place between March 2009 and September 2010, and follow-up studies were completed by April 2011.

4.7 Baseline Assessment

Baseline assessment was performed at least 24 hours following the initial approach to the patient. Any questions regarding participation in the study were answered at this visit, and informed consent for participation was taken and recorded on a standardised consent form. Participants were assigned a study number, such that all study information was anonymised from the point of consent. Consent forms and the log of participants was kept securely and solely within the Manchester Heart Centre.

4.7.1 Baseline clinical assessment

Baseline clinical assessment consisted of a detailed history and examination to determine functional status, NYHA class, and degree of compensation of heart failure. The following variables were recorded:

- NYHA class
- Aetiology of left ventricular systolic impairment (if known)
Details of previous myocardial infarctions and revascularisation procedures
• Full medication list
• Date of recent changes to cardiac medications
• Smoking status
• Weight
• Pulse rate
• Blood pressure
• Jugular venous pressure
• Heart sounds – presence of added sounds or murmurs
• Auscultation of lungs
• Oedema – degree and location

4.7.2 Blood sampling
Blood samples were taken using standard venepuncture technique by either the author or qualified clinical assistant at the baseline assessment visit. Samples were analysed for biochemical profile (including estimated glomerular filtration rate - eGFR) and full blood count.

4.7.3 Electrocardiography
Twelve lead electrocardiogram was recorded using a standard 10 electrode (4 limb and 6 chest) configuration, using a GE Marquette MAC 5500 ECG machine with automated analysis software. Heart rate and rhythm, PR interval and QRS complex duration were recorded.

4.7.4 Echocardiography
Echocardiographic assessment before and after resynchronisation forms the primary data set for this study. Detailed echocardiography was therefore performed according to a comprehensive protocol for image acquisition. Baseline echocardiography was performed in all patients by a single operator using a Vivid 7 Dimension echocardiography machine (GE Vingmed Ultrasound, Horten, Norway) with a 4MHz M4S probe for standard 2D imaging, colour flow mapping, pulsed wave (PW) and continuous wave (CW) Doppler and tissue
Doppler imaging (TDI), and a full volume matrix array 3 dimensional 3V probe for multi-plane and 3-dimensional imaging.

Conventional ECG electrodes (right arm, left arm, and left leg) were connected to the patient providing standard axial ECG limb leads I, II and III. The patient was positioned semi-recumbent in the left lateral position for parasternal and apical imaging, and in a supine position for subcostal imaging. The appropriate ECG lead to record during image acquisition was chosen in order to most clearly define the onset of the QRS complex, and therefore aid accuracy of subsequent measurements. Three cardiac cycles of each imaging plane and modality were acquired and digitally stored for later offline analysis. Doppler measurements were recorded in static respiration to minimise any respiratory effect on Doppler parameters. Respiratory manoeuvres were used as necessary to optimise 2D imaging. The baseline and scale of Doppler recordings were optimised to maximise the size of the velocity envelope without aliasing. Images were acquired according to a standardised protocol (Appendix 4).

i. Parasternal View
Imaging commenced with the 2D parasternal long axis view of the left ventricle, ensuring the left ventricular cavity was as horizontal within the image as possible. Colour flow mapping of the mitral and aortic valves were performed in this view, as well as a high resolution zoom image of colour flow across the mitral valve to allow measurement of the mitral regurgitation vena contracta. An M-mode recording was made through the sinus of the aortic root, the aortic valve leaflets and the left atrium. Modified long-axis view of the pulmonary valve was then obtained, recording a 2D image, colour flow mapping, and pulsed wave Doppler in the right ventricular outflow tract (RVOT) for determination of the right-ventricular pre-ejection period. Modified long-axis view of the tricuspid valve was then recorded, with colour flow mapping, and pulsed and continuous wave Doppler for determination of timing of diastolic flow and estimation of pulmonary artery systolic pressure.
Parasternal short axis views were then acquired, starting with a short axis view of the left ventricle at the level of the papillary muscle. 2D imaging was recorded, ensuring the ventricular cavity was as circular as possible. An M-mode recording with the cursor positioned through the centre of the left ventricular cavity was
recorded for determination of SPWMD. Colour tissue Doppler imaging of the left ventricle in short axis was performed. Frame rates were maximised for colour tissue Doppler images by using a narrow sector width, and minimising scanning depth as much as possible. The left marker identifying the start of the cardiac cycle was moved to an earlier position prior to storage of the colour tissue Doppler cycles, in order to allow clearer identification of the start of the QRS complex during later analysis. A colour tissue Doppler M-mode through the centre of the left ventricular cavity was then acquired. 2D imaging of the left ventricle at the level of the mitral valve was then performed, with colour flow mapping of the mitral valve in short axis. Short axis views at the level of the aortic valve were then obtained, with colour flow mapping of the aortic, tricuspid and pulmonary valves.

ii. Apical View
Initially a 2D image of the four chamber view was acquired. A high resolution zoomed image was taken of the left atrium for determination of left atrial area and volume. Mitral regurgitation was assessed by acquisition of the zoomed left atrial view with colour flow mapping for measurement of regurgitant jet area, and the colour velocity baseline was then adjusted so that aliasing velocity away from the transducer occurred at between 20-30cm/s, to allow measurement of the radius of the area of proximal flow convergence, and therefore quantification of mitral regurgitation by the proximal isovelocity surface area (PISA) method. Pulsed and continuous wave Doppler recordings were made of trans-mitral flow, with the cursor positioned at the leaflet tips for pulsed wave Doppler of left ventricular inflow, these allowed determination of the pattern of transmitral flow for assessment of diastolic function, timing of left ventricular filling, presence of diastolic mitral regurgitation, and measurement of the velocity-time integral (VTI) of the mitral regurgitation jet. An image focused upon the left ventricle by reducing scan depth to exclude the left atrium was then acquired for measurement of left ventricular volumes and ejection fraction by the modified Simpson’s method, and colour tissue Doppler imaging was acquired in the same view. A second colour tissue Doppler image was acquired in a similar view, with a slightly increased depth and sector width to allow incorporation of the tricuspid valve annulus into the image for measurement of right ventricular tissue Doppler
parameters. In acquisition of colour tissue Doppler images care was taken to ensure the plane of the left ventricle was as vertical as possible, in order to minimise the angle of incidence of the ultrasound beam and the segment of myocardium of interest.

In an apical five chamber view, pulsed and continuous wave Doppler was recorded across the left ventricular outflow tract, for determination of left-ventricular pre-ejection time and calculation of stroke volume by left ventricular VTI.

Attention was then focussed upon the right ventricle. An M-Mode recording through the tricuspid valve annulus was made to allow determination of the tricuspid annular plane systolic excursion (TAPSE). Colour flow mapping of the tricuspid valve was performed, with pulsed and continuous wave Doppler of the tricuspid valve for measurement of timing of right ventricular inflow, and estimation of pulmonary artery systolic pressure.

The apical two chamber view was acquired next. A zoomed image of the left atrium was acquired for determination of left atrial volume. An image focussed upon the left ventricle for determination of left ventricular volume and ejection fraction and a colour tissue Doppler image of the left ventricle were acquired.

The apical three chamber view was then performed. A high resolution zoomed image of the left atrium with colour flow mapping and a reduced colour baseline as described before was acquired, to provide an alternative view for quantification of mitral regurgitation by the PISA method. Continuous wave Doppler of the mitral valve was performed to record the VTI of the mitral regurgitation jet. 2D and colour tissue Doppler images focussed upon the left ventricle were acquired.

iii. Multiplane and 3D Echocardiography

Using the multi-array 3V probe, a standard apical 4 chamber view with the depth adjusted to focus upon the left ventricular cavity was obtained and optimised. The multi-plane imaging facility was activated, which allows simultaneous capture of 2-3 imaging planes at varying angles of rotation, specifically acquisition of apical 4, 2, and 3 chamber views of the same cardiac cycle (triplane imaging). This view was acquired in both standard 2D imaging, and with colour tissue Doppler imaging.
The 4D mode was then activated, and a full-volume 3D acquisition of the left ventricle acquired.

Full-volume 3D acquisition required a total of four consecutive cardiac cycles in order to obtain a full 3D sector encompassing the entire left ventricle. 3D acquisition software “stitches” these four cycles together to form a single full-volume image, however this process is highly dependent on each of the four individual cardiac cycles being of the same duration and acquired in exactly the same plane. Where this is not the case “stitch artefact” occurs, and the image appears distorted as the cycles do not match in duration when combined. In order to minimise stitch artefact volume acquisition was acquired in static respiration, ensuring the probe was held as still as possible, and that the heart rhythm was stable over the four cycles. The quality of the full volume acquisition was checked prior to storage by reviewing the images using the 9-slice function, which generates nine short axis slices through the left ventricular cavity from base to apex. Although all patients recruited into the study were in sinus rhythm, patients with heart failure often have an irregular cardiac rhythm due to frequent ventricular ectopic activity, and in a minority of patients unavoidable stitch artefact due to frequent ventricular ectopy resulted in poor quality 3D images which were not entered into subsequent analysis.

iv. Subcostal View
Lastly, the patient was returned to a supine position. The M4S probe was used to acquire subcostal images of the inferior vena cava (IVC). A 2D image and an M-mode image were acquired demonstrating visualisation of the IVC in normal respiration and in forced inspiration, for estimation of right atrial pressure.

Methods of subsequent analysis of the echocardiographic images are discussed in Chapter 5.

4.7.5 Six minute walk test
Six minute hall walk test was performed over a standard course within the Manchester Heart Centre building. The test was administered according to American Thoracic Society guidelines (161). The course consisted of a marked 30 metre distance over a length of straight and level corridor within the out-
patient area. Patients were asked in a standardised fashion to perform as many repetitions of the course as they were able within the six minute period. Total distance walked was recorded on the baseline assessment form.

4.7.6 Minnesota ‘Living With Heart Failure’ quality of life questionnaire

The Minnesota ‘Living With Heart Failure’ questionnaire is a widely used, reliable and well validated questionnaire for assessment of heart failure symptoms and quality of life (QoL) (162). It has been shown to be responsive to various interventions for heart failure including proven pharmacological therapies.

The questionnaire consists of a single A4 sheet, with 21 questions assessing both the most frequent physical symptoms and important psychological aspects of the heart failure syndrome, and the effects of heart failure on day-to-day life (Appendix 5). The patient is asked to rate each symptom from 0-5 based on how the patient perceives the symptom has affected there quality of life in the preceding 4 weeks. A score of zero implies no effect of that symptom on quality of life and a score of 5 a severe effect. An overall score is generated, minimum score 0, maximum 105. From specific subsets of questions individual physical (range 0-40) and mental scores (range 0-25) can also be derived. The total score has been shown to correlate well with NYHA class and other heart failure specific scoring systems (163).

Participants were asked to complete the questionnaire on their own, to avoid introduction of bias into the answers by either the researcher or another observer. Participants were encouraged to answer all questions, marking a score of zero for questions which were not relevant – for example questions asking about employment in a retiree. Total, physical and mental scores for each patient were calculated and recorded.

4.8 Cardiac Resynchronisation Therapy Device Implant

Following baseline assessment patients were subsequently admitted to Manchester Heart Centre for CRT device implant which was performed in a standard fashion. Procedures were usually performed under local anaesthetic.
with mild intravenous sedation given at the discretion of the operator and preference of the patient.

Devices were implanted in the left pre-pectoral area unless a specific indication for sub-pectoral or right-sided implantation existed. Leads were introduced via the subclavian vein. Right ventricular and right atrial active fixation pace-sense leads were positioned in a standard fashion, usually in the right ventricular apex and right atrial appendage. In the case of a CRT-D implant an implantable cardioverter-defibrillator (ICD) lead (usually dual coil) was positioned in the right ventricle instead of the pace-sense lead. Pacing and sensing characteristics (sensed P or R wave, pacing impedance and pacing threshold) of both right atrial and ventricular leads were tested and recorded.

Coronary sinus cannulation for left ventricular lead placement was performed using either a Medtronic Attain deflectable catheter which has an adjustable degree of curve to aid cannulation, or a pre-shaped Medtronic Attain Command catheter. A venogram of the coronary sinus system was obtained by injection of radio-opaque contrast through the guiding catheter. In cases where insufficient opacification of coronary sinus branches was achieved a balloon occlusion catheter was used to temporarily occlude the coronary sinus and allow full opacification of the coronary sinus system. Selection of lead position was based on coronary sinus anatomy at the discretion of the implanting physician, aiming to deliver the lead to the lateral wall, but accepting anterior or posterior positions if coronary sinus anatomy or pacing parameters were not appropriate. A variety of pacing leads are available for left ventricular pacing, each offering specific characteristics determining deliverability, stability and flexibility of subsequent device programming. A suitable lead was chosen based on the experience and preference of the operator. Pacing and sensing parameters of the left ventricular lead and the presence or absence of diaphragmatic stimulation were tested and recorded. A hard-copy print-out of the intracardiac electrogram recorded from the left-ventricular lead (in bipolar configuration) was taken for subsequent assessment of the intra-cardiac electrical delay. Leads were secured with non-absorbable sutures, connected to the appropriate device and the wound closed with absorbable sutures and Dermabond skin glue.

At the time of implant devices were programmed in the DDD mode with a base rate of 50 beats/min. Rate response was not turned on at implant unless there was
specific indication pre-implant of chronotropic incompetence. Programmable resynchronisation parameters were initially left at nominal settings which are:

- Paced AV delay 130ms
- Sensed AV delay 100ms
- RV-LV pacing offset 0-4ms

A standard 12 lead ECG was recorded in the few hours following the procedure. Postero-anterior chest x-ray was acquired on the same day, and lateral projection chest x-ray the day following the procedure, and from these the position of the left ventricular lead was recorded based upon a standardised 3x3 algorithm for the assessment of left ventricular lead position (164). Lead position was classified as either basal, mid or apical, and as either anterior, lateral or posterior. Patients were generally discharged on the day following the implant procedure.

4.9 Optimisation of Resynchronisation Parameters Post-Implant

A standard echocardiographic CRT optimisation protocol was performed according to current recommendations (165) within 4 weeks of implant, often the day following implantation.

i. Atrio-ventricular delay
This was assessed using trans-mitral Doppler. The baseline pattern of the E and A waves on transmitral Doppler were examined. Provided there was adequate separation of the E and A waves, and no significant truncation of the A wave, then the AV delay was left unchanged from nominal settings. Fusion of the E and A waves prompted progressive reduction in the AV delay until a more desirable pattern was obtained, aiming to maximise the period of diastolic filling. Truncation of the A wave prompted progressive prolongation of the AV delay until either the pattern was satisfactory, or intrinsic AV conduction occurred, in which case an intermediate value of AV delay which minimised A wave truncation but avoided intrinsic AV conduction was programmed.
**ii. Ventriculo-ventricular (VV) delay**

Optimisation of the offset in pacing stimuli between right and left ventricular leads was performed using a combination of tissue Doppler imaging and the velocity-time integral obtained by pulsed-wave Doppler across the left ventricular outflow tract. Baseline parameters for VTI and time-to-peak systolic velocity in the septum and lateral wall were measured. Provided systolic velocities were synchronous, and there was no significant septal-lateral delay in time to peak systolic velocities, then VV offset was left unchanged. Presence of residual dyssynchrony based on septal-lateral delay of >65ms prompted progressive change in the pacing offset between right and left ventricular stimuli in 10ms increments to a maximum of 40ms, first in the direction of LV pacing first and subsequently RV pacing first. LVOT VTI and septal-lateral delay were recorded at each pacing offset, and a final value chosen which optimised VTI and minimised delay.

Re-optimisation could be performed later in the study using the same protocol where clinical improvement had not been experienced at least 4 weeks following device implantation.

**4.10 Follow-Up Assessment**

All follow-up assessments took place in the Manchester Heart Centre, usually within the pacemaker clinic or a dedicated CRT clinic.

**4.10.1 Four week device check**

Routine clinical follow-up in the Manchester Heart Centre pacing clinic was performed approximately 4-6 weeks following implant to confirm satisfactory wound healing and to recheck electrical parameters. This visit was conducted by a cardiac physiologist specialising in pacemaker follow-up, unless a specific problem was identified.
4.10.2 Six month study assessment

The final follow-up study assessment was performed 6 months following device implant by the author, usually in the dedicated CRT clinic at Manchester Heart Centre.

Six month assessment included:

- Clinical assessment
- Blood sampling
- 6 minute walk test
- Minnesota quality of life questionnaire
- 12 lead ECG
- Echocardiography

All follow-up procedures were performed as per baseline assessment and as outlined above.
Chapter 5

Data Analysis

5.1 Electrocardiographic Analysis
5.2 Minnesota “Living With Heart Failure” Quality of Life Questionnaire Scoring
5.3 Echocardiographic Analysis
5.4 Intra-cardiac Electrogram Analysis
5.5 Statistics
5.1 Electrocardiographic Analysis

12 lead ECGs were analysed manually to confirm sinus rhythm at baseline and appropriate atrial sensing or pacing at follow-up. PR interval at baseline and QRS duration at baseline and follow-up were recorded based on the automated measurements generated by analysis software within the ECG machine. QRS morphology was classified according to the presence or absence of typical LBBB pattern.

5.2 Minnesota ‘Living With Heart Failure’ Quality of Life Questionnaire Scoring

The questionnaire was analysed according to the instructions issued by the University of Minnesota. The answers for each question were summed to produce a total score; where a question had not been completed it was scored zero. Physical scores were compiled based on questions 2-7, 12, and 13, and mental scores based on questions 17-21, as per the scoring instructions.

5.3 Echocardiographic Analysis

Echocardiographic images were analysed offline using Echopac software Version 7.1.2 (GE Vingmed Ultrasound) by a single operator. Intra- and inter-observer variability measures were calculated by repeat analysis of dyssynchrony parameters in a subset of 10 randomly selected studies by both the main operator and a second operator (Dr Satheesh Nair). All measurements were taken over three cardiac cycles, and the mean of the three values used in the analysis.

5.3.1 Cardiac chamber dimensions and volumes

Standard cavity and wall thickness dimensions of the following parameters were taken according to current American Society of Echocardiography recommendations on cardiac chamber quantification (166).
Left atrial area and volume and left ventricular volumes were calculated using the modified Simpsons biplane method. This is performed by tracing the endocardial border of the required structure, automated software then fills the traced area with a series of discs, assuming a circular cavity shape. The volume of the discs and area of the traced region is calculated and displayed. Left atrial volume measurement was performed at end-systole in the apical 4 chamber and 2 chamber views. Left ventricular volume measurements were performed at end-systole (LVvolS) and end-diastole (LVvolD) in the apical 4 and 2 chamber views. Atrial and ventricular biplane volumes were then calculated from the mean of the 4 and 2 chamber values.

Ejection fraction was calculated using the formula:

\[
\text{LV ejection fraction} = \left( \frac{\text{LVvolD} - \text{LVvolS}}{\text{LVvolD}} \right) \times 100
\]

Other parameters of left ventricular systolic function were also measured:

- Systolic velocities of the septal and lateral mitral annulus by tissue Doppler imaging
- Global circumferential and global longitudinal strain by speckle tracking in parasternal short axis and apical 4, 2, and 3 chamber views
5.3.2 Valvular regurgitation measurement and quantification

Mitral regurgitation was assessed by vena contracta width, ratio of regurgitant jet and left atrial area, and regurgitant volume and effective regurgitant orifice area (EROA) quantified using the proximal isovelocity surface area (PISA) method. Vena contracta was measured from a zoomed colour flow image of the mitral valve in the parasternal long-axis view. The image was reviewed frame-by-frame, and the minimal diameter of the regurgitant jet beyond the area of proximal flow convergence was measured.

Regurgitant jet area was determined by tracing the maximal mitral regurgitation jet area and calculating this as a proportion of total left atrial area in the 4 chamber view.

EROA and regurgitant volume (RegVol) were calculated according to the PISA method. The aliasing radius \( R_{\text{pisa}} \) of the flow convergence area proximal to the mitral valve leaflets was measured (Figure 5.1) and the relevant aliasing velocity \( V_{\text{alias}} \) recorded.

Figure 5.1: Colour flow image of the mitral regurgitation jet demonstrating measurement of the radius of the proximal flow convergence zone \( R_{\text{pisa}} \).
The VTI (VTI_{mr}) and peak velocity (V_{max}) of the mitral regurgitation jet were determined by tracing the continuous wave Doppler profile of the regurgitant jet. EROA and RV are then determined according to the following formulae:

\[
\text{EROA (mm}^2) = \frac{(V_{\text{alias}} \times 2\pi r^2)}{V_{\text{max}}}
\]

\[
\text{RegVol (mls)} = \text{EROA} \times \text{VTI}_{\text{mr}}
\]

Pulmonary artery pressure was estimated by the addition of right ventricular to right atrial pressure gradient and estimated right atrial pressure. Right ventricular to right atrial pressure gradient was calculated from peak velocity of the tricuspid regurgitant jet using the modified Bernoulli equation:

\[
\text{Gradient (mmHg)} = 4 \times (\text{peak velocity (m/s)})^2
\]

Right atrial pressure was estimated by the diameter and respiratory variation of the inferior vena cava based on American Society of Echocardiography criteria for right heart assessment (167):

<table>
<thead>
<tr>
<th>IVC diameter (cm)</th>
<th>Respiratory variation</th>
<th>RA pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.1</td>
<td>&gt;50%</td>
<td>&lt;5</td>
</tr>
<tr>
<td>≤2.1</td>
<td>&lt;50%</td>
<td>5-10</td>
</tr>
<tr>
<td>&gt;2.1</td>
<td>&gt;50%</td>
<td>5-10</td>
</tr>
<tr>
<td>&gt;2.1</td>
<td>&lt;50%</td>
<td>&gt;15</td>
</tr>
</tbody>
</table>

Table 5.1: Estimation of right atrial pressure based on IVC diameter and respiratory variation

### 5.3.3 Tissue Doppler and speckle tracking analysis

Tissue Doppler velocity parameters were analysed using GE Echopac Q-analysis software Version 7.1.2 and measured in accordance with current American Society of Echocardiography (ASE) recommendations for quantification of dyssynchrony where applicable (165).

Q-analysis software allows a region of interest (ROI) to be placed over the segment of myocardium to be interrogated. ASE recommend a minimum ROI
size of 5x10mm; for analysis of TDI parameters in this study a size of 7x10mm was chosen. A curve representing the velocity profile of the chosen region of interest is generated. The ROI is slowly moved over the image within the myocardial segment to be analysed such that the most consistent velocity curve for that segment is apparent. Timing of aortic valve opening and closure are measured from LVOT Doppler, and marked on the velocity profile. The time from onset of QRS complex to peak systolic velocity may then be measured. Only velocity peaks within the ejection period (between aortic valve opening and closure) were measured (Figure 5.2); where more than one peak existed within the ejection window then the highest peak was measured.

![Figure 5.2: Tissue Doppler analysis.](image)

The following parameters were recorded from TDI curves to allow calculation of inter- and intra-ventricular dyssynchrony parameters and parameters of systolic and diastolic function:

- Time to peak velocity in the septum and posterior wall in the short axis view
• Time to peak systolic velocity of 12 left ventricular segments (basal and mid segments of the inferior septum, lateral wall, inferior wall, anterior wall, posterior wall and anterior septum)

• Peak systolic velocity (S’) in basal septum and basal lateral wall

• Peak diastolic velocities (E’ and A’) in the basal septum and lateral wall

• Time to peak E’ in the basal septum and lateral wall

• Peak tricuspid annular systolic velocity

• Time to peak systolic velocity (S’) of tricuspid annulus

• Time to peak diastolic velocity (E’) of tricuspid annulus

No specific guideline for the analysis of speckle-tracking data currently exists. Peak systolic strain typically occurs later in the cardiac cycle than peak systolic velocity, often following aortic valve closure. GE Q-analysis 2D strain software was used for speckle tracking analysis. In each view the myocardium was identified by outlining the endocardial border and defining the width of the region of interest. The speckle tracking algorithm is then performed. A tracking score from 1-3 is generated by the software indicating the quality of tracking of the image. If tracking was poor (score 3) then the region of interest was manually readjusted taking particular care to define the affected segment. If tracking remained poor following adjustment of the ROI in two or more of the three cycles analysed then the segment was removed from analysis.

Strain curves are generated for each segment. As with tissue Doppler, the generated strain curves are often complex with multiple peaks. In the case of speckle tracking the point of maximal systolic or post-systolic strain was measured, without specifically taking the period of systolic ejection into account. In addition to regional values for each myocardial segment, circumferential and longitudinal views also generate a global strain curve which represents a mean value for all the segments in that view. The value and timing of the global curve was also recorded.

This analysis was performed in the short axis view for radial and circumferential strain parameters, and in the apical 4, 2 and 3 chamber views for parameters of longitudinal strain.
The following parameters were recorded:

- Time to peak radial strain in 6 short axis segments
- Time to peak circumferential strain in septum and posterior wall
- Time to peak global circumferential strain
- Time to peak longitudinal strain in 12 left ventricular segments (the same segments as for tissue Doppler velocity measures)
- Time to peak global longitudinal strain in apical 4, 2 and 3 chamber views
- Peak global circumferential strain in short axis view (%)
- Peak global longitudinal strain in apical views (%)

**5.3.4 Pulsed wave Doppler analysis**

Pre-ejection periods were determined by measuring the time from onset of the QRS complex to onset of systolic flow in the right or left ventricular outflow tract (see Figure 2.3, page 42). In order to further assess the timing of ventricular filling and changes in ventricular interaction, timing of peak tricuspid and mitral flow were also determined by measuring the time from onset of QRS complex to peak trans-tricuspid or trans-mitral diastolic flow. Time from mitral or tricuspid valve closure to opening, and right or left ventricular ejection time were measured to allow calculation of the myocardial performance index.

The following parameters were therefore measured from pulsed wave Doppler of mitral and tricuspid inflow and right and left ventricular outflow:

- Right ventricular pre-ejection period
- Left ventricular pre-ejection period
- Time to peak LV filling / peak mitral inflow
- Time to peak RV filling / peak tricuspid inflow
- Time from mitral valve closure to opening
- Left and right ventricular ejection time
- Left and right ventricular outflow tract VTI
Inter-ventricular mechanical delay (IVMD) was calculated as:

\[
\text{IVMD (ms)} = \text{Left ventricular pre-ejection period (ms)} - \text{right ventricular pre-ejection period (ms)}
\]

Inter-ventricular filling delay (IVFD) was calculated as:

\[
\text{IVFD (ms)} = \text{Time to peak LV filling (ms)} - \text{time to peak RV filling (ms)}
\]

Stroke volume (SV) was calculated as:

\[
\text{SV (mls)} = \pi \times \left( \frac{\text{LVOT diameter}}{2} \right)^2 \times \text{LVOT VTI}
\]

Cardiac output (CO) was calculated as:

\[
\text{CO (l/min)} = \text{SV (mls)} \times \text{Heart rate (bts/min)} / 100
\]

Myocardial performance index was calculated for right and left ventricles using the formula:

\[
\text{MPI} = \frac{\text{(Mitral / tricuspid valve closing to opening time – Ejection time)}}{\text{Ejection time}}
\]

The following parameters of atrio-ventricular synchrony were also measured:

- Diastolic filling time
- Presence of E:A fusion on transmitral flow
- Presence of pre-systolic mitral regurgitation

Diastolic filling time was determined as the total duration of the transmitral E and A waves and was expressed as a percentage of the total cardiac cycle (R-R interval). Presence of E:A fusion and pre-systolic mitral regurgitation were determined as binomial parameters recorded as 0 = not present, and 1 = present.
5.3.5 M-mode measurements

Septal-posterior wall M-mode delay was determined in grey scale imaging by measuring the time from peak downwards deflection of the septum to peak upwards deflection of the posterior wall (Figure 2.1, page 36). Where more than one deflection of either wall was evident the point of maximal deflection was chosen.

Septal-posterior wall M-mode delay using tissue Doppler (SPWM_{TDI}) was determined by measuring the time from change in septal velocity from negative to positive (blue-red interface) and posterior wall from positive to negative (red-blue interface; Figure 5.3). Where wall motion was complex and multiple velocity direction changes were seen (for example Figure 6.2, Chapter 6, page 117), the end of the longest period of normal motion was chosen for measurement.

![Figure 5.3: Measurement of septal-posterior wall m-mode delay using colour tissue Doppler (SPWM_{TDI}) from the time change in direction of septal motion (blue-red interface) to the change in direction of posterior wall motion (red-blue interface).](image-url)
5.3.6 3D echocardiography analysis

3D echocardiography data was analysed using TomTec 3D quantification software. The endocardium is outlined in the apical 4, 2 and 3 chamber views at end-diastole and end-systole. Automated endocardial detection software then generates a 3D volume of the left ventricle throughout the cardiac cycle. The following parameters were recorded:

- Left ventricular diastolic volume (mls)
- Left ventricular systolic volume (mls)
- Left ventricular ejection fraction (%)
- Systolic dyssynchrony index (SDI)

5.3.7 Dyssynchrony parameters

Using the above measures from several echocardiographic modalities multiple parameters of dyssynchrony were calculated. Each dyssynchrony parameter is shown below with an abbreviation which will be used in the following chapters.

i. Intra-ventricular dyssynchrony

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPWMD</td>
<td>Septal-posterior wall M-mode delay by grey scale imaging (ms)</td>
</tr>
<tr>
<td>SPWMD\textsubscript{TDI}</td>
<td>Septal-posterior wall M-mode delay by colour tissue Doppler imaging (ms)</td>
</tr>
<tr>
<td>SeptPostSAX\textsubscript{TDI}</td>
<td>Septal-posterior wall delay in time to peak velocity by tissue Doppler in short axis view (ms)</td>
</tr>
<tr>
<td>SeptLateral\textsubscript{TDI}</td>
<td>Septal-lateral delay in time to peak systolic velocity by Tissue Doppler in the apical 4 chamber view (ms)</td>
</tr>
<tr>
<td>12segment\textsubscript{TDI}</td>
<td>Standard deviation of time to peak systolic velocity in 12 LV myocardial segments by TDI in apical views</td>
</tr>
<tr>
<td>SeptPostRad\textsubscript{2DS}</td>
<td>Septal-posterior wall delay in time to peak systolic radial strain by speckle tracking in the short axis view (ms)</td>
</tr>
<tr>
<td>6segRad\textsubscript{2DS}</td>
<td>Standard deviation of time to peak systolic radial strain in 6 short axis segments by speckle-tracking 2D strain</td>
</tr>
<tr>
<td><strong>SeptPostCirc\textsubscript{2DS}</strong></td>
<td>Time to peak circumferential strain in septum - posterior wall by speckle tracking 2D strain in short axis view (ms)</td>
</tr>
<tr>
<td><strong>SeptLateral\textsubscript{2DS}</strong></td>
<td>Septal-lateral delay in time to peak systolic strain by speckle tracking 2D strain in apical 4 chamber view (ms)</td>
</tr>
<tr>
<td><strong>12segment\textsubscript{2DS}</strong></td>
<td>Standard deviation of time to peak longitudinal strain in 12 segments by speckle tracking in apical views</td>
</tr>
<tr>
<td><strong>3D SDI</strong></td>
<td>Three-dimensional systolic dyssynchrony index (SDI)</td>
</tr>
</tbody>
</table>

**ii. Inter-ventricular dyssynchrony**

| **LVPEP** | Left ventricular pre-ejection period (ms) |
| **RVPEP** | Right ventricular pre-ejection period (ms) |
| **IVMD** | Inter-ventricular mechanical delay (ms) |
| **IVFD** | Inter-ventricular filling delay (ms) |
| **RV-LV\textsubscript{TDI}** | Delay in peak velocity between tricuspid and lateral mitral annular systolic velocity by tissue Doppler (ms) |

**iii. Atrio-ventricular dyssynchrony**

| **DFT:RR** | Ratio of diastolic filling time to cardiac cycle length (%) |
| **E:A fusion** | Presence of fusion of E and A waves on trans-mitral flow |
| **Pre-systolic MR** | Presence of pre-systolic MR (PSMR) |

**5.3.8 Parameters for comparison between modalities**

In order to allow direct comparison of the values generated by different modalities of dyssynchrony assessment, in addition to the standardised parameters of dyssynchrony recorded above, the time to peak motion / velocity / strain in the posterior and (where relevant) lateral walls (mid-segment for short axis images and basal segment for long-axis images) were recorded for each of the modalities below:

- Grey scale short axis M-mode
- Colour tissue Doppler short axis M-mode
- Tissue Doppler velocity in short axis and long axis
- Radial 2D strain
- Circumferential 2D strain
- Longitudinal 2D strain

5.4 Intra-Cardiac Electrogram Analysis

The timing of the intracardiac electrogram sensed by the left ventricular pacing lead in relation to the QRS complex was determined by digitising the hard-copy of the electrogram generated by the pacing analyser at implant. This allowed the electrogram to be enlarged and printed at A4 size. The time from onset of the QRS complex to peak deflection on the intra-cardiac electrogram was then measured by hand.

5.5 Radiographic Determination of Left Ventricular Lead Position

Left ventricular lead position was determined using a 3x3 matrix method based on position of the lead tip determined in post-implant PA and lateral chest x-rays (164), giving a total of 9 possible lead positions.
In the PA projection, the heart shadow was divided into thirds from base to apex, and the lead position classified as either basal, mid or apical. In the lateral view the posterior semi-circumference of the cardiac shadow was also divided into thirds and lead position classified as either anterior, lateral or posterior.

5.6 Statistics

Data were transferred from the clinical data sheets and echocardiographic analysis worksheets to Microsoft Excel spreadsheets for initial data storage and processing. Spreadsheets were then imported into Statistical Package for Social Sciences (SPSS, SPSS Inc, Chicago) for statistical analysis. Results are presented
as mean +/- standard deviation (SD) unless otherwise stated. A probability value of <0.05 was considered statistically significant.

i. Assessment of intra- and inter-observer variability
Intra- and inter-observer variability were assessed using an absolute agreement two-way mixed model intra-class correlation co-efficient (ICC).

ii. Correlation between dyssynchrony measures and between dyssynchrony and echocardiographic response
Correlation between echocardiographic dyssynchrony parameters and electrical parameters was performed using Pearson correlation co-efficient. The relationship between the degree of baseline dyssynchrony and left ventricular reverse remodelling was assessed using Pearsons correlation co-efficient.

iii. Differences between responder and non-responder groups and between baseline and follow-up studies
The Shapiro-Wilk test was used to determine whether data was normally distributed where appropriate. Normally distributed data was analysed using either independent t-tests or paired-sample t-tests as appropriate. Non-normally distributed data was analysed using either Mann-Whitney U test or the Wilcoxon signed-rank test for paired data as appropriate. The chi-squared test was used to assess differences between groups for binomial parameters.

iv. Prediction of response to cardiac resynchronisation
To assess the role of dyssynchrony parameters in prediction of response to CRT receiver operating characteristic (ROC) curves were used. The area under the curve was recorded and an appropriate cut-off value chosen for optimal sensitivity and specificity of each parameter tested.

v. Multivariate analysis
Multivariate analysis was performed using a logistic regression step-wise model, with cut-off values of p<0.1 for entry of a parameter into the model and p>0.5 for removal during analysis.
Chapter 6

Baseline Assessment

Cardiac Resynchronisation Therapy Device Implant

Relationships Between Dyssynchrony Parameters

6.1 Study Population
6.2 Baseline Clinical Assessment
6.3 Baseline Echocardiographic Parameters
6.4 Feasibility of Echocardiographic Dyssynchrony Parameters
6.5 Intra- and Inter-Observer Variability of Echocardiographic Dyssynchrony Parameters
6.6 Cardiac Resynchronisation Therapy Device Implant Parameters
6.7 Relationships Between Echocardiographic Dyssynchrony Parameters
6.8 Discussion
6.1 Study Population

Recruitment of study participants commenced in March 2009 and was completed in September 2010; in this period 60 patients were enrolled into the study. Two patients decided not to proceed in the study, or failed to attend baseline assessment. Seven patients did not participate further in the study due to failure to meet inclusion criteria following analysis of baseline electrocardiographic and echocardiographic data. Data is therefore presented in this chapter for the 51 patients who fulfilled study criteria and completed baseline assessment.

6.2 Baseline Clinical Assessment

Baseline demographic and clinical data is shown in table 6.1. This demonstrates a preponderance of male patients, and a higher proportion of patients with underlying ischaemic heart disease as the cause of heart failure.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>66.9 (12.3)</td>
</tr>
<tr>
<td>Male / female</td>
<td>41 / 10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.5 (16.1)</td>
</tr>
<tr>
<td><strong>Aetiology of LV impairment</strong></td>
<td></td>
</tr>
<tr>
<td>Ischaemic (%)</td>
<td>58.8</td>
</tr>
<tr>
<td>Non-ischaemic (%)</td>
<td>41.2</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>47.0</td>
</tr>
<tr>
<td><strong>Diabetes (%)</strong></td>
<td>17.6</td>
</tr>
<tr>
<td><strong>Smoking (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11.8</td>
</tr>
<tr>
<td>No</td>
<td>35.3</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>52.9</td>
</tr>
<tr>
<td><strong>Myocardial infarction (%)</strong></td>
<td>54.9</td>
</tr>
<tr>
<td><strong>Revascularisation (%)</strong></td>
<td>35.2</td>
</tr>
<tr>
<td><strong>Heart rate (bts/min)</strong></td>
<td>71.1 (15.1)</td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>119.1 (23.0)</td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg)</strong></td>
<td>67.4 (10.0)</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td>3.04 (0.4)</td>
</tr>
</tbody>
</table>

Table 6.1: Baseline demographic and clinical parameters (n=51)
6.2.1 Medical therapy
Baseline medical therapy of participants is shown in table 6.2 expressed as percentage, except for frusemide equivalent dose which is shown as mean (SD). The frusemide equivalent dose is calculated on the basis that frusemide 40mg is equal to bumetanide 1mg.

<table>
<thead>
<tr>
<th>Medical therapy</th>
<th>Baseline (participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>78.4</td>
</tr>
<tr>
<td>Frusemide equivalent dose (mg)</td>
<td>59.2 (55.7)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>86.3</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>80.4</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>62.7</td>
</tr>
<tr>
<td>Digoxin</td>
<td>9.8</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>70.6</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>25.5</td>
</tr>
<tr>
<td>Lipid lowering therapy</td>
<td>74.5</td>
</tr>
</tbody>
</table>

Table 6.2: Baseline medical therapy of participants (n=51)

6.2.2 Laboratory measures
Baseline laboratory measures of renal function and haemoglobin are shown in table 6.3.

<table>
<thead>
<tr>
<th>Laboratory measure</th>
<th>Baseline (participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mmol/L)</td>
<td>10.4 (5.3)</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>119.0 (50.0)</td>
</tr>
<tr>
<td>Estimated GFR (mls/min)</td>
<td>59.1 (20.6)</td>
</tr>
<tr>
<td>Haemoglobin (mg/dL)</td>
<td>13.2 (1.6)</td>
</tr>
</tbody>
</table>

Table 6.3: Baseline laboratory values (n=51); GFR = glomerular filtration rate
6.2.3 Electrocardiographic parameters

Baseline electrocardiographic measures are shown in table 6.4, and the distribution of QRS complex duration in Figure 6.1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS duration (ms)</td>
<td>152.0 (26.6)</td>
</tr>
<tr>
<td>Typical LBBB pattern (%)</td>
<td>51.0</td>
</tr>
<tr>
<td>PR interval (ms)</td>
<td>191.5 (39.8)</td>
</tr>
</tbody>
</table>

Table 6.4: Baseline electrocardiographic parameters (n=51)

Figure 6.1: Distribution of QRS complex duration (n=51)

6.2.4 Quality of life questionnaire score and six minute walk distance

Baseline values for the Minnesota Living With Heart Failure quality of life questionnaire (QoL), and baseline six minute walk test distance are shown in table 6.5. The QoL questionnaire score is divided into three parts; the total score from 21 questions (possible range of scores 0-105), and a physical and mental component based on two subgroups of questions. The physical score is based on 9 questions (possible score 0-45), and the mental component on 5 questions (possible score 0-25).
**QoL score total**  
Physical component  23.8 (8.5)  
Mental component  11.7 (6.2)

**Six-minute walk test distance (m)**  280.5 (86.3)

*Table 6.5: Baseline QoL questionnaire scores and six minute walk distance (n=51)*

### 6.3 Baseline Echocardiographic Parameters

Baseline echocardiographic parameters are shown on the following pages. Parameters of left ventricular structure and geometry, and systolic and diastolic function are shown in table 6.6 overleaf. Baseline echocardiographic assessment of mitral regurgitation, left atrial structure and right heart parameters are shown in table 6.7 on page 104, and baseline measures of inter-ventricular, intra-ventricular and atrio-ventricular dyssynchrony are shown in table 6.8 on page 105.
### LV structure and geometry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventricular septal thickness (cm)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>Posterior wall thickness (cm)</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td>Left ventricular diameter end-diastole (cm)</td>
<td>6.7 (0.9)</td>
</tr>
<tr>
<td>Left ventricular diameter end-systole (cm)</td>
<td>5.9 (0.9)</td>
</tr>
<tr>
<td>Left ventricular long-axis length (cm)</td>
<td>9.3 (0.8)</td>
</tr>
<tr>
<td>Biplane left ventricular volume diastole (mls)</td>
<td>191.8 (60.6)</td>
</tr>
<tr>
<td>Biplane left ventricular volume systole (mls)</td>
<td>142.1 (50.0)</td>
</tr>
<tr>
<td>3D left ventricular volume diastole (mls)</td>
<td>201.5 (71.0)</td>
</tr>
<tr>
<td>3D left ventricular volume systole (mls)</td>
<td>155.2 (64.0)</td>
</tr>
<tr>
<td>Left ventricular sphericity index</td>
<td>0.45 (0.12)</td>
</tr>
</tbody>
</table>

### Left ventricular systolic function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional shortening (%)</td>
<td>11.5 (5.2)</td>
</tr>
<tr>
<td>Biplane left ventricular ejection fraction (%)</td>
<td>26.2 (7.3)</td>
</tr>
<tr>
<td>3D left ventricular ejection fraction (%)</td>
<td>24.3 (9.1)</td>
</tr>
<tr>
<td>Stroke volume (mls)</td>
<td>62.8 (25.9)</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>4.0 (1.7)</td>
</tr>
</tbody>
</table>

### Tissue Doppler / 2-dimensional strain

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral annular systolic velocity – septal (cm/s)</td>
<td>2.8 (1.3)</td>
</tr>
<tr>
<td>Mitral annular systolic velocity – lateral (cm/s)</td>
<td>3.1 (1.5)</td>
</tr>
<tr>
<td>Peak global strain – circumferential (%)</td>
<td>7.9 (3.3)</td>
</tr>
<tr>
<td>Peak global strain – longitudinal (%)</td>
<td>7.7 (2.7)</td>
</tr>
</tbody>
</table>

### Diastolic function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular myocardial performance index</td>
<td>0.73 (0.29)</td>
</tr>
<tr>
<td>Transmirtal E:A ratio</td>
<td>1.5 (1.1)</td>
</tr>
<tr>
<td>E:E’ ratio</td>
<td>23.0 (10.6)</td>
</tr>
</tbody>
</table>

Table 6.6: Baseline parameters of left ventricular structure and function (n=51)
### Left atrial structure
- Dimension (cm): 4.7 (0.6)
- Area (cm²): 27.8 (7.3)
- Biplane volume (mls): 96.0 (38.0)

### Mitral regurgitation
- MR jet area / LA area ratio: 0.28 (0.22)
- Vena contracta (cm): 0.3 (0.2)
- Effective regurgitant orifice area (mm²): 10.4 (9.9)
- Regurgitant volume (mls): 17.6 (16.8)

### Right heart parameters
- Right ventricular dimension (cm): 3.3 (0.7)
- TAPSE (cm): 1.8 (0.4)
- Tricuspid annular systolic velocity (cm/s): 6.8 (2.1)
- Estimated pulmonary artery pressure (mmHg): 29.4 (12.7)

Table 6.7: Baseline parameters of left atrial structure, mitral regurgitation and right heart parameters (n=51)
### Inter-ventricular dyssynchrony

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular PEP (ms)</td>
<td>135.9 (35.9)</td>
</tr>
<tr>
<td>Right ventricular PEP (ms)</td>
<td>97.3 (19.7)</td>
</tr>
<tr>
<td>IVMD (ms)</td>
<td>38.5 (35.5)</td>
</tr>
<tr>
<td>RV – LV&lt;sub&gt;TDI&lt;/sub&gt; (ms)</td>
<td>59.4 (52.2)</td>
</tr>
<tr>
<td>IVFD (ms)</td>
<td>23.7 (106.1)</td>
</tr>
</tbody>
</table>

### Intra-ventricular dyssynchrony

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPWMD (ms)</td>
<td>196.7 (128.7)</td>
</tr>
<tr>
<td>SPWMD&lt;sub&gt;TDI&lt;/sub&gt; (ms)</td>
<td>146.5 (135.5)</td>
</tr>
<tr>
<td>SeptPostSAX&lt;sub&gt;TDI&lt;/sub&gt; (ms)</td>
<td>35.8 (74.5)</td>
</tr>
<tr>
<td>SeptLateral&lt;sub&gt;TDI&lt;/sub&gt; (ms)</td>
<td>55.5 (62.3)</td>
</tr>
<tr>
<td>12segment&lt;sub&gt;TDI&lt;/sub&gt;</td>
<td>45.3 (19.5)</td>
</tr>
<tr>
<td>SeptPostRad&lt;sub&gt;2DS&lt;/sub&gt; (ms)</td>
<td>101.1 (187.4)</td>
</tr>
<tr>
<td>6segRad&lt;sub&gt;2DS&lt;/sub&gt;</td>
<td>71.0 (50.1)</td>
</tr>
<tr>
<td>SeptPostCirc&lt;sub&gt;2DS&lt;/sub&gt; (ms)</td>
<td>84.9 (157.3)</td>
</tr>
<tr>
<td>SeptLateral&lt;sub&gt;2DS&lt;/sub&gt; (ms)</td>
<td>94.8 (175.0)</td>
</tr>
<tr>
<td>12 segment&lt;sub&gt;2DS&lt;/sub&gt;</td>
<td>84.5 (27.8)</td>
</tr>
<tr>
<td>3D systolic dyssynchrony index</td>
<td>11.6 (5.3)</td>
</tr>
</tbody>
</table>

### Atrio-ventricular dyssynchrony

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFT:RR</td>
<td>0.47 (0.1)</td>
</tr>
<tr>
<td>Pre-systolic MR (%)</td>
<td>7.8</td>
</tr>
<tr>
<td>E:A fusion (%)</td>
<td>13.8</td>
</tr>
</tbody>
</table>

**Table 6.8**: Baseline parameters of dyssynchrony (n=51)
6.4 Feasibility of Echocardiographic Dyssynchrony Parameters

The feasibility of measurement for each echocardiographic modality of dyssynchrony assessment is shown below as the number of segments successfully analysed for each modality.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Segments analysed</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPWMD</td>
<td>42/51</td>
<td>82.4%</td>
</tr>
<tr>
<td>SPWMD&lt;sub&gt;TDI&lt;/sub&gt;</td>
<td>45/51</td>
<td>88.2%</td>
</tr>
<tr>
<td>Short axis tissue Doppler</td>
<td>92/102</td>
<td>90.2%</td>
</tr>
<tr>
<td>Apical tissue Doppler</td>
<td>560/612</td>
<td>91.5%</td>
</tr>
<tr>
<td>Radial strain</td>
<td>264/306</td>
<td>86.3%</td>
</tr>
<tr>
<td>Circumferential strain</td>
<td>94/102</td>
<td>92.1%</td>
</tr>
<tr>
<td>Longitudinal strain</td>
<td>498/612</td>
<td>81.4%</td>
</tr>
<tr>
<td>Pre-ejection period</td>
<td>112/112</td>
<td>100%</td>
</tr>
<tr>
<td>3D SDI</td>
<td>38/51</td>
<td>74.5%</td>
</tr>
</tbody>
</table>

Table 6.9: Feasibility of dyssynchrony parameter measurement (n=51)

SPWMD and SPWMD<sub>TDI</sub> parameters were limited by either short axis views with poor endocardial definition, or akinetic septal or posterior segments with no clear motion peak. Colour tissue Doppler M-Mode identified the timing of change of direction in motion in three cases where it was not apparent by grey-scale imaging. Short axis tissue Doppler and radial and circumferential strain analysis were limited by the quality of 2D imaging in the short axis view. Longitudinal 2D strain was limited by the quality of imaging, but also occasionally by poor tracking by the speckle tracking algorithm, particularly of basal septal and basal lateral segments, despite apparently adequate 2D images. Measurement was not possible in some speckle tracking segments due to a curve entirely opposite to normal direction of strain for the relevant segment, and therefore no measurable peak. 3D SDI measurement was limited predominantly by stitch artefact due to irregularities of cardiac rhythm and image quality.
6.5 Intra- and Inter-observer Variability of Echocardiographic Dyssynchrony Parameters

Intra- and inter-observer variability were measured by re-analysis of a subgroup of echocardiographic studies by the author and a second person as defined previously in Chapter 5. Degree of intra- and inter-observer agreement was measured by intra-class correlation co-efficient.

i. Intra-observer variability

Intra-class correlation co-efficients for intra-observer variability of each parameter of dyssynchrony are shown below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intra-rater co-efficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVPEP</td>
<td>0.989</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVMD</td>
<td>0.942</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to peak RV filling</td>
<td>0.997</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to peak LV filling</td>
<td>0.982</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPWMD</td>
<td>0.978</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPWMD_TDI</td>
<td>0.977</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SepPostSAX_TDI</td>
<td>0.966</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SepLateral_TDI</td>
<td>0.967</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12segment_TDI</td>
<td>0.809</td>
<td>0.007</td>
</tr>
<tr>
<td>SepPostRad2DS</td>
<td>0.94</td>
<td>0.002</td>
</tr>
<tr>
<td>SepPostCirc2DS</td>
<td>0.731</td>
<td>0.032</td>
</tr>
<tr>
<td>SepLateral2DS</td>
<td>0.85</td>
<td>0.008</td>
</tr>
<tr>
<td>12segment2DS</td>
<td>0.972</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 6.10: Intra-class correlation co-efficients for intra-observer variability in measurement of dyssynchrony parameters

ii. Inter-observer variability

Intra-class correlation co-efficients for inter-observer variability of each parameter of dyssynchrony are shown in table 6.11 overleaf.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Inter-rater co-efficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV PEP</td>
<td>0.882</td>
<td>0.002</td>
</tr>
<tr>
<td>IVMD</td>
<td>0.980</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to peak RV filling</td>
<td>0.882</td>
<td>0.003</td>
</tr>
<tr>
<td>Time to peak LV filling</td>
<td>0.976</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPWMD</td>
<td>0.825</td>
<td>0.012</td>
</tr>
<tr>
<td>SPWMD_{TDI}</td>
<td>0.894</td>
<td>0.001</td>
</tr>
<tr>
<td>SeptPostSAX_{TDI}</td>
<td>0.894</td>
<td>0.001</td>
</tr>
<tr>
<td>SeptLat_{TDI}</td>
<td>0.461</td>
<td>NS</td>
</tr>
<tr>
<td>12segment_{TDI}</td>
<td>0.365</td>
<td>NS</td>
</tr>
<tr>
<td>SeptPostRad_{2DS}</td>
<td>0.603</td>
<td>NS</td>
</tr>
<tr>
<td>SeptPostCirc_{2DS}</td>
<td>0.599</td>
<td>NS</td>
</tr>
<tr>
<td>SeptLat_{2DS}</td>
<td>0.679</td>
<td>NS</td>
</tr>
<tr>
<td>12segment_{2DS}</td>
<td>0.641</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 6.11: Intra-class correlation co-efficients for inter-observer variability in measurement of dyssynchrony parameters

**6.6 Cardiac Resynchronisation Therapy Device Implant Parameters**

Two patients died between baseline assessment and planned CRT implant, forty nine patients therefore underwent CRT.

The measured electrical parameters of the right atrial, right ventricular and left ventricular pacing leads at the time of implantation and delay between QRS complex and recorded LV electrogram are shown in table 6.12.
Right atrial
Pacing threshold (V)   1.2 (0.6)
Pacing impedance (ohms) 82.4 (102.5)
Sensed P wave (mV) 3.4 (1.9)

Right ventricular
Pacing threshold (V)   0.9 (0.8)
Pacing impedance (ohms) 2.2 (198.7)
Sensed R wave (mV) 3.1 (5.9)

Left ventricular
Pacing threshold (V)   1.7 (1.6)
Pacing impedance (ohms) 296.2 (501.6)
Sensed R wave (mV) 5.1 (7.7)

Onset QRS – LV electrogram (ms) 146.1 (29.8)

Table 6.12: Pacing parameters at CRT device implant (n=49)

In 48 patients transvenous left ventricular leads were positioned in a branch of the coronary sinus. In one patient the coronary sinus was not able to be cannulated, and the patient underwent epicardial lead placement via a mini-thoracotomy. The distribution of left ventricular lead position as determined by post-implant postero-anterior and lateral projection radiographs is shown below.

<table>
<thead>
<tr>
<th></th>
<th>Anterior</th>
<th>Lateral</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mid</td>
<td>17</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Apical</td>
<td>0</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6.13: Left ventricular lead position as determined by post-implant x-ray
6.7 Relationships Between Echocardiographic Dyssynchrony Parameters

6.7.1. Timing of posterior wall activation

In this section comparison between speckle tracking echocardiography and other echocardiographic modalities has been performed by comparing the timing of posterior wall activation measured by each modality. The value generated by each modality is shown in table 6.14.

<table>
<thead>
<tr>
<th>Echocardiographic Modality</th>
<th>Mean Posterior Wall Activation Time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-mode</td>
<td>435.9 (51.1)</td>
</tr>
<tr>
<td>M-mode TDI</td>
<td>417.2 (49.6)</td>
</tr>
<tr>
<td>Short axis TDI</td>
<td>226.9 (48.0)</td>
</tr>
<tr>
<td>Long-axis TDI</td>
<td>225.8 (48.6)</td>
</tr>
<tr>
<td>Radial strain</td>
<td>467.4 (93.2)</td>
</tr>
<tr>
<td>Circumferential strain</td>
<td>424.6 (93.8)</td>
</tr>
<tr>
<td>Longitudinal strain</td>
<td>466.8 (98.0)</td>
</tr>
</tbody>
</table>

Table 6.14: Mean value for timing of posterior wall activation by different echocardiographic modalities (n=51)

The relationship between these measures, expressed as correlation between measures by speckle tracking and measures by other echocardiographic modalities are shown in table 6.15 overleaf. Radial and circumferential strain demonstrated a high level of correlation, and both show modest correlation with longitudinal strain. M-mode and TDI M-mode values were highly correlated (r=0.84, p<0.001). M-mode values also showed significant correlation with both short and long axis tissue Doppler parameters (table 6.16) and radial, circumferential and longitudinal measures by 2D strain. Systolic dyssynchrony index by 3D echo is not shown, but showed no significant correlation with any other parameters.
### Table 6.15: Pearson's correlation coefficients between speckle tracking parameters of posterior wall activation and other echocardiographic modalities

<table>
<thead>
<tr>
<th></th>
<th>Radial strain</th>
<th></th>
<th>Circumferential strain</th>
<th></th>
<th>Longitudinal strain</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation</td>
<td>p-value</td>
<td>Correlation</td>
<td>p-value</td>
<td>Correlation</td>
<td>p-value</td>
</tr>
<tr>
<td>Radial strain</td>
<td></td>
<td></td>
<td>0.64</td>
<td>&lt;0.001</td>
<td>0.34</td>
<td>0.03</td>
</tr>
<tr>
<td>Circumferential strain</td>
<td></td>
<td></td>
<td>0.41</td>
<td>0.006</td>
<td>0.43</td>
<td>0.006</td>
</tr>
<tr>
<td>M-mode</td>
<td>0.38</td>
<td>0.01</td>
<td>0.37</td>
<td>0.015</td>
<td>0.43</td>
<td>0.005</td>
</tr>
<tr>
<td>M-mode TDI</td>
<td>0.54</td>
<td>&lt;0.001</td>
<td>0.40</td>
<td>0.007</td>
<td>0.44</td>
<td>0.005</td>
</tr>
<tr>
<td>Short axis TDI</td>
<td>0.45</td>
<td>0.002</td>
<td>0.19</td>
<td>NS</td>
<td>0.28</td>
<td>NS</td>
</tr>
<tr>
<td>Long axis TDI</td>
<td>0.39</td>
<td>0.008</td>
<td>0.32</td>
<td>0.03</td>
<td>0.32</td>
<td>0.037</td>
</tr>
</tbody>
</table>

### Table 6.16: Pearson's correlation coefficients for M-mode and tissue Doppler parameters of posterior wall activation

<table>
<thead>
<tr>
<th></th>
<th>Short axis TDI</th>
<th></th>
<th>Long axis TDI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation</td>
<td>p-value</td>
<td>Correlation</td>
<td>p-value</td>
</tr>
<tr>
<td>Short axis TDI</td>
<td></td>
<td></td>
<td>0.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>M-mode</td>
<td>0.32</td>
<td>0.036</td>
<td>0.42</td>
<td>0.004</td>
</tr>
<tr>
<td>M-mode TDI</td>
<td>0.43</td>
<td>0.004</td>
<td>0.49</td>
<td>0.001</td>
</tr>
</tbody>
</table>

---

111
6.7.2 Parameters of inter-ventricular dyssynchrony
Correlations between parameters of inter-ventricular dyssynchrony are shown below as correlation with IVMD in table 6.17.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak LV filling</td>
<td>0.654</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to peak RV filling</td>
<td>-0.04</td>
<td>NS</td>
</tr>
<tr>
<td>RV-LV&lt;sub&gt;TDI&lt;/sub&gt;</td>
<td>-0.17</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 6.17: Pearsons correlation co-efficient for inter-ventricular parameters of dyssynchrony

Increases in inter-ventricular dyssynchrony measured by IVMD are strongly correlated with increasing delay in the onset of LV filling, but show no significant correlation with timing of RV filling. Alternative assessment of inter-ventricular dyssynchrony by tissue Doppler imaging shows no significant correlation with IVMD.

6.7.3 QRS duration and echocardiographic parameters of dyssynchrony
Correlation between measures of posterior and lateral wall activation and QRS duration are shown in table 6.18.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior wall M-mode</td>
<td>0.28</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior wall M-mode TDI</td>
<td>0.34</td>
<td>0.02</td>
</tr>
<tr>
<td>Posterior wall short axis TDI</td>
<td>0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior wall long axis TDI</td>
<td>0.43</td>
<td>0.002</td>
</tr>
<tr>
<td>Posterior wall radial strain</td>
<td>0.26</td>
<td>0.09</td>
</tr>
<tr>
<td>Posterior wall circumferential strain</td>
<td>0.21</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior wall longitudinal strain</td>
<td>0.12</td>
<td>NS</td>
</tr>
<tr>
<td>Lateral wall long axis TDI</td>
<td>0.223</td>
<td>0.151</td>
</tr>
<tr>
<td>Lateral wall radial strain</td>
<td>0.411</td>
<td>0.006</td>
</tr>
<tr>
<td>Lateral wall longitudinal strain</td>
<td>0.478</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table 6.18: Pearsons correlation co-efficient for echocardiographic parameters of posterior and lateral wall activation and QRS duration
All echocardiographic parameters demonstrated very modest correlation with QRS duration, except circumferential and longitudinal 2D strain which correlated poorly. Table 6.19 below shows correlations between standard dyssynchrony parameters and QRS duration.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SeptLateral(_{TDI})</td>
<td>0.21</td>
<td>NS</td>
</tr>
<tr>
<td>12segment(_{TDI})</td>
<td>0.285</td>
<td>0.043</td>
</tr>
<tr>
<td>SeptPostRad(_{2DS})</td>
<td>-0.10</td>
<td>NS</td>
</tr>
<tr>
<td>6segRad(_{2DS})</td>
<td>0.257</td>
<td>0.085</td>
</tr>
<tr>
<td>SeptPostCirc(_{2DS})</td>
<td>0.40</td>
<td>0.005</td>
</tr>
<tr>
<td>SeptLat(_{2DS})</td>
<td>0.18</td>
<td>NS</td>
</tr>
<tr>
<td>12segment(_{2DS})</td>
<td>0.35</td>
<td>0.017</td>
</tr>
<tr>
<td>3D SDI</td>
<td>0.35</td>
<td>0.03</td>
</tr>
<tr>
<td>IVMD</td>
<td>0.42</td>
<td>0.002</td>
</tr>
<tr>
<td>LV PEP</td>
<td>0.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to peak LV filling</td>
<td>0.41</td>
<td>0.03</td>
</tr>
<tr>
<td>Time to peak RV filling</td>
<td>-0.02</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 6.19: Pearson's correlation coefficients between QRS duration and standard echocardiographic dyssynchrony parameters

Left ventricular pre-ejection and timing of left ventricular filling are both positively correlated with QRS duration. No relationship between timing of right ventricular filling and QRS duration was found. Limited correlation between QRS duration and standard echocardiographic dyssynchrony measures are seen.

6.7.4 Intra-cardiac electrical delay and echocardiographic parameters of intra-ventricular dyssynchrony

No significant correlation was found between any echocardiographic parameters or QRS duration and local electrical activation time measured from the left ventricular lead at CRT implant.
6.8 Discussion

This chapter has presented baseline demographic, clinical and echocardiographic data for the participants who completed baseline assessment. Baseline demographics demonstrate a higher proportion of patients with underlying ischemic heart disease as the cause of heart failure, and a preponderance of male patients. Clinical information suggests patients with predominantly NYHA class III symptoms on good medical therapy.

Baseline echocardiographic parameters are consistent with severe left ventricular systolic dysfunction. Baseline dyssynchrony parameters demonstrate a high degree of feasibility of measurement for the parameters studied. Intra-observer variability suggests relatively good intra-reader reproducibility of dyssynchrony measures, however inter-observer variability for several parameters is relatively poor.

Assessment of the relationship between parameters using correlation coefficients suggests modest correlation between some parameters and relatively poor correlation between others. In particular, radial strain correlates with measures of myocardial excursion by m-mode or TDI M-mode echocardiography, however measures of posterior wall activation by circumferential and longitudinal strain correlate poorly with other echocardiographic modalities, particularly tissue Doppler velocity measures. QRS duration tends to correlate to a greater degree with markers of inter-ventricular rather than intra-ventricular dyssynchrony. As a measure of delayed posterolateral wall activation, radial and longitudinal strain in the lateral wall correlated with QRS duration to the highest degree. Septal-posterior wall delay by circumferential strain also shows correlation with QRS duration.

6.8.1 Baseline patient characteristics

Baseline characteristics of the patients recruited into this study are comparable to previous studies of heart failure patients receiving CRT. Baseline mean left ventricular end-diastolic volume of 191.8mls and ejection fraction of 26.2% are
consistent with severe left ventricular systolic dysfunction, and compare similarly with the degree of left ventricular dilatation and dysfunction seen in studies by Yu (mean LV end-diastolic volume 193mls, (57)) and the CARE-HF study (median ejection fraction 25%, (25)). Likewise, cause of left ventricular dysfunction is approximately equally split between ischaemic and non-ischaemic aetiology, as in previous studies (CARE-HF 46% non-ischaemic, Bax study 56% (52)). The participants in this study were on good medical therapy for heart failure, with high percentages taking both ACE inhibitors and beta-blockers. In the CARE-HF study ACE inhibitor use was extremely high at 95%, compared with 86% in this study, conversely beta-blocker use in this study is higher at 80%, compared to 70% in CARE-HF.

Although recent studies have started to explore the role of cardiac resynchronization in patients with left ventricular dysfunction and mild heart failure symptoms, almost all studies of CRT have recruited patients with NYHA class III and IV heart failure symptoms. NYHA classification may be variable however, with the definition of each class potentially open to interpretation by the classifying physician (168). The degree of heart failure symptoms in the current study has also been assessed by use of the Minnesota Living With Heart Failure quality of life questionnaire and by six minute walk test. In a study by Bax et al the mean baseline value of six minute walk was 278m, and quality of life score 42 (53), and 298m and 37.3 respectively in a study by Yu (169). The baseline values for six minute walk distance of 280.5m and quality of life score of 50 in this study suggest a similar level of heart failure symptoms to previous studies. Overall, the clinical and echocardiographic characteristics of patients recruited into this study appear to represent a typical selection of patients considered for cardiac resynchronization therapy.

**6.8.2 Baseline echocardiographic dyssynchrony assessment**

Baseline echocardiographic dyssynchrony analysis in this study demonstrated variable levels of baseline intra-ventricular dyssynchrony based on specific echocardiographic parameters. Baseline values of SPWMD, SPWMD\textsubscript{TDI} and 12 segment TDI were all above previously specified cut-off values for prediction of response to CRT, whereas septal-lateral delay and parameters of inter-ventricular dyssynchrony were not. Mean baseline value of SPWMD of 196.7ms is similar
to Pitzalis original description of the parameter, with a reported mean of 192ms (39), although both these values are much higher than the study by Marcus et al which demonstrated a mean value of between 59 and 77ms (41). The reason for this variability is unclear. QRS duration between the studies are similar, although the study by Marcus et al contained a much greater proportion of patients with ischaemic left ventricular dysfunction, and a large spread of measured values ranging from -340ms to 525 ms. SPWMD was measured from M-mode images taken in the parasternal long axis view at the basal level of the left ventricle in the Marcus study, compared to a mid-cavity level short axis view in this study and as originally reported by Pitzalis, and the echocardiographic data in the Marcus study may therefore differ significantly. SPWMD\textsubscript{TDI} derived by colour tissue Doppler imaging has not been widely studied. The value obtained in this study appears to be markedly lower than the value derived from grey-scale imaging, although still above the reported cut-off value for prediction of response of 130ms. Sorrell et al reported that colour M-mode values were more reproducible than grey-scale measurements, although mean values for the two modalities in 42 patients were similar (46). Colour M-mode certainly provides a more defined point of measurement, although where septal motion is complex and more than one motion peak exists colour M-mode can produce difficulty in determining which is the predominant septal peak (Figure 6.2, overleaf). The methodology used in this study was to measure septal motion from the point of change in direction (change from blue to red) following the longest period of inward septal motion, however in cases where early septal motion is the predominant component of septal motion this may lead to measurement of a longer but less pronounced period of late septal motion, and subsequently a shorter SPWMD\textsubscript{TDI} value, not necessarily reflecting the degree of dyssynchrony present. Grey scale SPWMD tends to detect these cases more reliably provided endocardial definition is clear, although an altered methodology for analysis of SPWMD\textsubscript{TDI} specifically aimed at detection of early septal motion (the septal flash) would almost certainly be associated with greater equality of the values between SPWMD and SPWMD\textsubscript{TDI}. 

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Figure 6.2: Colour tissue Doppler m-mode for measurement of SPWMD<sub>TDI</sub>. In this example there are three separate phases of inwards systolic septal motion making determination of the correct point of measurement difficult.

Tissue Doppler velocity parameters measured in this study appear to differ a little from values previously reported. Bax initially reported mean values of baseline septal-lateral delay ranging from 71-93ms in three reports on the use of tissue Doppler imaging in 2003 and 2004 (51-53). The value in this study is lower at 55ms, although similar to the value of 58.1ms reported by Kuppahally et al in a 2011 study reporting no benefit of tissue Doppler parameters in the prediction of response to CRT (99). Yu et al reported a baseline value for 12 segment delay of 37.7ms in the original description of the technique in 2002 (49), although a higher value of 42.0ms in wide QRS complex patients in a report characterising dyssynchrony in 2003 (34). The value in this study is higher at 45.3ms, again similar to the value reported by Kuppahally of 44.2ms. There is not a clear explanation as to why the group of patients studied here should appear to have more dyssynchrony by one measure and less by another when compared to previously published values in demonstrably similar heart failure patients. This perhaps reflects the inherent variability in assessment of the parameters which will be discussed later.

Parameters derived from speckle tracking dyssynchrony in this study also appear to differ markedly from previously reported values. Baseline value for septal-posterior wall delay by radial strain in this study was 101.1±187.4ms. Previous
studies report much higher values; Delgado reports a baseline value of 180±135ms (79), Suffoletto 224±116ms (77) and Gorcsan 228.5ms (78). Fewer reports are available for other speckle tracking parameters, but in general values in this study appear to be lower than previous reports. Delgado reports a value for 6 segment radial strain of 107±71ms, septal-posterior wall circumferential strain of 162±128ms, septal-lateral longitudinal strain delay of 136±101ms and 12 segment longitudinal strain of 115±42ms, all higher than baseline values for this study despite apparently similar methodology (79). Mean QRS duration in the Delgado study was slightly higher than this study at 164.0ms, seemingly not a large enough difference to account for these discrepancies. Shi et al report a baseline value of 80.5ms for 12 segments longitudinal strain, which is more comparable with the baseline value in this study. These differences may reflect systematic variations in the method of analysis not apparent from available information, differences in the population studied, or simply poor reproducibility of the parameters.

6.8.3 Feasibility of echocardiographic dyssynchrony parameters
The feasibility of measurement of echocardiographic dyssynchrony parameters in this study compares similarly to previous reports. Pitzalis et al reported feasibility for SPWMD of 95.4% in 2005 (40), having not specifically stated a feasibility value in the original 2002 paper. Miyazaki et al also report a high value for SPWMD of 94% (88). Marcus et al reported a markedly different feasibility of only 45% in 2005 (41), in a paper clearly aimed at dismissing the value of this parameter. As previously described the methodology of Marcus et al differed slightly from this study and that of Pitzalis, and measurement of SPWMD at the basal LV level in the long axis view undoubtedly makes measurement more difficult, with less clear placement of the M-mode cursor through the centre of the cavity and more interference in the visualization of wall motion by intrusion of mitral valve leaflets and sub-valvar apparatus in the image. Sorrell et al do not specifically report the feasibility of SPWMD_{TDI}, however note that SPWMD_{TDI} datasets were available for comparison in all patients with SPWMD, suggesting that SPWMD_{TDI} feasibility is certainly no worse than SPWMD (46). In this study SPWMD_{TDI} feasibility was slightly higher, with colour M-mode imaging demonstrating evidence of a defined
change in direction of motion in some patients where one was not apparent on grey-scale imaging. In the PROSPECT trial, the reported feasibility of SPWMD was 71.7% (63); SPWMD_{TDI} was not examined. The reported feasibility of SPWMD analysis in current literature is therefore highly variable, however the value of 82.4% in this study appears to be consistent with previous reports. Overall feasibility for tissue Doppler assessment in this study, including short and long axis values is 91.3%. The PROSPECT study reported poor feasibility of tissue Doppler measures, with a value of 66.8% for septal-lateral delay and as low as 50.0% for 12 segment SD. The PROSPECT study appears to have been hampered by relatively poor quality echocardiography (70 of 498 echoes contained no measure of LV end-systolic volume despite core lab training and a defined protocol), and in particular tissue Doppler data obtained from Siemens echo machines was discarded due to poor image quality (170). Miyazaki et al report a much higher feasibility for TDI analysis of 96%, similar to the high value achieved in this study.

Feasibility for speckle tracking parameters in this study ranged from 86.3 – 91.5%. Miyazaki reported feasibility of 65% for radial and circumferential strain derived from short axis images, and 86.3% for longitudinal strain from apical images (88). Tanaka reported higher feasibility levels of 85-87% for radial and circumferential strain in short axis, and 84% for longitudinal strain in long axis (82).

Inter-ventricular dyssynchrony parameters derived from pulsed wave Doppler measures of either left or right ventricular outflow or inflow are usually performed with a high level of feasibility. This is confirmed in this study where left and right ventricular pre-ejection periods were able to be performed in all patients. Miyazaki also demonstrated a high feasibility of 97.7% for the measurement of pre-ejection periods (88), and even the PROSPECT study achieved a level of 94.6% for the measurement of left ventricular pre-ejection period, and 92.4% for interventricular mechanical delay.
6.8.4 Intra- and inter-observer variability in echocardiographic dyssynchrony parameters

High levels of inter-observer variability have previously been highlighted as a problem with several echocardiographic parameters of dyssynchrony, an issue reinforced by the disappointing results of the PROSPECT study. SPWMD has been reported to suffer from especially problematic inter-observer variability. Pitzalis initially reported very high levels of inter- and intra-observer agreement in 2002, with intra-class correlation coefficients of 0.91 and 0.96 respectively (39). As one might expect, Marcus subsequently reported very poor reproducibility for SPWMD. Although intra-class correlation coefficient was not performed, within-subject standard deviation measures suggested that one would expect 95% of pairs of measures by two observers to fall within a range of 141ms, a value too high in relation to the proposed cut-off to have any clinically useful role. Miyazaki et al reported relatively low intra- and inter-observer variability for SPWMD, with mean difference between two paired readings of 8.3% for intra-observer and 14.6% for inter-observer variability (88). In the PROSPECT study, intra- and inter-observer variability were measured using coefficient of variation (ratio of the standard deviation and mean difference between readings). SPWMD produced the worst intra- and inter-observer variability measures of any parameter in the study, with coefficient of variation of 24.3% for intra-observer and 72.1% for inter-observer variability (63). Sorrell reported markedly different variability for colour M-mode SPWMD than for SPWMD by grey scale imaging (46). For SPWMD they report relatively poor intra- and inter-observer correlation of 0.714 and 0.575, however for SPWMD_{TDI} variability improves to 0.967 and 0.929 respectively. In the current study intra-observer variability was good for both SPWMD and SPWMD_{TDI} with intra-class correlation coefficients of 0.958 and 0.968. However, inter-observer variability was relatively poor for both SPWMD and SPWMD_{TDI}.

In the PROSPECT trial tissue Doppler parameters were also prone to high levels of measurement variability. Variability for septal-lateral delay is not specifically reported in the study, however intra-observer variability by coefficient of variation for two tissue Doppler measures, including 12 segment SD were 11.4 and 15.8% and inter-observer variability for the same values 31.9% and 33.7% (63). Miyazaki et al also report relatively poor reproducibility of tissue Doppler
They report a mean difference between paired readings of 22.7% and 30.3% for intra- and inter-observer variability of septal to lateral delay. Lower values of 9.1% and 11.5% are reported for 12 segment SD. De Boeck et al have also examined intra- and inter-observer variability in tissue Doppler analysis. Inter-observer variability was tested by handing out still frame printouts of TDI velocity curves of 18 patients to nine members of the faculty of an international echocardiography congress dedicated to tissue Doppler imaging and resynchronization (171). Experts were asked to mark which velocity peak they would measure for each analysed segment. Intra-observer co-efficient of variation of 11.3% for septal-lateral delay and 12.9% for 12 segment SD were reported. Consensus of the expert faculty produced full agreement in only 3 of 18 cases, and a very modest intra-class correlation of 0.42. Burri et al report intra- and inter-observer variability in tissue Doppler analysis by 95% limits of agreement (ie. 95% of pairs of repeated values fall within these limits) (114).

Intra-ventricular dyssynchrony analysis by peak systolic velocity TDI demonstrated very poor variability, with a 95% limit of agreement of over 150ms for a parameter with a mean value of 50ms. Reproducibility of tissue Doppler parameters is highly dependent upon consistency in both acquisition and analysis of images. Variability may be introduced at the acquisition stage by changes in respiratory phase during or between acquisitions, or in the angle of incidence of the ultrasound beam with the myocardium. At the analysis stage marked variation in the shape and timing of the velocity curve can be produced from small movements of the region of interest within the interrogated segment of myocardium (Figure 6.3, overleaf). In addition it is frequent to encounter more than one systolic velocity peak for each segment. Although guidelines exist to determine which peak to measure, the fact that international faculty given still frame images, removing any variation in placement of the region of interest, were largely unable to agree on this demonstrates the considerable difficulties in producing consistency in tissue Doppler velocity analysis. As with SPWMD, in the current study intra-observer variability of tissue Doppler images was minimal with ICC ranging from 0.90 – 0.93 for tissue Doppler indices. Although inter-observer variability was satisfactory for short axis tissue Doppler measurements (ICC 0.90), long-axis measurements were poorly reproducible with ICC 0.14 for septal-lateral delay.
Figure 6.3: Colour Tissue Doppler analysis of the same cardiac cycle. These two frames show how a small change in the position of the basal lateral ROI can make a significant difference to the measured dyssynchrony value. In the left image the timing of septal and lateral peaks are identical, in the right image a small movement of the ROI has created a significant difference in timing between the two peaks.

Although not specifically tested in this study, two studies have reported on the test-test reliability of tissue Doppler parameters, and demonstrated poor agreement in parameters between multiple studies on the same patient. Gabriel et al report an inter-study correlation coefficient of only 0.28 for septal-lateral delay by tissue Doppler (172), and Vesely et al report a coefficient of 0.26 for the same parameter (173). Speckle tracking echocardiography may be less prone to some of the variability inherent in acquisition and analysis of tissue Doppler indices. Speckle tracking is based upon the movement of myocardial speckles in relation to each other, and effects such as extra-cardiac motion or angle of incidence are therefore not relevant. Variability may be introduced into image analysis by differences in the placement and width of the region of interest to be analysed, and then by the chosen strain peak to be measured. Miyazaki reported relatively low co-efficients of variation for inter-observer variability in measures of longitudinal strain (12.1% and 14.9% respectively for septal-lateral delay and 12 segment SD) but high variability for strain measures from the short axis view (88). Inter-observer variability for difference between earliest and latest segment for radial strain was
30.2%, and for circumferential strain 18.8%. Tanaka et al report intra- and inter-observer variability for radial strain of 10% and 17% respectively, for circumferential strain of 11% and 18% and for longitudinal strain of 13% and 19%. In this study intra-observer variability was least for radial strain and SD longitudinal strain, ICC 0.92 and 0.94, but intra-observer correlation for circumferential strain and septal-lateral delay by longitudinal strain was more modest at 0.61 and 0.54. Inter-observer correlation was relatively limited for radial and longitudinal strain, and extremely poor for circumferential strain.

Inter-ventricular dyssynchrony measured by pre-ejection period is less prone to variability in acquisition and analysis. The PROSPECT study reported relatively little intra- and inter-observer variability in the measurement of pre-ejection periods with coefficient of variation of 3.7% and 6.5% respectively (63). Miyazaki reported a mean difference of 5.6% for intra-observer and 5.9% for inter-observer variability of pre-ejection period measurement (88). Similarly low levels of intra- and inter-observer variability for these parameters were seen in the current study.

Variability in the image acquisition and analysis of echocardiographic dyssynchrony parameters is a significant problem, potentially limiting use of these parameters in a clinical setting. Relatively low levels of intra-observer variability for many parameters suggest that a single operator can produce reliable and therefore potentially meaningful results. However, a far greater degree of inter-observer variability in all but the most simply measured parameters suggests that expansion of the use of these parameters outside specialist centres and into ‘real-world’ echocardiography may be problematic. This was clearly demonstrated by the high levels of variability in acquisition and analysis of echocardiographic data seen in the PROSPECT study, which occurred despite core lab training in image acquisition and a pre-specified manual defining how echocardiographic data should be analysed. Zhang et al assessed the effect of a dedicated training program for tissue Doppler analysis of dyssynchrony parameters (174). They found that for two beginners who had received a short lecture, modest correlation with expert analysis in measurement of time to peak systolic velocities was seen, correlation coefficients
0.53 and 0.64. Analysis performed by graduates of a structured training program however produced a high degree of agreement with the expert, correlation coefficients 0.93 for both. Widespread training may therefore have a role in improving variability in the analysis of echocardiographic dyssynchrony parameters, provided a clear role for one or more parameters in the assessment of patients to receive CRT is defined.

6.8.5 Relationship between electrical and echocardiographic parameters
Early studies which characterized echocardiographic parameters of dyssynchrony reported a general trend for markers of both intra-ventricular and inter-ventricular dyssynchrony to increase with QRS duration. Haghjoo et al noted a relationship between QRS duration and inter-ventricular dyssynchrony, although no clear correlation between QRS duration and intra-ventricular dyssynchrony (30). Bleeke et al also report no relationship between QRS duration and septal-lateral delay by tissue Doppler (32), and Ghio et al confirm absence of correlation between QRS duration and intra-ventricular dyssynchrony, but a relatively strong correlation (r = 0.66) between QRS duration and inter-ventricular mechanical delay. In addition, Zakhama also reported no significant correlation between SPWMD and tissue Doppler parameters and QRS duration (36). Andrikopoulos et al studied the relationship between echocardiographic parameters and QRS duration as measured by signal-averaged ECG (SAECG), hypothesizing that signal-averaged ECG may better detect late depolarisation in the terminal portion of the QRS complex (175). Use of SAECG resulted in an overall reduction in mean QRS duration such that the proportion of patients with QRS >120ms was reduced from 73.5% to 60.4%. QRS duration by SAECG also correlated with inter-ventricular dyssynchrony, but not intra-ventricular dyssynchrony by septal-lateral delay. This study confirms these findings with significant correlations noted between QRS duration and left ventricular pre-ejection period and time to peak LV filling, but no significant correlation between QRS duration and right ventricular pre-ejection or filling times. Additionally only very limited correlations are seen between standard parameters of intra-ventricular dyssynchrony by tissue Doppler and 2D strain imaging and QRS duration. This suggests that increase in QRS duration is strongly associated with a global delay in left ventricular systolic
activation and subsequent diastolic filling, but not necessarily consistently associated with regional differences in timing of activation within the left ventricular myocardium.

Response to cardiac resynchronisation therapy is believed to arise from correction of delay in electrical and therefore mechanical activation of the posterolateral wall of the left ventricle, due to intra-cardiac conduction delay manifest as prolongation of the QRS complex on the surface ECG. As above, QRS duration and measures of intra-ventricular dyssynchrony show limited correlation and it is hypothesized that non-response may occur where conduction delay and QRS prolongation are not associated with underlying mechanical dyssynchrony. It has been demonstrated that left bundle branch block on the surface ECG is associated with a heterogeneous pattern of electrical activation of the posterolateral wall when assessed using intra-cardiac surface mapping. In particular relatively normal intra-cardiac activation sequences have been demonstrated in the presence of LBBB, suggesting absence of mechanical dyssynchrony despite LBBB, and perhaps explaining non-response to cardiac resynchronisation therapy, at least in part (28, 29). Echocardiography as a method of detecting mechanical dyssynchrony with the aim of more accurately identifying delayed activation of the posterolateral wall is a widely studied method for assessment of candidates for CRT. Studies examining the prevalence and nature of dyssynchrony have generally correlated QRS duration with a derived dyssynchrony parameter, for example IVMD or septal-lateral delay, rather than a single direct measure of posterolateral wall activation. Only very limited information is available which directly correlates echocardiography with the pattern of intra-cardiac electrical activation. In 2004 Fung et al studied seven patients with left ventricular systolic dysfunction and LBBB using concurrent intra-cardiac non-contact mapping and tissue Doppler echocardiography (29). Despite the presence of LBBB, three of seven patients had intact left bundle conduction with homogenous myocardial activation. This group demonstrated relatively little variation in mechanical activation times measured by tissue Doppler. The remaining patients demonstrated a specific site of conduction block, which was associated with more marked variation in time to peak velocity between myocardial segments, although no specific echocardiographic measures
were given. In 2007, a more detailed analysis of 23 patients was published by the same group (176). Homogenous electrical activation was seen in 8 of 23 patients, and conduction block in 15. Those with homogenous activation demonstrated a relatively limited response to CRT, and reverse remodelling was seen in only 2 of these 8 patients. In those with conduction block reverse remodelling was demonstrated in 12 of 15 patients. Tissue Doppler echocardiography was able to differentiate between the groups using the 12 segment SD method, latest activation tended to be seen in the mid-lateral segment. These studies suggest that LBBB is associated with conduction block and therefore delayed activation of the posterolateral wall of the left ventricle in roughly two-thirds of cases. One would therefore expect to see modest, but not extreme correlation between timing of posterior or lateral wall activation measured echocardiographically, and QRS duration. Parameters with the highest levels of correlation may be best placed to measure the delayed activation. Correlation between QRS duration and timing of posterior and lateral wall activation in the current study demonstrates the highest level of correlation between QRS duration and lateral longitudinal 2D strain. Relatively high correlation is also seen between short axis tissue Doppler timing of the posterior wall and radial strain in the lateral wall, findings consistent with the 2004 study by Fung et al.

Parameters of posterior wall activation derived by different echocardiographic modalities demonstrate significant, although only modest, correlation between measures of the same myocardial segment. This may reflect the relatively limited reproducibility of these parameters as discussed earlier, but may also represent variations in the specific aspect of myocardial mechanics measured by each modality. Tissue Doppler measures tend to be much shorter than those for M-mode motion or speckle tracking strain, reflecting the fact that peak myocardial velocity occurs shortly after depolarization, whereas greatest myocardial deformation occurs later in systole. The highest degree of correlation is seen between tissue Doppler M-mode and radial strain, as would be expected given these are measures of a relatively similar aspect of myocardial mechanics. Speckle tracking strain and velocity parameters correlate relatively poorly however, suggesting that the relationship between early systolic activation and peak deformation is not constant. Klemm et al demonstrated that in patients with
relatively normal electrical activation mechanical dyssynchrony was associated with slow wall motion with echocardiographic hypokinesia noted in the relevant segments (119). The authors hypothesise that this related to ischaemia or infarction affecting myocardial thickening in the relevant segment, however other factors such as loading conditions and the degree and location of any myocardial fibrosis present may also influence the relative timing of early and late systolic events. Myocardial fibres are arranged in a complex formation, with mid-myocardial fibres orientated circumferentially, and sub-endocardial and sub-epicardial layers orientated in an opposing helix running between base and apex. These layers are affected differently depending on the nature of the underlying disease process. In normal hearts electrical activation begins in the sub-endocardium near the apex in the septal region (177) and then spreads from apex to base and from sub-endocardium to sub-epicardium. In the presence of myocardial and conduction system disease, this activation pattern is likely to be disturbed and the relative influence of the exact site of conduction impairment and aetiology of heart failure may have differing impacts on measures of dyssynchrony by different modalities and in varying planes. Longitudinal strain measured from apical views is predominantly influenced by myocardial deformation occurring in the sub-endocardial and sub-epicardial layers, whereas circumferential strain measured in short axis views is mainly representative of deformation in the mid-myocardium. The relationship between electrical activation and measures of mechanical dyssynchrony is therefore complex and prone to change dependent upon several variables. This is likely to explain the relatively limited correlation seen between measures by different echocardiographic modalities, and suggests different modalities may be best suited to measure dyssynchrony in certain disease processes or patterns of systolic dysfunction, although changes in mechanical measures not directly related to abnormal electrical activation are likely not to be amenable to correction by CRT.

Study of the relationships between dyssynchrony parameters in this chapter suggests that lateral radial and longitudinal strain and short axis tissue Doppler of the posterior wall correlate best with QRS duration as an indirect measure of delayed posterolateral wall activation. Further study, ideally using intra-cardiac
electrical mapping concurrently with detailed echocardiographic assessment, is necessary to fully determine whether any single echocardiographic measure is truly representative of delays in electrical activation. Although lateral strain and short axis tissue Doppler measures of posterolateral wall activation show correlation with QRS duration, derived parameters involving these measures – eg. septal-lateral or septal-posterior delay – show much more limited correlation. This may be due to extra variability introduced into parameters by the use of measures from more than one segment, again reflecting the inherent inconsistency in determination of these measures.

Overall this chapter demonstrates participants recruited to this study are representative of patients with heart failure studied in previous reports of the effects of CRT in terms of both clinical and echocardiographic measures. We report that the feasibility of measurement of the parameters studied is relatively high, and intra-observer variability in measurement of M-mode and tissue Doppler parameters is relatively low. Intra-observer variability in speckle tracking parameters appears to be greater than that for tissue Doppler, and inter-observer variability for parameters other than pre-ejection periods from pulsed-wave Doppler appears to be sufficiently high enough to preclude routine clinical use, although this variability in analysis may be minimized by appropriate training. Correlation between dyssynchrony parameters appears to be relatively limited, most likely reflecting both inconsistencies introduced during image acquisition and analysis, and the variable effects of the disease process upon electrical activation and myocardial mechanics.
Chapter 7

Echocardiographic and Clinical Effect of Cardiac Resynchronisation Therapy

Echocardiographic Dyssynchrony Parameters and Response to Resynchronisation

7.1 Study Population
7.2 Effect of Cardiac Resynchronisation Therapy in All Patients
7.3 Echocardiographic Response
7.4 Clinical Response
7.5 Echocardiographic Dyssynchrony Parameters and Response to Cardiac Resynchronisation Therapy
7.6 Correlation Between Dyssynchrony Parameters and Reverse Remodelling
7.7 Dyssynchrony Parameters and Prediction of Response to Cardiac Resynchronisation Therapy
7.8 Survivors and Non-Survivors
7.9 Discussion
7.1 Study Population

Fifty-one patients underwent baseline assessment. Two patients died prior to planned CRT implantation and forty-nine patients therefore underwent CRT. Two patients failed to attend for follow-up assessment, and follow-up data is available on forty-seven patients. Of these patients, six died during the follow-up period (two suffered sudden death, three progressive heart failure and one suffered an extensive stroke), and one patient requested removal of the device due to complications. The deaths have been labelled echocardiographic and clinical non-responders. Paired clinical and echocardiographic follow-up data is therefore available on forty patients.

7.2 Effect of Cardiac Resynchronisation Therapy in All Patients

The overall effect of CRT on measures of clinical response after six months follow-up is shown below in table 7.1.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Six months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class</td>
<td>3.02 (0.36)</td>
<td>1.98 (0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6MW (m)</td>
<td>292.8 (83.5)</td>
<td>334.1 (97.3)</td>
<td>0.006</td>
</tr>
<tr>
<td>Qol total</td>
<td>48.9 (18.5)</td>
<td>33.6 (21.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Qol physical</td>
<td>23.4 (8.8)</td>
<td>17.5 (11.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Qol mental</td>
<td>11.9 (6.4)</td>
<td>7.2 (6.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 7.1: Effect of CRT upon clinical outcome measures (n=40)

CRT was associated with highly significant improvements in NYHA class and six minute walk distance, and marked reduction in total, physical and mental quality of life scores.
Changes in laboratory measures following CRT are shown below in table 7.2. No significant changes in laboratory measures of renal function or in haemoglobin were seen following CRT.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Six months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mmol/l)</td>
<td>10.3 (5.9)</td>
<td>11.2 (7.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>121.5 (55.2)</td>
<td>127.5 (48.3)</td>
<td>NS</td>
</tr>
<tr>
<td>eGFR (mls/min)</td>
<td>58.5 (20.8)</td>
<td>55.1 (21.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>13.2 (1.5)</td>
<td>12.9 (1.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 7.2: Changes in laboratory measures following CRT (n=40)

Table 7.3 on the following page shows changes in echocardiographic parameters of cardiac structure and function between baseline and follow-up for all participants. Significant reductions in all LV volume measures as well as increases in stroke volume, cardiac output, left ventricular filling time and global circumferential strain were seen. No significant changes were seen in myocardial performance index, myocardial systolic velocities, global longitudinal strain, mitral regurgitation or parameters of diastolic or right ventricular function.

7.3 Echocardiographic Response

Based on echocardiographic response criteria of ≥15% reduction in left ventricular end-systolic volume, 67.5% of patients were classified as echocardiographic responders. Comparative changes in LV volumes, parameters of LV function, mitral regurgitation, and markers of diastolic and right ventricular function between responders and non-responders are shown in table 7.4 on page 133.
<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>6 months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV volume diastole (mls)</td>
<td>199.3 (59.4)</td>
<td>168.1 (63.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV volume systole (mls)</td>
<td>149.4 (51.4)</td>
<td>110.9 (54.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>25.9 (7.1)</td>
<td>36.4 (11.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV diameter diastole (cm)</td>
<td>6.7 (0.9)</td>
<td>6.4 (1.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>11.4 (5.0)</td>
<td>17.1 (9.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke volume (mls)</td>
<td>65.4 (25.8)</td>
<td>76.1 (27.1)</td>
<td>0.042</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>4.1 (1.7)</td>
<td>4.9 (1.8)</td>
<td>0.014</td>
</tr>
<tr>
<td>3D volume diastole (mls)</td>
<td>204.7 (72.5)</td>
<td>175.2 (57.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>3D volume systole (mls)</td>
<td>157.9 (67.1)</td>
<td>122.5 (53.5)</td>
<td>0.015</td>
</tr>
<tr>
<td>3D ejection fraction (%)</td>
<td>24.4 (8.8)</td>
<td>28.8 (8.9)</td>
<td>0.035</td>
</tr>
<tr>
<td>LV MPI</td>
<td>0.76 (0.30)</td>
<td>0.66 (0.26)</td>
<td>NS</td>
</tr>
<tr>
<td>LA volume (mls)</td>
<td>97.7 (39.1)</td>
<td>105.7 (47.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Sphericity index</td>
<td>0.45 (0.11)</td>
<td>0.40 (0.09)</td>
<td>0.005</td>
</tr>
<tr>
<td>Systolic velocity – septum (cm/s)</td>
<td>3.0 (1.3)</td>
<td>3.4 (1.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic velocity – lateral (cm/s)</td>
<td>3.2 (1.4)</td>
<td>3.3 (1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Global circumferential strain (%)</td>
<td>7.7 (3.2)</td>
<td>10.1 (4.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Global longitudinal strain (%)</td>
<td>8.1 (2.6)</td>
<td>8.0 (3.0)</td>
<td>NS</td>
</tr>
<tr>
<td>MR regurgitant orifice area (mm²)</td>
<td>10.6 (10.2)</td>
<td>12.5 (14.3)</td>
<td>NS</td>
</tr>
<tr>
<td>MR regurgitant volume (mls)</td>
<td>18.2 (17.1)</td>
<td>19.8 (21.9)</td>
<td>NS</td>
</tr>
<tr>
<td>MR jet / LA area ratio</td>
<td>0.29 (0.23)</td>
<td>0.24 (0.16)</td>
<td>NS</td>
</tr>
<tr>
<td>E:A ratio</td>
<td>1.5 (1.1)</td>
<td>1.4 (1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>E:E’ ratio</td>
<td>22.2 (10.0)</td>
<td>24.3 (15.1)</td>
<td>NS</td>
</tr>
<tr>
<td>DFT:RR ratio</td>
<td>47.4 (9.2)</td>
<td>51.6 (7.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>RV dimension (cm)</td>
<td>3.3 (0.7)</td>
<td>3.3 (0.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary artery pressure (mmHg)</td>
<td>28.1 (10.5)</td>
<td>31.2 (11.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Tricuspid annular systolic velocity (cm/s)</td>
<td>6.8 (2.1)</td>
<td>6.8 (2.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 7.3:** Overall change in echocardiographic measures from baseline to follow-up for all participants (n=40)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responders (n=27)</th>
<th>Non-responders (n=13)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV volume diastole (mls)</td>
<td>197.6 (56.4)</td>
<td>147.5 (49.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV volume systole (mls)</td>
<td>148.4 (50.6)</td>
<td>92.1 (45.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>25.9 (7.0)</td>
<td>39.9 (11.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>10.8 (4.9)</td>
<td>19.0 (10.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke volume (mls)</td>
<td>65.7 (24.4)</td>
<td>82.3 (23.7)</td>
<td>0.015</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>4.0 (1.5)</td>
<td>5.3 (1.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>3D volume diastole (mls)</td>
<td>208.3 (79.4)</td>
<td>155.6 (45.6)</td>
<td>0.011</td>
</tr>
<tr>
<td>Sphericity index</td>
<td>0.44 (0.12)</td>
<td>0.38 (0.09)</td>
<td>0.013</td>
</tr>
<tr>
<td>LV myocardial performance index</td>
<td>0.78 (0.37)</td>
<td>0.67 (0.21)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic velocity – septum (cm/s)</td>
<td>3.0 (1.4)</td>
<td>3.6 (1.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic velocity – lateral (cm/s)</td>
<td>3.1 (1.2)</td>
<td>3.7 (1.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Global circumferential strain (%)</td>
<td>7.3 (3.0)</td>
<td>11.6 (4.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global longitudinal strain (%)</td>
<td>8.3 (2.6)</td>
<td>8.5(3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>MR regurgitant orifice area (mm²)</td>
<td>11.4 (11.0)</td>
<td>9.0 (10.3)</td>
<td>NS</td>
</tr>
<tr>
<td>MR regurgitant volume (mls)</td>
<td>19.9 (18.0)</td>
<td>12.9 (17.1)</td>
<td>NS</td>
</tr>
<tr>
<td>MR jet / LA area ratio</td>
<td>0.30 (0.20)</td>
<td>0.20 (0.15)</td>
<td>0.019</td>
</tr>
<tr>
<td>E:A ratio</td>
<td>1.3 (1.0)</td>
<td>1.3 (1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>E:E’ ratio</td>
<td>22.6 (9.5)</td>
<td>22.2 (12.8)</td>
<td>NS</td>
</tr>
<tr>
<td>DFT:RR</td>
<td>46.9 (10.0)</td>
<td>51.4 (7.0)</td>
<td>0.047</td>
</tr>
<tr>
<td>Pulmonary artery pressure (mmHg)</td>
<td>26.6 (9.4)</td>
<td>29.9 (11.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Tricuspid annular systolic velocity (cm/s)</td>
<td>6.9 (2.1)</td>
<td>6.9 (2.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 7.4:** Changes in selected echocardiographic parameters between baseline and follow-up in responders and non-responders (n=40)
Echocardiographic responders demonstrated significant improvement in all measures of LV volume and geometry, as well as increases in ejection fraction, fractional shortening, and global circumferential strain. Non-significant reduction in PISA measures of mitral regurgitation was seen, with significant reduction in mitral regurgitation measured by jet / LA area ratio. No changes in global longitudinal strain or measures of diastolic and right ventricular function were seen. In non-responders there were no significant changes in left ventricular volumes and geometry, or in parameters of right ventricular and diastolic function. There was a significant increase in mitral regurgitation in the non-responder group.

Table 7.5 shows comparison of the baseline clinical and electrical parameters between echocardiographic responders and non-responders:

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-responders</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>63.7 (13.3)</td>
<td>70.8 (10.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex M/F (%)</td>
<td>74.1 / 25.9</td>
<td>89.5 / 10.5</td>
<td>NS</td>
</tr>
<tr>
<td>Aetiology (%DCM)</td>
<td>55.5</td>
<td>26.3</td>
<td>0.047</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>155.4 (26.3)</td>
<td>144.4 (28.0)</td>
<td>NS</td>
</tr>
<tr>
<td>LBBB (%)</td>
<td>63.0</td>
<td>36.8</td>
<td>NS</td>
</tr>
<tr>
<td>QRS – LVEGM (ms)</td>
<td>144.9 (29.3)</td>
<td>150.6 (30.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 7.5: Baseline clinical and electrocardiographic differences between echocardiographic responders and non-responders (n=40)

Echocardiographic non-responders were significantly more likely to have ischaemic aetiology of left ventricular dysfunction. Non-responders also showed a tendency to be older (p=0.054), and have less typical LBBB morphology on baseline ECG (p=0.07), although these changes were not statistically significant.

7.4 Clinical Response

Clinical response as defined in study methods occurred in 28 of 46 patients (40 with paired data and 6 deaths) and clinical response rate was 60.9%. Clinical response
occurred in 61.5% of patients with ischaemic and 60% of patients with non-ischaemic cardiomyopathy (p=0.58). Changes in individual clinical measures between responders and non-responders are shown in table 7.6 on the following page. By definition, clinical responders demonstrated significant reduction in all parameters of clinical response.

7.4.1 Relationship of clinical to echocardiographic response
Echocardiographic and clinical response was seen in 22 patients (47.8%) and neither echocardiographic nor clinical response in 13 patients (28.3%). Six patients (13%) demonstrated clinical response without echocardiographic response, and five (10.9%) demonstrated echocardiographic but not clinical response. The echocardiographic changes in left ventricular volumes and ejection fraction in both clinical responders and non-responders are shown in table 7.7 on the following page.

Clinical responders demonstrated highly significant reduction in left ventricular volumes and increase in ejection fraction, however clinical non-responders also demonstrated significant reduction in end-systolic volume and increase in ejection fraction, although the absolute change was not as marked. When change in left ventricular volumes is compared between clinical responders and non-responders, there is no significant difference (table 7.8 below).

<table>
<thead>
<tr>
<th>Change in:</th>
<th>Responders</th>
<th>Non-responders</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV diastolic volume (mls)</td>
<td>35.6 (40.8)</td>
<td>21.1 (55.2)</td>
<td>NS</td>
</tr>
<tr>
<td>LV systolic volume (mls)</td>
<td>43.3 (36.2)</td>
<td>27.4 (41.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>11.5 (10.4)</td>
<td>8.3 (8.6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 7.8: Change in echocardiographic parameters in clinical responders and non-responders (n=40)

Within echocardiographic non-responders, left ventricular volumes and ejection fraction showed no significant differences between clinical responders and non-responders.
<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th></th>
<th>Non-Responders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Six months</td>
<td>p-value</td>
<td>Baseline</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.07 (0.38)</td>
<td>1.75 (0.52)</td>
<td>&lt;0.001</td>
<td>2.94 (0.42)</td>
</tr>
<tr>
<td>6-minute walk test (m)</td>
<td>315.0 (87.4)</td>
<td>368.3 (84.6)</td>
<td>0.001</td>
<td>253.3 (61.9)</td>
</tr>
<tr>
<td>Total QoL score</td>
<td>49.3 (19.5)</td>
<td>26.7 (17.3)</td>
<td>&lt;0.001</td>
<td>45.4 (20.1)</td>
</tr>
<tr>
<td>Physical QoL score</td>
<td>23.6 (9.0)</td>
<td>14.5 (9.9)</td>
<td>&lt;0.001</td>
<td>21.4 (9.4)</td>
</tr>
<tr>
<td>Mental QoL score</td>
<td>11.7 (6.5)</td>
<td>5.7 (5.6)</td>
<td>&lt;0.001</td>
<td>11.0 (6.9)</td>
</tr>
</tbody>
</table>

Table 7.6: Changes in clinical parameters in responders and non-responders (n=40)

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th></th>
<th>Non-Responders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Six months</td>
<td>p-value</td>
<td>Baseline</td>
</tr>
<tr>
<td>LV diastolic volume (mls)</td>
<td>206.9 (57.4)</td>
<td>171.3 (65.9)</td>
<td>&lt;0.001</td>
<td>181.7 (62.9)</td>
</tr>
<tr>
<td>LV systolic volume (mls)</td>
<td>154.5 (49.3)</td>
<td>111.1 (54.7)</td>
<td>&lt;0.001</td>
<td>137.7 (56.7)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>26.0 (7.3)</td>
<td>37.5 (12.2)</td>
<td>&lt;0.001</td>
<td>25.6 (6.8)</td>
</tr>
</tbody>
</table>

Table 7.7: Changes in echocardiographic parameters in clinical responders and clinical non-responders (n=40)
7.5 Echocardiographic Dyssynchrony Parameters and Response to Cardiac Resynchronisation Therapy

Comparison of baseline dyssynchrony parameters between echocardiographic responders and non-responders is shown below in table 7.9.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responders (n=27)</th>
<th>Non-responders (n=13)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inter-ventricular dyssynchrony:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV pre-ejection period (ms)</td>
<td>148.18 (35.6)</td>
<td>130.8 (27.9)</td>
<td>NS</td>
</tr>
<tr>
<td>IVMD (ms)</td>
<td>47.2 (33.9)</td>
<td>40.0 (23.3)</td>
<td>NS</td>
</tr>
<tr>
<td>RV-LV TDI (ms)</td>
<td>55.9 (62.7)</td>
<td>60.1 (54.3)</td>
<td>NS</td>
</tr>
<tr>
<td>IVFD (ms)</td>
<td>34.2 (117.9)</td>
<td>24.2 (86.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to peak RV filling (ms)</td>
<td>599.9 (84.9)</td>
<td>553.9 (88.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Time to peak LV filling (ms)</td>
<td>634.1 (89.7)</td>
<td>579.1 (55.6)</td>
<td>0.022</td>
</tr>
<tr>
<td><strong>Intra-ventricular dyssynchrony:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPWMD (ms)</td>
<td>210.3 (135.4)</td>
<td>190.6 (113.7)</td>
<td>NS</td>
</tr>
<tr>
<td>SPWMD TDI (ms)</td>
<td>172.2 (135.3)</td>
<td>162.3 (125.9)</td>
<td>NS</td>
</tr>
<tr>
<td>SeptPostSAX TDI (ms)</td>
<td>39.2 (57.8)</td>
<td>29.8 (85.0)</td>
<td>NS</td>
</tr>
<tr>
<td>SeptPostRad2DS (ms)</td>
<td>126.1 (177.3)</td>
<td>34.7 (199.0)</td>
<td>NS</td>
</tr>
<tr>
<td>6segmentRadial2DS</td>
<td>75.5 (47.2)</td>
<td>70.8 (43.5)</td>
<td>NS</td>
</tr>
<tr>
<td>SeptpostCirc2DS (ms)</td>
<td>88.0 (171.3)</td>
<td>125.1 (131.7)</td>
<td>NS</td>
</tr>
<tr>
<td>SeptLat TDI (ms)</td>
<td>48.7 (68.4)</td>
<td>86.9 (90.9)</td>
<td>NS</td>
</tr>
<tr>
<td>12segment TDI</td>
<td>45.7 (21.3)</td>
<td>43.5 (15.6)</td>
<td>NS</td>
</tr>
<tr>
<td>SeptLat2DS (ms)</td>
<td>117.8 (139.0)</td>
<td>96.6 (205.0)</td>
<td>NS</td>
</tr>
<tr>
<td>12segment2DS</td>
<td>79.3 (25.9)</td>
<td>93.9 (32.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to GCS (ms)</td>
<td>395.6 (73.1)</td>
<td>374.7 (52.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to GLS (ms)</td>
<td>448.9 (66.4)</td>
<td>421.6 (121.0)</td>
<td>NS</td>
</tr>
<tr>
<td>3D SDI</td>
<td>11.2 (5.5)</td>
<td>11.7 (6.0)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Atrio-ventricular dyssynchrony:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFT:RR ratio (%)</td>
<td>51.4 (7.0)</td>
<td>52.0 (7.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 7.9: Baseline dyssynchrony parameters in echocardiographic responders and non-responders (n=40)
Although there was a general trend towards higher values of baseline dyssynchrony in responders, no significant difference in any single baseline intra-ventricular dyssynchrony parameter was noted between the echocardiographic responder and non-responder groups. Conventional parameters of inter-ventricular dyssynchrony also showed no significant differences, left ventricular pre-ejection period and IVMD were slightly but not significantly longer in responders.

To further assess possible mechanisms of response and non-response changes in dyssynchrony parameters between baseline and follow-up were assessed in both responders and non-responders. This is shown in table 7.10 overleaf.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responders Baseline</th>
<th>Responders Six months</th>
<th>p-value</th>
<th>Non-responders Baseline</th>
<th>Non-responders Six Months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inter-ventricular dyssynchrony:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVPEP (ms)</td>
<td>148.2 (35.6)</td>
<td>141.5 (27.3)</td>
<td>NS</td>
<td>130.8 (27.9)</td>
<td>135.5 (28.7)</td>
<td>NS</td>
</tr>
<tr>
<td>RVPEP (ms)</td>
<td>100.9 (21.9)</td>
<td>119.2 (29.6)</td>
<td>0.005</td>
<td>90.7 (11.1)</td>
<td>121.4 (28.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>IVMD (ms)</td>
<td>47.2 (33.9)</td>
<td>22.3 (27.6)</td>
<td>0.002</td>
<td>40.0 (23.3)</td>
<td>14.1 (26.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Time to peak RV filling (ms)</td>
<td>599.9 (84.9)</td>
<td>583.4 (55.3)</td>
<td>NS</td>
<td>574.5 (100.5)</td>
<td>630.7 (133.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to peak LV filling (ms)</td>
<td>634.1 (89.7)</td>
<td>641.9 (75.8)</td>
<td>NS</td>
<td>592.6 (48.4)</td>
<td>613.3 (105.8)</td>
<td>NS</td>
</tr>
<tr>
<td>IVFD (ms)</td>
<td>34.2 (117.9)</td>
<td>58.5 (69.2)</td>
<td>NS</td>
<td>17.7 (102.5)</td>
<td>-17.4 (85.8)</td>
<td>NS</td>
</tr>
<tr>
<td>RV-LV TDI (ms)</td>
<td>55.9 (62.7)</td>
<td>39.1 (73.8)</td>
<td>0.016</td>
<td>60.1 (54.3)</td>
<td>65.3 (38.0)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Intra-ventricular dyssynchrony:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPWMD (ms)</td>
<td>216.3 (124.0)</td>
<td>35.8 (146.4)</td>
<td>0.003</td>
<td>170.1 (127.5)</td>
<td>52.9 (130.4)</td>
<td>NS</td>
</tr>
<tr>
<td>SPWMD TDI (ms)</td>
<td>176.1 (136.6)</td>
<td>34.1 (131.1)</td>
<td>&lt;0.001</td>
<td>188.3 (126.8)</td>
<td>11.8 (180.7)</td>
<td>NS</td>
</tr>
<tr>
<td>SeptPostRad 2DS (ms)</td>
<td>144.8 (4.3)</td>
<td>4.3 (90.2)</td>
<td>0.004</td>
<td>63.6 (172.1)</td>
<td>58.6 (113.8)</td>
<td>NS</td>
</tr>
<tr>
<td>6segment 2DS</td>
<td>78.7 (51.3)</td>
<td>42.5 (36.7)</td>
<td>0.012</td>
<td>64.7 (43.8)</td>
<td>52.7 (15.4)</td>
<td>NS</td>
</tr>
<tr>
<td>SeptPostCirc 2DS (ms)</td>
<td>91.6 (184.5)</td>
<td>21.6 (134.7)</td>
<td>NS</td>
<td>125.1 (131.7)</td>
<td>12.8 (114.4)</td>
<td>NS</td>
</tr>
<tr>
<td>SeptLat TDI (ms)</td>
<td>49.8 (73.9)</td>
<td>37.0 (63.6)</td>
<td>NS</td>
<td>92.8 (92.4)</td>
<td>69.7 (35.6)</td>
<td>NS</td>
</tr>
<tr>
<td>12segment TDI</td>
<td>46.8 (22.4)</td>
<td>34.2 (15.2)</td>
<td>0.01</td>
<td>43.0 (16.2)</td>
<td>41.2 (12.4)</td>
<td>NS</td>
</tr>
<tr>
<td>SeptLat 2DS</td>
<td>139.6 (144.5)</td>
<td>39.7 (98.1)</td>
<td>0.005</td>
<td>155.7 (144.9)</td>
<td>38.6 (85.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>12segment 2DS</td>
<td>77.6 (25.5)</td>
<td>61.3 (22.9)</td>
<td>0.006</td>
<td>93.1 (29.5)</td>
<td>70.4 (18.3)</td>
<td>0.014</td>
</tr>
<tr>
<td>Time to GCS (ms)</td>
<td>403.2 (81.9)</td>
<td>375.9 (51.8)</td>
<td>NS</td>
<td>375.7 (51.6)</td>
<td>370.4 (59.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to GLS (ms)</td>
<td>470.4 (70.0)</td>
<td>447.0 (97.0)</td>
<td>NS</td>
<td>423.3 (66.5)</td>
<td>419.9 (93.3)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Atrio-ventricular dyssynchrony:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFT:RR ratio (%)</td>
<td>46.9 (10.0)</td>
<td>51.4 (7.0)</td>
<td>0.047</td>
<td>45.1 (15.5)</td>
<td>52.0 (7.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 7.10: Changes in parameters of dyssynchrony in echocardiographic responders and non-responders following resynchronisation (n=40)
Significant changes in several radial parameters of dyssynchrony were seen in responders, as well as significant reduction in some parameters of long axis dyssynchrony. Diastolic filling time increased significantly in responders, and inter-ventricular mechanical delay was reduced consequent upon an increase in right ventricular pre-ejection period. Similar changes in inter-ventricular parameters were seen in the non-responder group with an increase in RV pre-ejection period, and associated reduction in inter-ventricular delay. However, although some changes in intra-ventricular dyssynchrony were seen in the non-responder group, these changes were not so marked as in the responder group.

In order to investigate whether the absolute value of change in dyssynchrony parameters following CRT is a factor in the likelihood or degree of response, the change in parameters between baseline and follow-up values were compared between responders and non-responders. No significant differences in the changes in any intra-ventricular dyssynchrony parameter was seen, or in IVMD or pre-ejection periods. Only parameters of ventricular filling demonstrated significant change from baseline to follow-up between responders and non-responders, shown below in table 7.11.

<table>
<thead>
<tr>
<th>Change in:</th>
<th>Responders</th>
<th>Non-responders</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time peak RV filling (ms)</td>
<td>16.5 (69.2)</td>
<td>-56.2 (85.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>Time peak LV filling (ms)</td>
<td>-7.8 (77.1)</td>
<td>-20.6 (85.6)</td>
<td>NS</td>
</tr>
<tr>
<td>IVFD (ms)</td>
<td>-24.3 (85.5)</td>
<td>35.1 (76.5)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

**Table 7.11**: Differences in the changes in dyssynchrony parameters from baseline to 6 months between responders and non-responders.
### 7.6 Correlation Between Dyssynchrony Parameters and Reverse Remodelling

In order to further assess the relationship between measures of baseline dyssynchrony and response, and also between change in dyssynchrony measures following resynchronisation and response, correlation coefficients were performed between baseline parameters of dyssynchrony and the change in LV systolic volume at follow-up, and between the changes in dyssynchrony parameters and LV systolic volume. Correlations between baseline dyssynchrony and reverse remodelling are shown in table 7.12 below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation co-efficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVPEP</td>
<td>0.31</td>
<td>0.05</td>
</tr>
<tr>
<td>LVPEP</td>
<td>0.43</td>
<td>0.005</td>
</tr>
<tr>
<td>IVMD</td>
<td>0.34</td>
<td>0.032</td>
</tr>
<tr>
<td>Time to pk LV filling</td>
<td>0.40</td>
<td>0.009</td>
</tr>
<tr>
<td>SPWMD</td>
<td>0.39</td>
<td>0.018</td>
</tr>
<tr>
<td>SPWMD_TDI</td>
<td>0.41</td>
<td>0.012</td>
</tr>
<tr>
<td>SepPostRad_2DS</td>
<td>0.229</td>
<td>NS</td>
</tr>
<tr>
<td>6segRad_2DS</td>
<td>0.301</td>
<td>NS</td>
</tr>
<tr>
<td>SepPostCirc_2DS</td>
<td>0.19</td>
<td>NS</td>
</tr>
<tr>
<td>SepLateral_2DS</td>
<td>-0.011</td>
<td>NS</td>
</tr>
<tr>
<td>12segment_2DS</td>
<td>-0.09</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 7.12:** Correlation of baseline dyssynchrony parameters with degree of reverse remodelling

No significant correlation was seen between baseline values for time to peak RV filling, 3D SDI, DFT:RR ratio, septal-lateral delay, 12 segment TDI and RV-LV\_TDI. Modest correlations were seen with other parameters, in particular baseline left ventricular pre-ejection period, time to peak LV filling, SPWMD and SPWMD\_TDI. No speckle tracking parameters demonstrated significant correlation between baseline dyssynchrony and reverse remodelling. Correlation between the change in dyssynchrony parameters and reverse remodelling are shown overleaf in table 7.13.
Table 7.13: Correlation between change in dyssynchrony parameters and degree of reverse remodelling

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation co-efficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVPEP</td>
<td>-0.17</td>
<td>NS</td>
</tr>
<tr>
<td>LVPEP</td>
<td>0.29</td>
<td>NS</td>
</tr>
<tr>
<td>IVMD</td>
<td>0.086</td>
<td>NS</td>
</tr>
<tr>
<td>SPWMD</td>
<td>0.22</td>
<td>NS</td>
</tr>
<tr>
<td>SPWMD&lt;sub&gt;TDI&lt;/sub&gt;</td>
<td>0.32</td>
<td>NS</td>
</tr>
<tr>
<td>SepPostRad&lt;sub&gt;2DS&lt;/sub&gt;</td>
<td>0.41</td>
<td>0.021</td>
</tr>
<tr>
<td>6segRad&lt;sub&gt;2DS&lt;/sub&gt;</td>
<td>0.39</td>
<td>0.033</td>
</tr>
<tr>
<td>SepPostCirc&lt;sub&gt;2DS&lt;/sub&gt;</td>
<td>0.028</td>
<td>NS</td>
</tr>
<tr>
<td>SepLateral&lt;sub&gt;2DS&lt;/sub&gt;</td>
<td>0.058</td>
<td>NS</td>
</tr>
<tr>
<td>12segment&lt;sub&gt;2DS&lt;/sub&gt;</td>
<td>-0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

No significant correlation was seen between reverse remodelling and changes in 3D SDI, DFT:RR, IVFD and TDI measures. Very modest and non-significant correlations were noted with change in LVPEP (r=0.29, p 0.065), time to peak RV filling (r=0.28, p 0.082) and SPWMD<sub>TDI</sub> (r=0.32, p 0.07). Significant although still modest correlations were seen with reduction in radial strain parameters by speckle tracking.

7.7 Dyssynchrony Parameters and Prediction of Response to Cardiac Resynchronisation Therapy

The role of echocardiographic dyssynchrony parameters in the prediction of response to CRT was assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) and sensitivity and specificity at appropriate cut-off values are reported.
7.7.1 Prediction of echocardiographic response

The parameters with the greatest value in the prediction of echocardiographic response were parameters of inter-ventricular dyssynchrony and timing of ventricular filling. ROC curve for LV pre-ejection period (Figure 7.1) is shown below and curves for time to peak RV filling (Figure 7.2) and time to peak LV filling (Figure 7.3) on the following page.

Area under curve 0.683 At cut-off of 140ms:
Sensitivity 55.6%
Specificity 73.7%

Figure 7.1: ROC curve for prediction of echocardiographic response - left ventricular pre-ejection period
Area under curve 0.677 At cut-off 545ms
Sensitivity 81.5%
Specificity 55.6%

**Figure 7.2**: ROC curve for prediction of echocardiographic response - time to peak right ventricular filling

Area under curve 0.708 At cut-off 602ms
Sensitivity 70.4%
Specificity 68.4%

**Figure 7.3**: ROC curve for prediction of echocardiographic response - time to peak left ventricular filling
For parameters of intra-ventricular dyssynchrony the greatest area under the curve was seen for septal-lateral delay by longitudinal 2D strain. The ROC curve for this parameter is shown below (Figure 7.4).

Poor predictive values were found for SPWMD, SPWMD_{TDI}, septal-lateral tissue Doppler, septal-posterior wall delay by circumferential strain, 12 segment 2D strain, and 3D SDI, all had AUC <0.55. Area under the curve, sensitivity and specificity values for the remaining parameters are shown overleaf in table 7.14, which have modest value in the prediction of echocardiographic response. Speckle tracking parameters do not appear to provide additional value in the prediction of response compared to established M-mode and tissue Doppler parameters, and very few echocardiographic parameters had an AUC better than that for QRS duration alone.

![ROC curve for prediction of echocardiographic response - septal-lateral delay by 2D longitudinal strain](image)

<table>
<thead>
<tr>
<th>Area under curve</th>
<th>0.578</th>
</tr>
</thead>
<tbody>
<tr>
<td>At cut off 68ms</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>71.4%</td>
</tr>
<tr>
<td>Specificity</td>
<td>50.0%</td>
</tr>
</tbody>
</table>

**Figure 7.4:** ROC curve for prediction of echocardiographic response - septal-lateral delay by 2D longitudinal strain
<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVMD</td>
<td>0.604</td>
<td>48.1%</td>
<td>57.9%</td>
</tr>
<tr>
<td>Cut off 40ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFT:RR ratio</td>
<td>0.579</td>
<td>70.4%</td>
<td>47.4%</td>
</tr>
<tr>
<td>Cut off 42%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 segment TDI</td>
<td>0.565</td>
<td>66.7%</td>
<td>31.6%</td>
</tr>
<tr>
<td>Cut off 32ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal-post radial strain</td>
<td>0.585</td>
<td>60%</td>
<td>62.5%</td>
</tr>
<tr>
<td>Cut off 130ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 segment radial strain</td>
<td>0.567</td>
<td>73%</td>
<td>50%</td>
</tr>
<tr>
<td>Cut off 51ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration</td>
<td>0.63</td>
<td>92.6%</td>
<td>21.1%</td>
</tr>
<tr>
<td>Cut off 120ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cut off 150ms</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 7.14**: AUC, sensitivity and specificity values for selected echocardiographic and ECG parameters in prediction of echocardiographic response to CRT

### 7.7.2 Prediction of clinical response

Overall parameters of inter-ventricular dyssynchrony and ventricular filling were also associated with greatest value in prediction of clinical response, although intra-ventricular dyssynchrony by 12 segment tissue Doppler was associated with the single highest value for area under the curve. The ROC curve for 12 segment TDI is shown overleaf (Figure 7.5) and AUC, sensitivity and specificity values for other parameters with AUC >0.55 are shown in table 7.15 on page 148.
Area under curve  0.692  At cut-off 32 ms
Sensitivity  78.6%
Specificity  50.0%

**Figure 7.5:** ROC curve for prediction of clinical response - 12 segment tissue Doppler
Table 7.15: AUC, sensitivity and specificity values for selected echocardiographic and ECG parameters in prediction of clinical response to CRT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVMD</td>
<td>0.568</td>
<td>46.4%</td>
<td>55.6%</td>
</tr>
<tr>
<td>Time to peak RV filling</td>
<td>0.623</td>
<td>75.0%</td>
<td>47.1%</td>
</tr>
<tr>
<td>Time to peak LV filling</td>
<td>0.612</td>
<td>46.4%</td>
<td>61.1%</td>
</tr>
<tr>
<td>DFT:RR ratio</td>
<td>0.617</td>
<td>75.0%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Septal-lateral TDI</td>
<td>0.573</td>
<td>42.9%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Septal-post circ strain</td>
<td>0.595</td>
<td>78.6%</td>
<td>46.7%</td>
</tr>
<tr>
<td>Septal-lateral 2DS</td>
<td>0.595</td>
<td>69.6%</td>
<td>50.0%</td>
</tr>
<tr>
<td>QRS duration</td>
<td>0.574</td>
<td>92.9%</td>
<td>22.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53.6%</td>
<td>50.0%</td>
</tr>
</tbody>
</table>

7.7.3 Multivariate analysis
Multivariate analysis demonstrated no significant independent predictors of response to CRT. Aetiology of heart failure was the closest parameter to reaching significance, non-ischaemic aetiology odds ratio for echocardiographic response of 3.5 (0.98 – 12.5) p=0.054.

7.8 Survivors and Non-Survivors
Six patients died during the six month period following CRT implant; 5 deaths were cardiac in origin (2 sudden death and 3 progressive heart failure), and one death was due to stroke. The baseline echocardiographic characteristics of the patients who
died were compared to survivors to evaluate any differences in cardiac function or levels of baseline dyssynchrony between survivors and non-survivors. No significant differences in left ventricular volumes, ejection fraction, diastolic function or right ventricular size and function were seen between survivors and non-survivors. No significant differences in inter- or intra-ventricular dyssynchrony parameters were seen. Non-survivors had significantly shorter left ventricular filling times than survivors, perhaps reflecting a higher heart rate in this group (mean baseline heart rate in survivors 63 beats/min, non-survivors 82 beats/min), although the ratio of LV filling to cardiac cycle time was also significantly less in non-survivors (47.8 (9.1) in survivors vs 37.7 (4.9) in non-survivors, p=0.01), suggesting there was greater impairment of left ventricular filling time in non-survivors.

7.9 Discussion

This chapter has presented a detailed clinical and echocardiographic assessment of the response to cardiac resynchronisation therapy. Overall, marked improvement in clinical measures were seen following CRT, and as a whole the study population demonstrated evidence of significant reverse remodelling at follow-up, with reduction in left ventricular volumes and increase in ejection fraction. Discordance was apparent between clinical and echocardiographic response, with clinical non-responders demonstrating similar improvement in echocardiographic measures to clinical responders, and echocardiographic responders demonstrating similar echocardiographic changes whether clinical response was present or not. This suggests the mechanisms underlying clinical and echocardiographic response are not necessarily the same, perhaps because placebo effect plays a role in clinical response. Echocardiographic responders also demonstrated changes in several other echocardiographic parameters, including measures of mitral regurgitation, left ventricular filling time and global circumferential strain. Significant worsening of mitral regurgitation was noted in echocardiographic non-responders. Although
global circumferential strain was seen to increase only in responders, global longitudinal strain did not change in either group. Measures of echocardiographic dyssynchrony did not appear to be helpful in the prediction of response to cardiac resynchronisation. Although an overall trend towards greater dyssynchrony in echocardiographic responders was seen, no significant baseline differences in dyssynchrony parameters were demonstrated between responders and non-responders, and ROC curve analysis suggested that no single parameter had sufficient value at prediction of response to be clinically useful. However, changes in dyssynchrony parameters following resynchronisation do provide insights into the mechanism of response to resynchronisation. Reduction in inter-ventricular dyssynchrony was seen in both echocardiographic responders and non-responders, whereas more marked changes in intra-ventricular dyssynchrony were seen in responders compared to non-responders.

7.9.1 Overall response to cardiac resynchronisation therapy
Cardiac resynchronisation therapy is a widely studied treatment for heart failure and the expected clinical and echocardiographic response is now well documented. The overall response to cardiac resynchronisation therapy in this study was comparable to previous reports. The MIRACLE study, one of the first randomised CRT studies, reported an improvement in heart failure symptoms by at least one NYHA class in 68% of patients undergoing CRT, compared with 38% in the medical therapy group (23). This study also demonstrated a median increase in six minute walk distance of 39 metres, and reduction in the Minnesota QoL score by -18 points. These results are comparable to the mean NYHA class reduction of 1.04 attributable to CRT in this study, as well as the mean 41.3 metre increase in 6 minute walk distance and 15.3 point reduction in total QoL score.

In terms of echocardiographic response, varying degrees of reverse remodelling have been reported following CRT. Yu et al report a reduction in end-diastolic volume from 179mls to 156mls after 3 months of CRT (69). End-systolic volume reduced from 136mls to 107mls, and ejection fraction increased from 25.9% to 33.9%, values similar to the results reported in this study. Bax reported more
modest, although statistically significant, reductions in volume following six months of CRT. In his 2004 study LV end-diastolic volume fell from 259mls to 237mls and end-systolic volume from 201mls to 173mls (53). Left ventricular ejection fraction in the study increased from 23% to 28%, the more modest remodelling perhaps reflecting the higher volumes and more severe left ventricular dysfunction present before CRT in this cohort of patients. Overall the results of CRT in the current study appear to be representative of the effects of CRT in previously reported studies.

7.9.2 The issue of definition of response

There remains no agreed definition to determine response to CRT, and numerous methods for classification of response have been reported previously. It is important to highlight that response and outcome are not necessarily the same. Very few studies have reported outcome data for CRT. The CARE-HF and COMPANION studies demonstrated reduction in mortality attributable to CRT, and the 2007 NICE Technology Appraisal reported that for 50 year olds the median survival increase attributable to CRT was 23% (178). Markers of response reported in non-outcome studies do not necessarily equate with prognostic benefit. Yu examined the relationship of clinical and echocardiographic parameters of response and outcome (169). This study demonstrated that echocardiographic remodelling following CRT was associated with improved survival, but that no changes in clinical parameters following CRT were able to predict outcome.

Response to CRT may be classified as echocardiographic, clinical or a combination of the two. Reduction ≥15% in left ventricular end-systolic volume, used as the measure of echocardiographic response in this study, has become a widely adopted method for classification of echocardiographic response, although changes in ejection fraction, diastolic volume, and left ventricular diameter have also been used. Fornwalt et al examined relationships between 17 different parameters of response across 26 studies, and found very poor correlations between the different measures (179). Antonio et al demonstrated that of several echocardiographic definitions, change in ejection fraction correlated best with improvement in VO₂ max measured by cardiopulmonary exercise testing, although high levels of discordance were seen.
between echocardiographic and metabolic improvement (27). Bleeker et al reported that measures of clinical response including NYHA class, six minute walk test and QoL score correlate well with each other, and that agreement in classification of response and non-response was present between clinical and echocardiographic parameters on 76% of occasions (180). Reported clinical response rates are generally higher than echocardiographic response, and disagreement between clinical and echocardiographic classifications mainly occurs where patients respond clinically without meeting a pre-defined echocardiographic end-point. This suggests that clinical response may be associated with a spectrum of echocardiographic response. A clinical responder may not meet a pre-determined echocardiographic cut-off point, however the degree of change in echocardiographic parameters between clinical responders and clinical non-responders who do not show echocardiographic response may be different. In this study we examined the differences in echocardiographic remodelling between clinical responders and non-responders in those classified as echocardiographic non-responders. No significant differences were found between the remodelling characteristics of clinical responders and non-responders, suggesting that the mechanism of clinical response in these cases is not related to any beneficial effect on ventricular remodelling. This suggests the mechanisms involved in clinical and echocardiographic response are not the same. Placebo effect may of course play a significant role here and clinical response in the absence of echocardiographic response may be nothing more than this (181). Discrepancies between echocardiographic and clinical response may be avoided by the use of a combined clinical and echocardiographic end-point, although the acknowledgement that echocardiographic and clinical response are different in mechanism means a combined end-point risks losing the echocardiographic relationship between response and outcome, and diluting any data which may assess potential differences in the mechanism of echocardiographic and clinical response. Although it is clearly attractive from a methodological point of view to classify patients as responders or non-responders, response to CRT is likely to represent a spectrum of response encompassing complex interactions in the changes between clinical improvement, echocardiographic improvement and prognosis.
7.9.3 Echocardiographic response to resynchronisation

In addition to evidence of reverse remodelling and increase in ejection fraction seen following CRT, resynchronisation is associated with numerous other changes detectable echocardiographically which have been examined in the current study. Change in several parameters confirming reverse left ventricular remodelling were seen, including left ventricular diameter, fractional shortening, left ventricular sphericity index and left ventricular volumes measured using 3D echo. Stroke volume and cardiac output also increased significantly. In a detailed echocardiographic study of the effects of CRT, similar findings were reported by St John Sutton et al (182). In addition to volumetric parameters and measures of cardiac output, this study reported significant reduction in mitral regurgitation, and improvements in left ventricular filling time and myocardial performance index. In the current study no significant overall change in mitral regurgitation measured by either jet area or PISA method was seen. Left ventricular MPI was also unchanged, although significant increase in left ventricular filling time was seen.

Changes in more detailed parameters of left ventricular systolic function have also been reported following resynchronisation. Bax et al report significant increases in septal and lateral wall systolic velocities following CRT, a change not reproduced in the overall results of the current study. In a comprehensive study of left ventricular mechanics before and after CRT using tissue Doppler and speckle tracking, Zhang et al noted significant improvement in circumferential strain following CRT, but no significant changes in measures of longitudinal function by either systolic velocities or 2D strain (183), findings reproduced by the current study. Kaufman et al also report similar findings, with significant increases in parameters of radial and circumferential strain following CRT, but not longitudinal strain (184). The explanation for these changes is unclear. Circumferential strain is predominantly influenced by mid-myocardial fibres arranged circumferentially, whereas longitudinal function is predominant upon sub-endocardial and sub-epicardial fibres, arranged in an opposing helical structure. Fibres are affected differently by the underlying disease process, with ischaemia tending to result in sub-endocardial abnormalities, and fibrosis due to myopathic processes predominantly affecting the
mid-myocardial circumferential layer when examined using magnetic resonance imaging (185). Circumferential fibres may be more prone to dysfunction in the presence of abnormal electrical activation, and more amenable to improvement with normalisation of activation, or longitudinal fibres may be abnormal in advanced heart failure to such an extent that they are unable to improve. This requires further investigation.

7.9.4 Responders and non-responders
Echocardiographic response defined by $\geq$15% reduction in left ventricular end-systolic volume occurred in 67.5% of patients. This is comparable to the rate of echocardiographic response reported in previous studies. By definition, echocardiographic responders demonstrated significant reduction in left ventricular systolic volume, associated with significant reductions in diastolic volume and increases in ejection fraction, stroke volume and cardiac output. Volumes measured by 3D echo also reduced significantly in responders but not non-responders. Echocardiographic response was associated with changes in other parameters of left ventricular function. Global circumferential strain improved significantly in echocardiographic responders, but not in non-responders, however global longitudinal strain showed no change in either. As discussed above, the mechanism for this remains unclear. There was a trend towards improvement in myocardial systolic velocities in the responder group (septal $p=0.16$, lateral $p=0.11$), but no change in the non-responder group.

Mitral regurgitation worsened significantly in the non-responder group over 6 months of follow-up, whereas there was a significant reduction in mitral regurgitation measured by the jet area method in responders, and a trend towards reduction in regurgitation quantified by the PISA method. Left ventricular filling time improved significantly in both responders and non-responders. No significant changes in diastolic function by E:A or E:E’ ratio or in parameters of right heart structure and function were seen between responders and non-responders. Echocardiographic responders were more likely to have a non-ischaemic aetiology of heart failure, and although QRS duration was not significantly different between
the groups QRS morphology showed a relevant although non-significant trend; 63.0% of responders having typical LBBB pattern on the ECG versus only 36.8% in non-responders (p=0.07). These findings are consistent with previous studies. Zhang et al demonstrated that ischaemic aetiology of heart failure was associated with a higher rate of death and hospitalisation than non-ischaemic aetiology following CRT (186). Analysis of data from the CARE-HF study also demonstrated a lesser degree of reverse remodelling in patients with ischaemic compared to non-ischaemic aetiology, although outcomes remained similar between the two groups (187). Left bundle branch block morphology, as opposed to non-specific intra-ventricular conduction delay has also been shown to be associated with greater response to CRT. Rickard et al demonstrated greater improvements in left ventricular dimensions and ejection fraction in those with LBBB compared to RBBB or non-specific intra-ventricular conduction delay, although no difference in mortality between the groups (188).

7.9.5 Dyssynchrony parameters before resynchronisation therapy
Numerous studies have argued that the presence of mechanical dyssynchrony detected by echocardiography has greater power for the prediction of response to CRT than QRS duration alone. Studies have predominantly been single centre and conducted by renowned experts. The only multi-centre trial of echocardiographic parameters to date reported very disappointing results (63). Several investigators have reported specific cut-off values for echocardiographic parameters in prediction of response to resynchronisation, claiming greater sensitivity and specificity in the use of these values than for the ECG.

Pitzalis reported that SPWMD was able to almost completely separate responders and non-responders, with baseline values for SPWMD of 246ms in echocardiographic responders, and 110ms in non-responders, claiming an area under the curve by receiver operating characteristic curve of 0.95 (39). The current study did not demonstrate any significant baseline difference in SPWMD between responders and non-responders (210.3ms vs 190.6ms, p=0.68). SPWMD measured by colour M-mode TDI has been reported to be more reproducible than SPWMD by
grey scale imaging (46), and equally predictive of response (47), however no significant baseline differences between responders and non-responders were seen in our patients. Sensitivity and specificity values derived from ROC curve analysis also suggested no useful role for M-mode parameters in the prediction of response. Bax and Yu have both been strong proponents for the use of tissue Doppler parameters in the assessment of patients undergoing CRT. Bax proposed the use of septal-lateral delay in 2003, subsequently reporting a sensitivity and specificity of 92% for the prediction of echocardiographic response to CRT (53). In the current study septal-lateral delay by TDI appears to have no role in the prediction of response to CRT; there is no significant baseline difference between responders and non-responders, and indeed delay actually appears to be higher in non-responders (48.7ms vs 86.9ms, p=0.17). Yu reported the use of an index composed by the standard deviation of time to peak systolic velocity in 12 myocardial segments in 2003 (50). The report states that the 12 segment index was able to entirely differentiate responders from non-responders at a cut-off of 32.6ms, a sensitivity and specificity of 100%. Our study again fails to demonstrate the usefulness of the 12 segment index in prediction of response. Baseline values for the index are not significantly different between echocardiographic responders and non-responders, with a mean value in all patients appearing to be significantly above the proposed cut-off value (45.7ms vs 43.5ms, p=NS). ROC curve analysis suggested that both septal-lateral delay and the 12 segment index were not associated with greater sensitivity or specificity for prediction of echocardiographic response than QRS duration.

Parameters of inter-ventricular dyssynchrony have also been shown to have some role in the prediction of response to CRT. Wiesbauer et al reported that aortic pre-ejection interval and IVMD were able to predict response to CRT at cut-off values of 140ms and 60ms respectively (62). Although the values were significantly different between responders and non-responders, ROC analysis demonstrated relatively modest predictive value with AUC of 0.63 for aortic pre-ejection interval, and 0.61 for IVMD. Aksoy et al also report useful predictive value for aortic pre-ejection interval (61). This study reports a rather unconventional cut-off value of 180.5ms,
yielding a sensitivity of 92.3% but a not very helpful specificity of 39%. Interestingly although LV pre-ejection period was seen as a predictor in this study IVMD was not significantly different between responders and non-responders, suggesting co-existing prolongation of the RV pre-ejection period in responders, certainly not the typical pattern generally described in this setting. Lafitte et al report relatively limited predictive value for LV pre-ejection period alone, but increased sensitivity and specificity when combined in a multi-parametric strategy (110).

Bordachar reports poor predictive value of simple echocardiographic parameters including LV pre-ejection period and IVMD with high levels of overlap between responders and non-responders (189). Baseline values of IVMD in the current study were not significantly different between responders and non-responders. Baseline values of LV pre-ejection period showed a trend towards longer values in responders (148.2 vs 130.8, p-0.13), and time to left ventricular peak filling was significantly longer in responders, a value which was shown in the previous chapter to highly correlate with IVMD and QRS duration. Although ROC curve analysis in our study demonstrated an area under the curve slightly greater than that of the Weisbauer study, the related sensitivity and specificity values suggest that these parameters do not add significantly to QRS duration for prediction of echocardiographic response. Inter-ventricular dyssynchrony measured by tissue Doppler also showed no significant difference between responders and non-responders, as previously shown by Bax et al (51).

Overall the current study suggests that tissue Doppler intra-ventricular dyssynchrony parameters do not appear to have a role in the prediction of response to CRT, and that the role of inter-ventricular dyssynchrony parameters is fairly limited. Similar findings have been reported by Kuppahally (99), who demonstrated no significant difference in tissue Doppler or 3D echo dyssynchrony parameters between responders and non-responders. Miyazaki et al also reported poor predictive value of Doppler and tissue Doppler parameters (88), noting only M-mode measurements had an AUC above the line of no information by ROC curve analysis, and even so the predictive value remained limited. These two reports and the current study appear to confirm the results of the PROSPECT study which demonstrated very limited utility.
for the use of M-mode, Doppler and tissue Doppler parameters in the prediction of response to CRT (63).

Tissue Doppler performed in the short axis view for the calculation of time to peak systolic velocity in the septum and posterior wall has not been widely evaluated. Whilst no significant differences were found in baseline measures between responders and non-responders, Parsai et al reported that the utility of short axis tissue Doppler lay in the identification of specific patterns of velocity profiles in the identification of the septal flash (45). This will be discussed in the following chapter.

Several studies have reported on the utility of speckle tracking strain parameters for the prediction of response to CRT. Tanaka et al reported in the STAR study that dyssynchrony identified by radial or transverse strain was predictive of response to CRT (82), although not circumferential or longitudinal strain. Radial strain had the greatest value, with a reported sensitivity of 86% and specificity of 67%. Tatsumi reported a strain index derived from the mean difference between peak and end-systolic strain for 6 short axis or 18 long-axis segments (81). The radial strain index provided the best predictive value, with AUC of 0.87. Delgado et al also report septal-posterior wall delay by radial strain to predict response (AUC 0.88), but not circumferential strain. (79) Conversely, Artis report the value of circumferential strain in prediction of response (83), specifically that the time delay in peak circumferential strain between the anterior and inferior walls is associated with an AUC of 0.89. Contrary to these studies, two further studies report the poor predictive power of speckle tracking parameters. Miyazi et al report that no speckle tracking parameters were associated with an AUC above the line of no information (88), and Knebel et al also report that 2D strain measures failed to predict response (55). The utility of speckle tracking parameters in the prediction of response to CRT therefore remains unclear. Results from the current study are consistent with the reports of Miyazaki and Knebel, in that no significant differences between responders and non-responders were found in the baseline speckle tracking parameters of dyssynchrony measured. Septal-posterior wall delay by radial strain would appear to be different from a glance at the mean values (126.1ms vs 34.7ms).
however the statistical difference between these values is hampered by the high standard deviations of the parameter, perhaps reflecting relatively limited reliability of the measure, and ROC curve analysis confirms the limited overall value of this parameter.

In addition to the assessment of baseline differences in dyssynchrony parameters between responders and non-responders and the use of these parameters in prediction of response, we also assessed any relationship between the degree of baseline dyssynchrony measured and the extent of left ventricular reverse remodelling. This demonstrated only very limited correlations between baseline dyssynchrony measures and the extent of remodelling, again suggesting the mechanism of response to CRT is complex, and different between patients.

### 7.9.6 Dyssynchrony parameters after resynchronisation therapy

Although the data presented suggest that echocardiographic dyssynchrony parameters do not have a helpful role in the assessment of likelihood of response to CRT, change in dyssynchrony parameters following resynchronisation may still provide insight into the mechanism of response to resynchronisation therapy. Study of the changes in dyssynchrony parameters following resynchronisation in both responders and non-responders demonstrates that parameters of inter-ventricular dyssynchrony tend to improve in both responders and non-responders. Marked reduction in IVMD is seen in both groups, predominantly as a consequence of prolongation of the RV pre-ejection period rather than shortening of the LV pre-ejection period. The relationship between left and right ventricular filling also appears to be different between responders and non-responders. Responders demonstrate a slight reduction in time to peak RV filling with consequent (although not significant) increase in the offset between right and left ventricular filling (with RV filling first). Non-responders demonstrate a marked (and significant) increase in time to peak RV filling, leading to a reversal in the offset between LV and RV filling (with LV filling first). The degree of change in the LV-RV offset is significantly different between responders and non-responders, as is the degree of
change in RV pre-ejection period. The potential relevance of these apparent changes in ventricular inter-action will be explored further in the following chapter.

Several parameters of intra-ventricular dyssynchrony appear to improve in responders. Marked reductions in SPWMD and SPWMD_{TDI} are seen, as well as significant improvements in other parameters of radial dyssynchrony measured by 2D strain. Radial dyssynchrony measured by TDI does not reduce significantly. Changes in parameters of longitudinal dyssynchrony in responders in the current study were variable. Septal-lateral delay by TDI does not change significantly, however septal-lateral delay by speckle tracking shows marked and significant reduction, and 12 segment dyssynchrony models by both TDI and speckle tracking also show significant reduction in the responder group. Bleeker et al suggested that resynchronisation of intra-ventricular dyssynchrony as measured by septal-lateral delay was mandatory for response to CRT (150), with no significant change in intra-ventricular dyssynchrony seen in non-responders. Correlation between reduction in dyssynchrony and reverse remodelling was relatively modest however (r=0.4).

Conversely, Celikyurt et al demonstrated similar degree of reduction in tissue Doppler measures of long-axis dyssynchrony in both responders and non-responders (151). Gorscan et al also argue that resynchronisation is the predominant mechanism of response to CRT, although appear to base their argument solely on the above study by Bleeker et al (190).

Some changes in intra-ventricular dyssynchrony are also seen in the non-responder group, although these changes appear to be less marked. SPWMD and SPWMD_{TDI} both appear to reduce in the non-responder group, although not significantly so. Other parameters of radial strain do not change significantly. Longitudinal strain parameters measured by speckle tracking improve significantly in non-responders, but there are no significant changes in tissue Doppler measures.

Overall, resynchronisation appears to be associated with similar changes in conventional parameters of inter-ventricular dyssynchrony in both responders and non-responders to CRT. However analysis of ventricular interaction in terms of
timing of diastolic filling, rather than systolic ejection appears to demonstrate significant differences in ventricular interaction between responders and non-responders. Intra-ventricular dyssynchrony is also seen to reduce to some degree in both responders and non-responders, however significant reduction is seen in a greater number of dyssynchrony parameters in responders, suggesting that resynchronisation of baseline intra-ventricular dyssynchrony is important in the mechanism of response to CRT. It may be the case that although intra-ventricular resynchronisation is important in the mechanism of response to CRT, echocardiographic parameters of dyssynchrony have too high a degree of variability in application in the individual patient, and analysis of multiple echocardiographic parameters is therefore able to demonstrate only a trend towards greater resynchronisation in responders. Inter-ventricular interaction may also be relevant, and the relationship between changes in inter-ventricular and intra-ventricular dyssynchrony may also influence CRT response. The inability of echocardiographic dyssynchrony measures to accurately predict echocardiographic response is likely to reflect several factors, including poor reproducibility of echocardiographic acquisition and analysis of these parameters, complex interaction of electrical and mechanical cardiac activity, and a more complex mechanism of response to CRT than solely the correction of intra-ventricular dyssynchrony. The individual variation in mechanism of response to CRT will be explored in the following chapter.
Chapter 8

Mechanisms of Echocardiographic Response to Resynchronisation Therapy

8.1 Study Population
8.2 Rationale
8.3 Methods
8.4 Results
8.5 Role of Dyssynchrony Parameters
8.6 Role of Electrocardiographic Parameters
8.7 Discussion
8.1 Study Population

This chapter examines paired baseline and follow-up echocardiographic data of the 40 patients who completed the six month follow-up period following CRT. In order to more fully understand the mechanisms involved in response to CRT, an individualised assessment of the 40 paired data sets was made, to determine whether patterns existed within changes at the individual level which may suggest one or more mechanisms for response or absence of response.

8.2 Rationale

Correction of intra-ventricular dyssynchrony is thought to be the predominant mechanism by which CRT results in left ventricular remodelling, although several researchers have suggested that correction of intra-ventricular dyssynchrony may not be the sole mechanism for response to CRT, and that the mechanism of improvement in cardiac structure and function may differ between patients. Parsai demonstrated presence of a septal flash (early contraction of the ventricular septum detected as inward excursion of the septum within the pre-ejection period on 2D or colour TDI M-mode imaging) and its elimination following CRT to be a strong predictor of subsequent reverse remodelling, and in addition that changes in atrio-ventricular synchrony and ventricular interaction appeared to be important in echocardiographic and clinical response (45).

8.3 Methods

Paired echocardiographic data were examined to individually assess the apparent mechanism of response or reason for non-response. A worksheet was used to record pre- and post-CRT dyssynchrony parameters in each patient and assess for changes
attributable to CRT. Particular attention was paid to the presence and subsequent elimination of a septal flash, changes in intra-ventricular dyssynchrony measures, and parameters of atrio-ventricular and inter-ventricular interaction. Further analysis to investigate mechanistic changes was performed where necessary, as prompted by the initial examination. Each patient was classified according to apparent mechanism of response into one of the four groups below, determined by the predominant change (or lack of change) seen in dyssynchrony parameters before and after CRT.

Group 1: Septal flash
Patients characterised predominantly by presence of baseline septal flash with or without elimination of septal flash following CRT

Group 2: Atrio-ventricular interaction
Patients with predominant changes in atrio-ventricular interaction characterised by either elimination of pre-systolic MR and improvement in left ventricular filling pattern, or elimination of A wave truncation

Group 3: Inter-ventricular interaction
Patients with changes seen predominantly in parameters of ventricular interaction – inter-ventricular mechanical delay and inter-ventricular filling delay

Group 4: Others
Patients without changes in any of the above parameters

8.4 Results

Group 1 – Septal flash (22 patients)
Septal flash was identified in 22 of 40 patients at baseline (55%), and eliminated in 18 patients post-CRT. Echocardiographic response occurred in 15 of these 18 patients. In the three non-responders one patient had persisting E:A fusion post-CRT with reduced left ventricular filling time (DFT:RR ratio <40%), one patient had marked residual radial dyssynchrony despite elimination of septal flash, and one
patient had a 10% reduction in LV volume associated with clinical response, but did not meet criteria for echocardiographic response.

Septal flash was not eliminated in 4 patients following CRT. One of these patients had persisting septal flash in the presence of a poor LV lead position (apical posterior position in the middle cardiac vein) following initial displacement of the lead from a lateral vein, and did not respond echocardiographically. The three remaining patients demonstrated echocardiographic response despite persistent septal flash, but in the presence of markedly improved parameters of radial dyssynchrony (mean reduction in SPWMD and \( SPWMD_{TDI} \) 190.0ms). In two of these three the duration of the septal flash was reduced by >50% following CRT, and the pattern of septal motion was modified such that the septal flash was not the predominant septal excursion.

**Group 2 – Atrio-ventricular interaction (4 patients)**

Pre-systolic mitral regurgitation (PSMR) in association with long PR interval (mean PR interval 251ms) was seen in 3 patients. In all patients PSMR was abolished following CRT, all were echocardiographic responders. In one of these patients pre-systolic tricuspid regurgitation was seen, and also abolished following CRT.

Shortened ventricular filling and truncation of the trans-mitral and trans-tricuspid A wave were identified in one patient at baseline. Ventricular filling pattern was normalised following CRT and this patient was an echocardiographic responder.

**Group 3 – Inter-ventricular interaction (12 patients)**

Five responders without baseline septal flash and with no clear changes in either radial dyssynchrony parameters or atrio-ventricular interaction were identified. In these patients marked changes in ventricular interaction as measured by the relative timing of left and right ventricular filling and ejection were noted.

Four of these five responders had a negative MV-TV filling offset (IVFD) at baseline (ie. peak tricuspid inflow occurring after peak mitral inflow), compared to a mean positive value of 34.2ms at baseline in responders overall. In three of these
patients the offset was reversed at follow-up, and in a fourth the negative offset was markedly reduced from -236ms to -72ms. The fifth patient had a small positive offset of 30ms which increased to 79ms at follow-up. In all five an increase in IVMD measured by pre-ejection periods was also seen, compared to the significant reduction seen in IVMD in responders overall.

In seven non-responders which were not explained by persisting septal flash and radial dyssynchrony, a similar baseline pattern of ventricular interaction was seen which did not change following CRT. Five patients had a negative IVFD at baseline which persisted at follow-up, and two patients had a positive baseline offset which became negative at follow-up. No significant change in IVMD was seen in these patients.

Of the five responders in this category, three had non-ischaemic aetiology of heart failure, whereas in non-responders six of the seven had ischaemic aetiology.

Changes in IVMD and IVFD (offset between peak mitral and tricuspid inflow) in these 12 patients compared with all other responders are shown in table 8.1.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>V-V interaction responders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVMD</td>
<td>14.8 (16.0)</td>
<td>41.2 (24.4)</td>
<td>0.013</td>
</tr>
<tr>
<td>IVFD</td>
<td>-66.0 (101.3)</td>
<td>55.9 (72.8)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>V-V interaction non-responders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVMD</td>
<td>24.3 (18.9)</td>
<td>7.2 (29.5)</td>
<td>NS</td>
</tr>
<tr>
<td>IVFD</td>
<td>-37.4 (77.6)</td>
<td>-65.1 (35.6)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>All other responders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVMD</td>
<td>54.6 (32.6)</td>
<td>18.1 (26.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVFD</td>
<td>57.0 (111.0)</td>
<td>59.1 (70.4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 8.1**: Changes in IVMD and IVFD offset in V-V responders, non-responders and other responders

In responders the increase in IVMD was mediated via an increase in LV pre-ejection period from 127.3±3.0ms to 147.9±31.2ms, with little change in RV pre-ejection period. The change in filling offset was driven primarily by a reduction in the time to
peak tricuspid inflow, associated with a modest increase in time to peak mitral inflow. In non-responders there was a modest increase in both LV and RV pre-ejection periods, more marked in the RV, leading to a non-significant reduction in IVMD. Time to peak filling also increased for both TV and MV in non-responders, again to a greater extent for tricuspid inflow, increasing the negative degree of filling offset.

**Group 4 – Others (2 patients)**

Two patients had no evidence of septal flash or significant radial dyssynchrony and a positive MV-TV offset at baseline. No apparent alteration in either atrio-ventricular synchrony or ventricular interaction was seen by the parameters measured and both were non-responders.

The overall findings of this individual analysis are summarised in table 8.2.

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-responders</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Septal flash</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eliminated</td>
<td>15</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Not eliminated</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td><strong>Atrio-ventricular interaction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pre-systolic MR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eliminated</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td><strong>Atrio-ventricular interaction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short filling</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eliminated</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>V-V interaction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(MV-TV offset)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased / positive</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Worsened / negative</td>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>27</td>
<td>13</td>
<td>40</td>
</tr>
</tbody>
</table>

*Table 8.2: Summary of echocardiographic assessment of mechanism for response and non-response*
In this analysis each patient was characterised by the predominant mechanism apparent for individual response to CRT, although some overlap was seen. One patient who responded due to elimination of septal flash and one ventricular interaction responder both had PSMR which was eliminated by CRT. Two patients classified as PSMR responders also had apparently favourable changes in ventricular interaction. Variable changes in TV and MV filling offset (IVFD) were seen in septal flash responders, but no patient who responded in the septal flash group had a negative offset at follow-up.

8.5 Role of Dyssynchrony Parameters

Patients with septal flash show a high rate of echocardiographic response in this analysis; 83.3% if septal flash is eliminated post-CRT and 75% even where septal flash persists. By definition septal flash was identified echocardiographically by M-mode or tissue Doppler M-mode in all 22 patients. The role of other intra-ventricular dyssynchrony parameters in the identification of this group was examined by comparing these parameters between those with septal flash and those without. The results are shown in table 8.3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Septal flash</th>
<th>No septal flash</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPWMD</td>
<td>279.2 (101.3)</td>
<td>113.8 (77.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPWMD$_{TDI}$</td>
<td>236.8 (119.8)</td>
<td>95.3 (98.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SepLateral$_{TDI}$</td>
<td>73.0 (93.5)</td>
<td>44.0 (47.1)</td>
<td>NS</td>
</tr>
<tr>
<td>12segment$_{TDI}$</td>
<td>50.9 (18.0)</td>
<td>35.9 (18.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>SepPostRad$_{2DS}$</td>
<td>141.2 (198.5)</td>
<td>76.7 (187.2)</td>
<td>NS</td>
</tr>
<tr>
<td>SepPostCirc$_{2DS}$</td>
<td>114.7 (194.3)</td>
<td>57.0 (124.6)</td>
<td>NS</td>
</tr>
<tr>
<td>SepLateral$_{2DS}$</td>
<td>114.3 (188.4)</td>
<td>72.7 (182.9)</td>
<td>NS</td>
</tr>
<tr>
<td>12segment$_{2DS}$</td>
<td>85.7 (29.3)</td>
<td>84.0 (29.3)</td>
<td>NS</td>
</tr>
<tr>
<td>3D SDI</td>
<td>12.5 (6.3)</td>
<td>10.7 (4.6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 8.3: Comparison of baseline dyssynchrony parameters between septal flash and non-septal flash groups
SPWMD and SPWMD_{TDI} were significantly different between those with septal flash and those without, with a mean value for both well above the accepted cut-off of 130ms in those with septal flash. Septal-posterior delay by radial strain also demonstrated a mean value above this cut-off for patients with septal flash and below the cut-off for those without, but the high standard deviation indicates high levels of variability and overlap in this measure making it unhelpful in many cases and not significantly different. 12 segment TDI demonstrated a significant difference between septal flash and non-septal flash patients, although for both the values are above the accepted cut-off of 32.6ms. Although there was a trend towards higher levels of dyssynchrony in septal flash patients, no other parameters were found to be significantly different.

8.6 Role of Electrocardiographic Parameters

QRS morphology was examined in the septal flash and ventricular interaction groups to determine whether baseline ECG morphology provided any further information. Of 22 patients with baseline septal flash 19 (86.4%) had LBBB morphology of the QRS complex. Conversely, of 12 patients classified in the ventricular interaction group, all 5 responders and 5 of the 7 non-responders had non-LBBB morphology QRS complexes.

8.7 Discussion

Studies assessing the prediction of response to CRT to date have principally focused upon identification of baseline intra-ventricular dyssynchrony, on the basis that reduction or elimination of intra-ventricular dyssynchrony is thought to be the predominant mechanism by which echocardiographic response to CRT occurs.
Bleeker et al report that in responders septal-lateral delay by tissue Doppler reduced from a mean of 115ms to 32ms, whilst in non-responders a less marked fall from 106ms to 79ms was seen. Response was never seen without 20% or more reduction in dyssynchrony (150). They interpreted these findings by suggesting that intra-ventricular resynchronisation is mandatory for response to CRT, despite a relatively modest correlation between resynchronisation and remodelling. Gorcsan et al also argue that left ventricular resynchronisation is important in response on the basis that the weight of pathophysiological evidence suggests this, whilst conceding that cause and effect remain to be proven (190). Celikyurt and Faber also offer evidence supporting the role of resynchronisation in echocardiographic response. Faber et al report 83% response rate in those in whom correction of LV dyssynchrony was seen, as opposed to 15% where LV dyssynchrony was either not present at baseline or unchanged following CRT (191). Celikyurt et al note a slightly higher degree of resynchronisation in echocardiographic responders than in non-responders, although conclude that the reported change in intra-ventricular dyssynchrony may not be sufficient explanation for the reduction in left ventricular volume (151). Conversely, Pouleur et al report data from the MADIT-CRT trial, a randomised multi-centre trial of CRT in patients with severe left ventricular systolic dysfunction but mild heart failure symptoms (87). They note that although improvement in cardiac function measured by increase in global strain was seen in 72% of patients, and reduction in dyssynchrony in 78%, there was little correlation between dyssynchrony reduction and contractile improvement (r=0.22). Perry et al also report little evidence of a relationship between resynchronisation and response, noting that despite 76% of patients having evidence of clinical or echocardiographic response, intra-ventricular dyssynchrony was unchanged following CRT (192).

In the current study we noted in the previous chapter that a significant reduction in inter-ventricular and some parameters of intra-ventricular dyssynchrony was seen in responders following CRT, but that similar although less marked changes were also seen in non-responders. No significant correlation between the degree of left ventricular remodelling and either baseline dyssynchrony or change in dyssynchrony
following CRT was found. The need for intra-ventricular resynchronisation to occur to produce response is also questioned in a study by Leclerq et al (193). This paper reports the effects of atrial pacing, biventricular pacing and left ventricular pacing in seven dogs with heart failure and LBBB. Mechanical synchrony was assessed with tagged magnetic resonance imaging, electrical synchrony by epicardial mapping and response by acute changes in haemodynamics. They demonstrate that biventricular and left ventricular pacing are both associated with virtually identical improvements in haemodynamic parameters and similar improvements in mechanical synchrony, despite increased electrical dispersion with LV pacing and reduced electrical dyssynchrony with biventricular pacing.

Some authors have therefore questioned whether correction of intra-ventricular dyssynchrony is the main mechanism by which CRT exerts its beneficial effect. Cleland argues that the mechanism of response to resynchronisation remains unclear, and that resynchronisation may be a misnomer, preferring the term ‘atrio-biventricular pacing’ (152). He argues that atrio-ventricular, inter-ventricular and intra-ventricular dyssynchrony frequently co-exist in heart failure patients, and that response to CRT may reflect changes in any or all of these, and additionally that reduction in mitral regurgitation and regulation of cardiac rhythm may play a role; the relative importance of each potential mechanism probably differing from patient to patient.

Parsai et al attempted to unravel the relative roles of possible mechanisms of CRT response in 161 patients, in a similar fashion to the analysis presented here (45). In their report perceived mechanisms of response or non-response are divided into five groups:

1. Dyssynchrony group – identified by presence of septal flash
2. $\text{Filling}_{\text{short}}$ group – no dyssynchrony, inadequate filling due to foreshortened AV delay and A wave truncation
3. $\text{Filling}_{\text{long}}$ – no dyssynchrony, impaired filling due to prolonged AV delay
4. L-R interaction – no dyssynchrony but exaggerated passive motion of septum due to septal infarction in presence of IVMD >40ms
5. Others – with none of the above findings

Response was defined by a combination of either reverse remodelling and / or ≥1 reduction in NYHA class. Intra-ventricular dyssynchrony was defined on the basis of a septal flash – very early septal motion occurring within the pre-ejection period. This may be identified on M-mode imaging, colour TDI M-mode and by tissue Doppler velocity profile (Figure 8.1 A-C, overleaf).

Parsai et al report presence of septal flash in 54% of patients, which was eliminated in 88% following CRT, all of whom demonstrated reverse remodelling and symptomatic improvement. All those who retained septal flash failed to respond. In the current study septal flash was found in an almost identical proportion of patients, and although a greater degree of variability in response to elimination or persistence of septal flash following CRT was found, presence of septal flash at baseline and elimination post-CRT were still associated with a high rate of reverse remodelling. In addition to M-mode imaging, Parsai noted that the presence and elimination of septal flash could also be detected by radial tissue Doppler velocity imaging. Septal flash produces a characteristic double-peak motion of the septum, with very early septal contraction and later post-systolic motion. Elimination of septal flash post-CRT in the Parsai study was associated with co-ordinated septal and posterior wall motion with mirrored velocities on radial tissue Doppler. Although similar changes were noted in our study, these patterns were not sufficiently consistent to be useful as a sole parameter. The characteristic early septal activation of the septal flash may also be detected using speckle tracking radial strain, however the pattern of strain curves seen in septal flash patients in our study was inconsistent with a wide variability (Figure 8.2, page 174), and therefore septal-posterior delay by radial strain was not significantly different between septal flash and non-septal flash patients.
Figure 8.1 A-C: Echocardiographic modalities for detection of septal flash. Standard m-mode imaging demonstrates early systolic inward motion of the septum (figure 8.1A, top left). Colour tissue Doppler M-mode demonstrates early motion away from the probe in blue (figure 8.1B, top right). Tissue Doppler velocity curve of the septum demonstrates an early velocity peak occurring prior to aortic valve opening (AVO; figure 8.1C, bottom).
Figure 8.2: Radial strain curves in a patient with baseline septal flash demonstrating the variability in curves between cardiac cycles. The strain curve for the anterior septum is shown in yellow. In the first cardiac cycle (left) the predominant septal strain peak is the early peak of the septal flash. In the second cardiac cycle (right) the strain pattern is different with the highest septal peak now post-systolic. Septal flash would not be identified by measurement of timing of peak systolic strain in the second cycle.

Duckett et al examined the role of septal flash by echocardiographically characterising the degree of septal flash and correlating this with the pattern of intracardiac conduction assessed by non-contact mapping (194). Those with minimal or no septal flash had homogenous endocardial activation, whereas those with large septal flash had activation characterised by a specific area of conduction block, early activation of the septum and late activation of the anterior and inferior walls. This study also confirmed that presence of septal flash and associated conduction block was associated with a greater acute haemodynamic response to CRT.

The study by Parsai et al reported changes in atrio-ventricular interaction to be the predominant mechanism of response to CRT in 23% of patients. Long filling pattern characterised by fusion of E and A waves and pre-systolic MR was seen in 16 patients, but only resolved following CRT in 11, of whom 5 showed reverse remodelling. Correction of a prolonged filling pattern and elimination of PSMR was unable to be achieved in two patients due to persisting sinus tachycardia and intolerance of beta-blockade. In the current study pre-systolic mitral regurgitation
was abolished post-CRT in all those where it was present at baseline (Figure 8.3), and all showed reverse remodelling. One patient was a non-responder in the presence of a persistent septal flash, although also demonstrated E and A fusion and short diastolic filling time but without pre-systolic MR, this filling pattern was not improved following CRT.

Figure 8.3: Continuous wave Doppler of the mitral valve demonstrating pre-systolic mitral regurgitation (left) and elimination of pre-systolic mitral regurgitation following CRT (right).

Short LV filling with truncation of the transmitral A wave was seen in 21 patients (13%) in the Parsai study and resolved in 19, 16 of whom showed reverse remodelling. This pattern was only seen in one patient in our study, who also demonstrated echocardiographic response. The mechanism by which CRT results in correction of A wave truncation is unclear, given that CRT cannot prolong the AV delay without intrinsic AV conduction occurring. Potential mechanisms include the possibility that LV activation actually takes longer via a paced QRS complex in some patients, increasing the pre-ejection period and allowing the atrial component of filling to complete, or that the presence of CRT allows intensified medical therapy with beta-blockade, slowing intrinsic AV conduction.
Olshansky et al examined data from the COMPANION study, to assess the role of electrical atrio-ventricular dyssynchrony in response to CRT (195). They report that in those with first degree atrio-ventricular block (PR interval >200ms), the rate of mortality and heart failure hospitalisation was significantly less following CRT than in those with normal PR interval. Although this was not an echocardiographic study, in a different study Nof et al report that in 26 patients with pre-systolic mitral regurgitation all had first degree AV block, with a normal PR interval in those without (196). In all patients PSMR was abolished following CRT.

Tournoux et al examined the role of atrio-ventricular dyssynchrony in the prediction of response to CRT (154). Atrio-ventricular dyssynchrony was assessed based upon the ratio of left ventricular filling time to cardiac cycle length. They report that a ratio \( \leq 39\% \) predicted response (defined as 25% or more increase in left ventricular dP/dt) with a specificity of 100% although a sensitivity of only 40%. No data regarding the PR interval, or the presence or elimination of PSMR is reported, although one would anticipate improvement in atrio-ventricular interaction to be the mechanism by which CRT occurred in this group of patients. These studies suggest that long PR interval and adverse atrio-ventricular interaction with PSMR frequently co-exist and that improved atrio-ventricular interaction and elimination of pre-systolic mitral regurgitation are an important component of CRT response. In fact, Kyriacou et al argue that the effects of restoration of optimal atrio-ventricular interaction and intra-ventricular synchrony are so closely linked that it is difficult to determine at which point the effect of each is the dominant influence (155).

The role of atrio-ventricular interaction in CRT response prompts recollection of earlier studies highlighting a potential role for dual chamber pacing in patients with heart failure, which demonstrated short term improvement at least in part attributed to optimised left ventricular filling and elimination of pre-systolic mitral regurgitation. CRT may therefore accomplish this advantageous change in atrio-ventricular interaction whilst avoiding the adverse effects of unopposed right ventricular pacing on left ventricular systolic function.

The final group of responders noted in the Parsai study are those with abnormal ventricular interaction, defined as passive motion of an infarcted ventricular septum
due to early RV contraction, in the setting of a mean IVMD of 50ms. This finding is reported to correct following CRT, presumably due to prolongation of the RV pre-ejection period and consequent reduction in IVMD as seen in responders in our study, although detailed echocardiographic changes post-CRT in this group are not specifically reported by Parsai et al. This description suggests a different mechanism of response to that seen in those classified as inter-ventricular interaction responders in this study, who are characterised by minimal IVMD at baseline, which is increased following CRT. We have also been able to report more detailed echocardiographic characterisation of change in ventricular interaction, with changes in the sequence of left and right ventricular filling appearing to be particularly important after resynchronisation. Rather than a delay in the onset of RV ejection induced by CRT as suggested in the Parsai study, this analysis noted a delay in the onset of LV ejection and a paradoxical increase in IVMD in those showing reverse remodelling associated with changes in inter-ventricular interaction. This leads to alteration in the relationship of left and right ventricular filling, such that right ventricular filling occurring prior to left ventricular filling following CRT appears to promote reverse remodelling (Figure 8.4).

**Figure 8.4:** Pulsed wave Doppler of the tricuspid valve demonstrating changes in the timing of right ventricular filling before and after CRT. Pre-CRT (left) the predominant component of right ventricular filling occurs very late in the cardiac cycle, whereas post-CRT (right) right ventricular filling is normalised, with onset of filling mid-cardiac cycle and distinct E and A waves
Changes in the timing of ventricular interaction related to CRT have not been widely studied. Kerwin et al studied inter-ventricular synchrony in 13 patients with dilated cardiomyopathy using blood pool scintigraphy (197). They demonstrated an overall relationship between reduced inter-ventricular dyssynchrony following CRT and increases in left ventricular ejection fraction. However of these 13 patients, 4 demonstrated improved left ventricular systolic function despite unchanged or worsened inter-ventricular dyssynchrony following CRT. All 4 patients had non-specific intra-ventricular conduction delay rather than LBBB on the ECG. The mechanism and underlying physiology of response noted in the ventricular interaction group in our study is unclear. Increase in IVMD and the apparent changes in timing of ventricular filling suggest that rather than resynchronisation of right and left ventricular function, a specific but non-simultaneous pattern to the sequence of ventricular filling and ejection of both right and left ventricles is advantageous. Left and right ventricles share the inter-ventricular septum, and changes in filling pressures and volume in one chamber may have marked effects on the other, particularly in patients with heart failure where the heart is significantly enlarged and externally constrained by the effects of a chronically stretched and stiff pericardium (198).

Cardiac output is dependent upon optimised filling and ejection of both left and right ventricles, and our analysis suggests that a pattern of right ventricular filling occurring before left ventricular filling promotes maximal cardiac output and subsequent ventricular remodelling following CRT. One may hypothesise that where left ventricular precedes right ventricular filling, the action of external pericardial constraint may result in impairment of right ventricular filling and pre-load, leading to an overall reduction in cardiac output. Reversing this sequence may allow the right ventricle to fill without constraint, potentially increasing left ventricular contractility by reduction in left ventricular size and therefore myocardial fibre stretch, and altering the LV pressure-volume relationship from the downslope to the plateau of the Frank-Starling curve. This mechanism would potentially be analogous to experimental external constraint devices for treatment of heart failure (199).
Patients falling into the ventricular interaction group predominantly have non-specific conduction delay on ECG rather than LBBB, suggesting that non-LBBB QRS morphologies may pre-dispose to adverse filling sequences, which are subsequently corrected by CRT in a modest proportion of patients. The mechanism by which CRT induces these favourable changes in filling sequence is unclear. LV pre-ejection period is seen to increase, perhaps because global LV activation is slower via a paced QRS complex than it was via intrinsic conduction. This reflects the knowledge that intrinsic ventricular activation times may be relatively normal despite LBBB on the surface ECG, and presumably this is equally or more likely to occur in non-LBBB QRS prolongation. This delayed LV activation and increase in IVMD appears to be beneficial in this cohort of patients as it modifies the relationship between left and right ventricular filling such that the right ventricle can fill appropriately before the left ventricle.

In summary, this analysis demonstrates that individual response to CRT is dependant on several mechanisms involving intra-ventricular, inter-ventricular and atrio-ventricular synchrony, the relative importance of each mechanism varying between patients. Although aspects of these mechanisms may be assessed echocardiographically, this study suggests that a single echocardiographic measure of dyssynchrony is unlikely to predict response to CRT with sufficient accuracy to be clinically useful.
Chapter 9

Summary and Conclusions

9.1 Feasibility and Reproducibility of Echocardiographic Dyssynchrony Parameters
9.2 Relationship Between Echocardiographic and Electrocardiographic Parameters
9.3 Effects of Cardiac Resynchronisation Therapy
9.4 Echocardiographic Dyssynchrony Parameters and Prediction of Response to Resynchronisation
9.5 Mechanism of Response to Resynchronisation Therapy
9.6 Study Limitations
9.7 Suggested Areas for Further Investigation
9.8 Conclusion
This study has reported a detailed analysis of echocardiographic parameters in patients undergoing cardiac resynchronisation therapy. Patients recruited into the study represented a typical heart failure population undergoing CRT based on experience reported in previous trials. Baseline parameters of cardiac structure and function, including left ventricular volumes and ejection fraction as well as symptomatic measures such as NYHA class, quality of life score and six minute walk distance were comparable to patients enrolled into previous studies of resynchronisation therapy.

The primary aims of the study were to assess the role of echocardiographic dyssynchrony parameters in the prediction of response to resynchronisation therapy, with a particular focus upon parameters derived from speckle tracking echocardiography, and also to assess the mechanisms of response to resynchronisation by examination of changes in dyssynchrony parameters and other echocardiographic measures.

9.1 Feasibility and Reproducibility of Echocardiographic Dyssynchrony Parameters

The feasibility of echocardiographic dyssynchrony measures is generally fairly consistent throughout previously reported studies. M-mode measures are highly dependent on image quality and clear patterns of wall motion, and are often easier to measure in patients with dilated cardiomyopathy and difficult in the presence of infarction with thinning and akinesia of either the septum or posterior wall. Feasibility therefore depends upon both the quality of the echocardiographic study, as well as the relative proportions of ischaemic and non-ischaemic heart failure in the population studied. The reported values of 82.4% for SPWMD and 88.2% for SPWMD_{TDI} in this study are comparable to previous reports.

Tissue Doppler and speckle tracking parameters are also highly dependent upon image quality for feasibility of measurement, and on the basis of previous studies are
usually reported to be feasible in approximately 85-95% of cases. As discussed previously the PROSPECT study is exceptional in that the quality of echocardiography appears to have been relatively poor with feasibility of tissue Doppler parameters as low as 50% reported (63). Single centre studies overseen by high profile researchers have often reported that echocardiographic dyssynchrony parameters are highly reproducible. Pitzalis reported an intra-class correlation co-efficient of 0.91 for inter-observer variability in SPWMD analysis (39). Yu demonstrated that a correlation of 0.93 can be achieved for tissue Doppler parameters following a short analysis training program (174). However, other researchers have questioned whether the reproducibility of echocardiographic parameters is sufficient for routine use. De Boeck et al demonstrated very poor agreement of faculty members at an international conference (171), and data from the PROSPECT study cast doubt on the usefulness of these parameters in the wider echocardiographic community. Dyssynchrony parameters derived from speckle tracking echocardiography are hypothetically less prone to the variability of acquisition and analysis inherent in tissue Doppler measures. Inter-observer variability for speckle-tracking has mostly been reported by co-efficient of variation rather than correlation co-efficient. Miyazaki and Tanaka report inter-observer variation ranging from 10-18% for radial, circumferential and longitudinal strain (82, 88).

In our study we confirmed similar findings, with relatively high intra-observer reproducibility, suggesting that a single observer tends to perform similar measurements each time on the same data set, but relatively poor inter-observer variability, particularly for tissue Doppler and speckle tracking parameters. This suggests that despite instruction of the correct method of analysis, a second observer is unable to replicate the primary reader’s analysis sufficiently for these measures to be clinically useful. The point at which variability is introduced into the analysis is unclear. Test-test reliability of tissue Doppler measures has been shown to be poor, and variability in acquisition of images is likely to be a factor in this (173). In this study echocardiographic acquisition was not a source of variability, as both readers analysed the same images. The primary points of variation are likely to be in
placement of the region of interest, selection of the velocity peak to be measured, and identification of the onset of the QRS complex, from where to start measurement.

Overall, this study has confirmed findings previously reported by others, in that feasibility and reproducibility of dyssynchrony parameters by a single operator may be relatively high, but that inter-observer reproducibility is poor, probably limiting routine clinical use.

9.2 Relationship Between Echocardiographic and Electrocardiographic Parameters

QRS prolongation has conventionally been used as a marker of electrical dyssynchrony, and therefore implied mechanical dyssynchrony, to determine indication for CRT in patients with heart failure. Electrical mapping studies have demonstrated that LBBB is associated with delayed intra-cardiac conduction in roughly two-thirds of cases, whilst in some cases intra-cardiac conduction is normal despite the surface ECG (28, 29). When intra-cardiac conduction is abnormal this may occur as a specific site of conduction block, or as homogenously delayed left ventricular activation. This perhaps explains why markers of inter-ventricular dyssynchrony correlate more closely with QRS duration than intra-ventricular measures, as delay in LV activation and subsequent LV filling will likely by present in all cases where conduction is abnormal, whereas intra-ventricular dyssynchrony is more likely only in the smaller proportion of patients where there is a specific site of block.

Whilst the relationship between QRS duration and the presence of mechanical dyssynchrony is not linear, we have demonstrated in this study that measures of posterior wall activation by tissue Doppler or lateral wall activation by speckle tracking correlate most closely with QRS duration. This suggests these parameters may be best placed to detect the presence of mechanical dyssynchrony, although detection of early septal activation by septal flash rather than late posterolateral wall
activation may well be a more appropriate measure. Echocardiographic parameters of dyssynchrony demonstrated only modest correlation within and between echocardiographic modalities in this study. This probably reflects a combination of factors including limited reproducibility of the parameters and the differing aspects of cardiac function which may affect each parameter. In particular, tissue Doppler tends to measure early systolic events with peak velocity representing initial activation, whereas M-mode and speckle tracking parameters tend to measure late systolic events which may be influenced not only by electrical activation, but by loading conditions and factors affecting regional wall motion such as ischaemia.

9.3 Effects of Cardiac Resynchronisation Therapy

The overall effect of cardiac resynchronisation therapy upon cardiac structure and function in this study was largely similar to previously reported single centre studies and multi-centre trials. Clinically, significant improvements in NYHA class, quality of life scores and six minute walk distance were seen. Echocardiographically, marked reduction in left ventricular systolic and diastolic volumes were seen as measured by both 2D and 3D echocardiography, with corresponding increase in ejection fraction and fractional shortening. Favourable changes in several other parameters including left ventricular diameter, sphericity index, stroke volume, cardiac output and ratio of cardiac cycle to LV filling time were also seen. Left ventricular function assessed by global circumferential strain improved significantly, but global longitudinal strain was unchanged. Global circumferential strain has been shown to be an important predictor of future heart failure events (76). Global circumferential strain is linearly related to mid-wall myocardial fibre function and is reported to represent a better marker of overall cardiac contractility than longitudinal strain which measures predominantly endocardial and epicardial changes (166, 200). These findings which suggest a predominant effect of resynchronisation upon mid-wall circumferential function have been reported previously (183), although the
mechanism by which this aspect of myocardial function is particularly affected by CRT remains unclear.

Several studies of CRT have demonstrated significant reduction in mitral regurgitation following resynchronisation (182, 201). Ypenburg et al suggested that early changes in mitral regurgitation following CRT related to improvement in papillary muscle dyssynchrony, and later changes reflected improved lateral wall dyssynchrony (201). Left ventricular reverse remodelling resulting in reduction in leaflet tethering and annular dilatation will also have a significant role. In our study changes in mitral regurgitation were not as marked as those reported previously. Mitral regurgitation was unchanged following CRT overall, however in echocardiographic responders a trend towards reduction in quantitative measures of mitral regurgitation was seen and a significant reduction in jet area ratio. In non-responders significant worsening of MR was seen.

The relationship between clinical and echocardiographic response was also explored. Previous investigators have reported relatively poor correlation between echocardiographic and clinical response (169, 202). Although it is convenient from a research perspective to classify response to CRT as a binary phenomenon, response is likely to represent a spectrum ranging through no improvement or prevention of further deterioration, to marked improvement in both echocardiographic and clinical measures. We demonstrated that in echocardiographic non-responders, there is no significant difference in left ventricular volumes and ejection fraction between those who demonstrated clinical response and those who did not. This suggests that clinical response may occur via improvement in parameters of haemodynamic status and cardiac function other than reverse remodelling, or that placebo effect plays a role in clinical response. It is likely that both these factors are relevant.
9.4 Echocardiographic Dyssynchrony Parameters and Prediction of Response to Resynchronisation

Numerous single centre studies have reported upon the utility of echocardiographic dyssynchrony parameters to predict response to CRT with greater sensitivity and specificity than QRS duration (50, 52). Other studies, in particular the multi-centre PROSPECT study, have found the utility of these parameters to be limited and unhelpful (63). This study has found that echocardiographic parameters of dyssynchrony do not appear to have a useful role in the prediction of echocardiographic response to CRT. No single parameter of intra-ventricular dyssynchrony was significantly different between echocardiographic responders and non-responders, and analysis by receiver operating characteristic (ROC) curve suggested that intra-ventricular dyssynchrony parameters have no greater predictive value than QRS duration.

Parameters of inter-ventricular dyssynchrony appear to provide some further information, in particular measures suggesting delay in global LV activation (left ventricular pre-ejection period and time to peak left ventricular filling) have AUC values greater than that for QRS duration alone, although sensitivity and specificity values remain limited.

Study of the mechanism of echocardiographic response in chapter 8 however suggests echocardiography for the detection of intra-ventricular dyssynchrony may still play a role in the assessment of CRT response. The presence of a septal flash (early inwards motion of the septum occurring within the LV pre-ejection period) is highly predictive of response to CRT, particularly when septal flash is eliminated following resynchronisation. In this study 83% of this group demonstrated echocardiographic response, and in the study by Parsai et al all demonstrated echocardiographic and clinical response (45). Septal flash is detected echocardiographically. Early septal motion is often apparent visually, however precise assessment of the timing and degree of septal deflection can easily be accomplished using either 2D or colour tissue Doppler M-mode (see Figures 8.1, page 173). Tissue Doppler velocity profiles and speckle tracking radial strain may
also demonstrate typical features of septal flash (Figures 8.1 and 8.2, pages 173 and 174), but with less consistency.

9.5 Mechanism of Response to Resynchronisation Therapy

Individual analysis of paired echocardiographic examinations in this study suggested that response to CRT is complex and involves multiple mechanisms, the relative importance of which vary from patient to patient. Elimination of baseline intra-ventricular dyssynchrony manifest as septal flash appears to be the predominant mechanism of improvement in cardiac function following CRT. This group of patients typically have LBBB morphology QRS complex on the ECG. However, changes in atrio-ventricular and inter-ventricular interaction are also demonstrated to be important in CRT response. Elimination of pre-systolic MR and normalisation of left ventricular filling pattern by increasing LV filling time and minimising E:A fusion is also strongly associated with response, without consistent evidence of baseline inter- or intra-ventricular dyssynchrony. Correction of atrio-ventricular interaction occurs without the adverse effect upon left ventricular function of unopposed right ventricular pacing seen in early studies of pacing in heart failure. Opposing changes in atrio-ventricular interaction are also seen in some patients. In the study by Parsai et al correction of shortened LV filling and A wave truncation was seen as the predominant mechanism of response in 10% of patients, although this mechanism was only identified in 1 of the 40 patients in this study.

Changes in ventricular interaction were also identified as an important component of response by both this study and by Parsai et al (45), although the description of the patterns of ventricular interaction differs between the two studies. Parsai noted abnormal ventricular interaction characterised by early right ventricular activation in the presence of passive motion of an infarcted ventricular septum, although did not characterise these findings further. In this study we have examined ventricular interaction by assessment of changes in the timing of right and left ventricular
ejection and filling, and identified a subgroup of patients where left ventricular filling precedes right ventricular filling which appears to disadvantageous. This group of patients tend not to have a typical LBBB morphology on ECG. Correction of this adverse filling pattern is achieved by prolongation of left ventricular activation and filling times, and a consequent paradoxical increase in inter-ventricular dyssynchrony measured by IVMD. In those patients in whom this filling pattern is reversed following CRT the rate of response is high, but where the filling pattern remains unchanged or worsened patients tend to be non-responders. Although this group of patients is relatively small, it appears that adverse filling patterns are more likely to be reversed in those with non-ischaemic aetiology of heart failure, however the overall response rate in this group based on the current study is <50%.

9.6 Study Limitations

The sample size of this study is comparable to numerous other single-centre studies of CRT previously published, although is relatively small. Despite this many findings similar to those seen in larger studies of CRT have been reproduced. Although no significant differences in baseline dyssynchrony parameters between responders and non-responders were seen in this study, there was a clear trend towards a greater degree of baseline dyssynchrony in responders, and a larger sample size may have brought these changes to significance, although would be unlikely to change the overall conclusion that these parameters have insufficient sensitivity and specificity in assessment of CRT response to be in routine clinical use.

9.7 Suggested Areas for Further Investigation

The mechanism of response to resynchronisation in individual patients certainly merits further investigation. Changes in ventricular interaction appear to be
important based on both this study and the Parsai study, although the precise mechanism by which CRT modifies ventricular interaction, and the physiological mechanism by which remodelling occurs in this setting remain unclear. Further investigation of this phenomenon by combined echocardiographic and invasive haemodynamic measurements during or immediately after device implant to determine how ventricular filling pressures and the timing of systolic and diastolic events are altered by pacing would provide additional information.

In addition, it is clear that a single echocardiographic parameter is unable to predict response to CRT because the mechanism of response to CRT is variable. However, echocardiography is well placed to detect the presence of several potentially modifiable factors prior to CRT implantation, and a study which prospectively assessed an algorithm incorporating electrocardiographic assessment of QRS duration and morphology, combined with echocardiographic assessment for septal flash, abnormal LV filling patterns and signs of adverse ventricular interaction may well provide the elusive prediction of CRT response with greater accuracy than previously studied parameters.

Lastly, abnormal atrio-ventricular and perhaps inter-ventricular interaction may not be confined to patients with broad QRS complexes, and study of the role of CRT in patients with narrow QRS but abnormalities in these parameters will perhaps broaden the role of CRT to provide symptomatic and echocardiographic improvement in a greater proportion of heart failure patients.

9.8 Conclusion

Cardiac resynchronisation therapy has dramatically altered the treatment options available for a proportion of patients with heart failure and the associated clinical, echocardiographic and prognostic benefits are supported by a wealth of published evidence.
Echocardiography is important in the assessment of heart failure aetiology and as part of the pre-implant workup for CRT, however the search for echocardiographic parameters of mechanical dyssynchrony to provide a greater prediction of response to CRT than QRS duration has proved disappointing. This study has demonstrated that no single echocardiographic parameter of dyssynchrony is able to predict response to CRT, although echocardiography provides important mechanistic and physiological insights into the mechanism by which response to CRT occurs. The results of this study therefore suggest that dyssynchrony assessment by echocardiography currently has no clinical role in the pre-selection of patients undergoing CRT. Research should now move away from attempts to identify a single predictive echocardiographic parameter and focus upon greater understanding of the mechanisms involved in response to CRT. Echocardiography will remain an important tool in the assessment of patients with heart failure and in the future study of the effects of CRT.
Appendices

Appendix 1: Patient information sheet
Appendix 2: Patient consent form
Appendix 3: Letter to patients’ general practitioner
Appendix 4: Echocardiographic acquisition protocol
Appendix 5: Minnesota Living With Heart Failure quality of life questionnaire
Appendix 1: Participant information sheet

PARTICIPANT INFORMATION SHEET

Project Title: Electrocardiographic and echocardiographic parameters of dyssynchrony in cardiac resynchronisation therapy

Principal Investigator: Dr R S Khattar

- We would like to invite you to take part in a research study looking at the selection of patients with heart failure to receive a specialised type of pacemaker (also called cardiac resynchronisation therapy)
- This sheet provides you with information about the study and how it involves you
- Before you decide it is important for you to understand why the research is being done and what it will involve
- Please take time to read the following information carefully before deciding whether or not to take part

What is the purpose of the study?
In heart failure, the heart is unable to pump sufficient blood around the body. This is usually due to damage to the heart muscle, often as a result of heart attack or high blood pressure. Heart failure leads to symptoms such as breathlessness, and swelling in the legs. In many cases this can be controlled with medication. However when the symptoms are not controlled, a special pacemaker device can help some people. Biventricular pacemakers (also called cardiac resynchronisation therapy, or CRT) can help the heart muscle to contract more efficiently, improving the symptoms of heart failure.
This device can only help patients who have poorly coordinated heart muscle contraction. At the moment an electrical recording (ECG) is used to decide whether a patient may benefit from CRT. However, this is not ideal, and only 70% or so of patients get benefit from the pacemaker.
This study will compare measurements of the heart taken using ultrasound (echocardiography) to measurements taken using the ECG, to determine if ultrasound measurements are more accurate in determining which patients will benefit from the pacemaker.

Who is doing the study?
This study is being run by the Manchester Heart Centre at the Manchester Royal Infirmary. The principal investigator (Dr R S Khattar) is a Consultant Cardiologist in this department. The tests will be carried out in the Manchester Heart Centre which is located at the Manchester Royal Infirmary site.
Why have I been chosen?
Your doctor believes that you have symptoms of heart failure which are not well controlled using medications, and that you may be interested in taking part in the study.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and a study appointment will be arranged at the Manchester Heart Centre. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. For your safety the study team will, if you agree, inform your family doctor about your participation in this study.

What happens if I take part?
If you are considered suitable for the study, we will arrange an appointment for you to come to the Manchester Heart Centre for enrolment into the study on a date convenient to you.

Visit 1: Baseline Assessment
We will ask you to sign the consent form to take part in the study. You will undergo assessment including a full medical history, and physical examination. We will ask you to complete a questionnaire about your symptoms, and a blood test will be taken. An ECG recording and an ultrasound scan of your heart will then be performed and carefully analysed.

The results of your ECG recording and the ultrasound scan will determine whether you are suitable to receive a biventricular pacemaker. If the tests suggest you may benefit from a pacemaker then you will be invited to undergo the procedure and you will also do a test on an exercise bike. This involves wearing a mask which measures how much oxygen your body uses during exercise. If the test suggests you will not benefit, then you will not receive a pacemaker, but we will ask you to come back in 3 months time to check on your progress. In this case, you may be asked to do the exercise bike test.

You will always receive a pacemaker as part of the study if you would get one normally. No patients will be denied a pacemaker when they would normally be given one. Some extra patients may be given a pacemaker when they would not get one normally.

Visit 2: Pacemaker implant
If the tests suggest that you may benefit from a pacemaker, then you will be called to the Manchester Royal Infirmary for this to be performed. Pacemaker implantation is performed under local anaesthetic with sedation (rather than a general anaesthetic). It involves a small incision (approximately 7-8cm) under the collarbone, usually on the left side. The pacemaker leads are placed through a
vein under the collarbone, and then attached to the pacemaker box. The pacemaker is implanted under the skin. The wound will be stitched closed. The procedure typically takes 60-90 minutes. You will stay in hospital overnight. The following day further x-rays and a check of the pacemaker function will be performed. If these are satisfactory you will be discharged home.

**Visit 3: Pacemaker check**
If you have had a pacemaker implanted, you will be recalled approximately four weeks following the procedure to recheck the pacemaker function, and ensure the wound has healed normally. This visit will last approximately 15 minutes.

**Visit 4: Twelve weeks after first visit**
You will be asked to return for further review regardless of whether you have had a pacemaker or not. You will be asked about your current health and a physical examination will be carried out. We will ask you to complete a questionnaire about your symptoms, and a blood test and echocardiogram will be performed.

**Visit 5: End of study**
After 24 weeks, you will be asked to return for further review regardless of whether you have had a pacemaker or not. You will be asked about your current health and a physical examination will be carried out. We will ask you to complete a questionnaire about your symptoms, and a blood test and echocardiogram will be performed. If you had the exercise bike test at the start of the study, this will be repeated. This visit will last for approximately 90 minutes.

**Follow up Visit:** We will ask you to come to the Manchester Heart Centre. You will be asked about your current health and a physical examination will be carried out. A member of the team conducting the study will discuss all the findings and your current health status.

**What will I have to do?**
You must be willing to attend the scheduled visits. You should be willing to undergo the pacemaker implantation procedure if the test chosen for you suggests you may benefit. If you are female you must not be pregnant at the start of the study.

**How does this research study differ from what would happen normally?**
Patients with heart failure would usually undergo an ECG and echocardiogram as part of their routine care. When a patient receives a pacemaker normally, they would be seen again in an out-patient clinic and often a further echocardiogram will be performed.
In this study we will perform more in-depth assessments of heart function at the start and end of the study. These assessments include a more detailed echocardiogram scan as well as specific blood tests, a questionnaire, a test of walking distance, and the exercise bike test, all of which would not usually be performed in routine clinical care.
What are the possible side effects, disadvantages and risks in taking part in the study?
If you are chosen to receive a pacemaker implant the procedure will be discussed with you in detail. Pacemaker implantation is associated with small risks of:

- **Infection** – this may be treated with antibiotics, but if severe may require a further procedure and removal of the pacemaker
- **Bleeding/bruising** – occasionally a further procedure is necessary if this is severe
- **Pneumothorax** – this occurs if the lining of the lung is damaged; air can leak from the lung, causing the lung to partly or completely collapse, this may require a drainage tube to be inserted to re-expand the lung
- **Lead displacement** – occasionally one of the pacemaker leads may become dislodged, requiring a further procedure to reposition it

The risk of a complication arising as a result of the procedure is approximately 1% (1 in 100 cases). The procedure uses x-rays to guide the leads, which involves a small radiation dose which is closely monitored. The research procedure will not involve any additional x-ray exposure to that during a standard biventricular pacemaker implant.

Blood samples will be taken during the study. Drawing blood from a vein with needle may cause some discomfort and occasionally results in bruising.

We do not know who will benefit from a pacemaker and you may be one of the approximately 30% of patients that does not benefit. Although we hope ultrasound is more accurate at predicting benefit, it is possible that benefit will be less when ultrasound is used.

What are the possible benefits of taking part?
It is hoped the study will help determine the best way to select patients for biventricular pacemakers, so that nearly all patients who receive them will benefit from them in the future.

It is possible that you will be assigned to a group which tells us you may benefit from a pacemaker, when this would not be performed as part of routine care. You may then receive benefit from a pacemaker when normally you would not have received one.

The tests performed during the study will also offer a detailed assessment of your cardiac condition which would not normally be performed.

At the follow up visit we will discuss your current health based on the results of the tests you had during the study period. If you do have any health problems, we can also put you in touch with the right person to help.

What if new information becomes available?
Sometimes during a research study, new information becomes available about the subject being tested. If this happens, your study doctor will tell you, and discuss whether you want to continue in the study. If you decide to withdraw, your study doctor will make arrangements for your care to continue. If you decide to continue you will be asked to sign an updated consent form. Occasionally, your study doctor
might consider it to be in your best interests to withdraw you from the study. He/she will explain this and arrange for your care to continue.

What happens if I become unable to consent to the research during the study?
If you lose the capacity to consent to the research study during your participation, you will be withdrawn from the study. Any data collected up until that point will still be used.

What are the costs of taking part?
You will not be paid a fee to take part in the study. We will aim to schedule study appointments at the same time as routine visits, in order to minimise journeys to the hospital.

What if there is a problem?
If you have a concern about any aspect of the study, you should ask to speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you should contact the Patient Advice and Liaison Service (PALS) on 0161 276 8686.
In the event that something does go wrong and you are harmed during the research and this is due to someone’s negligence then you may have grounds for a legal action for compensation against Central Manchester and Manchester Children’s NHS Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study kept confidential?
All the clinical information you provide will be encoded (so that your personal details such as name and address are secure) and stored securely in a password protected computer.
Some parts of your medical records and the data collected for the study will be looked at by representatives of regulatory authorities and by authorised people to check that the study is being carried out correctly.

What will happen to my samples?
Your samples will be encoded so that your personal details are not stated on the sample. Some of the blood tests will be performed at another hospital. Your sample will be securely transported between the hospital laboratories. Afterwards your blood samples will be discarded.

What will happen to the results?
The results will be published in medical journals. However, no individual will be identifiable from these. You will be invited to discuss the findings with the principal investigator.

Have the ethics committee approved this study?
The study has been approved by an appropriate local Research Ethics committee.
If you wish to obtain further advice about this research you may contact one of the study investigators:

1. Dr Rajdeep S Khattar, Consultant Cardiologist  0161 276 6576
2. Dr Matthew Luckie, Clinical Research Fellow  0161 276 4574
3. Heather Iles-Smith, Research Nurse  0161 276 7958

Manchester Heart Centre,
Manchester Royal Infirmary,
Oxford Road
Manchester
M13 9WL
Appendix 2: Patient consent form

Study Number: R000176  Patient Identification Number for this trial:

CONSENT FORM FOR STUDY PARTICIPANTS

Title of Project: Electrocardiographic versus Echocardiographic Parameters of dyssynchrony in cardiac resynchronisation therapy

Principal Investigator: Dr R S Khattar

I confirm that I have read and understand the information sheet Version 1.9 dated 9th February 2009 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

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

I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from the Manchester Heart Centre, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research.

I agree to my GP being informed about my participation in the study.

I am happy to give permission for collection of blood samples and to undergo the tests involved as part of the study.

I agree to take part in the above study.

_________________  ____________________  ____________________
Name of Patient  Date  Signature

_________________  ____________________  ____________________
Name of Person taking consent  Date  Signature
(if different from researcher)

_________________  ____________________  ____________________
Researcher  Date  Signature
Appendix 3: Letter to General Practitioner

Date:

Title of Project: Electrocardiographic and Echocardiographic parameters of dyssynchrony in cardiac resynchronisation therapy

Principal Investigator: R S Khattar

GP Address

Dear Dr,

Re: Patient Name Patient DOB

The above patient has been recruited to a study which is currently running in the Manchester Heart Centre, Manchester Royal Infirmary.

The study is assessing the efficacy of electrocardiographic versus echocardiographic parameters of dyssynchrony in the selection of patients with heart failure to receive biventricular pacemakers/cardiac resynchronisation. I have enclosed a copy of the patient information sheet regarding this study, and I will write to you with relevant study results in due course.

Assessments performed during the study will include the Minnesota heart failure questionnaire, serum Brain Natriuretic Peptide (BNP) measurement, cardiopulmonary exercise testing and detailed echocardiography.

Thank you for your co-operation in this matter. Please do not hesitate to contact me if you have any concerns or questions.

Yours Sincerely,

Dr Matthew Luckie
Research Fellow, Cardiology
Appendix 4: Echocardiographic acquisition protocol

Attach ECG electrodes
Acquire 3 cardiac cycles
Note patient positioning and respiratory manoeuvres used on echo log sheet

**Parasternal Long Axis View**
- 2D image
- Zoom of colour flow MV for vena contracta
- Colour flow AV
- Colour flow AV
- M-mode of AO/LA

**Modified Parasternal Long Axis View**
- 2D image of RVOT / PV
- PW Doppler RVOT
- Colour flow TV
- Colour flow TV
- PW Doppler TV
- CW Doppler TV

**Parasternal Short Axis View**
- 2D aortic valve level
- Colour flow TV
- Colour flow MV
- M-mode LV
- Colour TDI LV – 3 cycles with left marker moved back
- Colour TDI M-mode

**Apical 4-Chamber View**
- 2D 4-chamber
- 2D zoomed on LA
- Zoom on MV / MR
- Zoom on MV / MR with colour baseline reduced to 20-30cm/s
- CW Doppler of MR
PW Doppler of mitral inflow (in breath hold)

PW Doppler of LVOT

PW Doppler for IVRT

TDI Colour loop of LV only – 3 cycles with left marker moved back

TDI colour loop of LV and RV free wall (RV free wall only if not possible to include all) – 3 cycles with left marker moved back

Colour flow AV

CW Doppler of AV

Colour flow TV

PW Doppler TV

CW Doppler TV

2D RV view

TAPSE M-mode

**Apical 2-Chamber View**

2D of LV / LA

2D zoomed on LV

2D zoomed on LA

Colour flow MV

Colour TDI – 3 cycles with left marker moved back

**Apical 3-Chamber View**

2D of LV / LA / AV

2D image zoomed on LV

Colour flow MV

Zoom of MV / MR

Zoom of MV / MR with colour baseline reduced to 20-30cm/s

CW Doppler MR

Colour TDI – 3 cycles with left marker moved back

**Subcostal View**

IVC diameter at rest / in forced expiration

**3D Probe**

LV loops for LV volumes

3D colour for MR

Dyssynchrony loops

Triplane image

Triplane image with colour TDI
Appendix 5: Minnesota Living With Heart Failure quality of life questionnaire

**MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE**

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

<table>
<thead>
<tr>
<th>Question</th>
<th>No</th>
<th>Very Little</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. causing swelling in your ankles or legs?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>2. making you sit or lie down to rest during the day?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>3. making your walking about or climbing stairs difficult?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>4. making your working around the house or yard difficult?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>5. making your going places away from home difficult?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>6. making your sleeping well at night difficult?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>7. making your relating to or doing things with your friends or family difficult?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>8. making your working to earn a living difficult?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>9. making your recreational pastimes, sports or hobbies difficult?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>10. making your sexual activities difficult?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>11. making you eat less of the foods you like?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>12. making you short of breath?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>13. making you tired, fatigued, or low on energy?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>14. making you stay in a hospital?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>15. costing you money for medical care?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>16. giving you side effects from treatments?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>17. making you feel you are a burden to your family or friends?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>18. making you feel a loss of self-control in your life?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>19. making you worry?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>20. making it difficult for you to concentrate or remember things?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
<tr>
<td>21. making you feel depressed?</td>
<td>0</td>
<td>1 2 3 4 5</td>
<td></td>
</tr>
</tbody>
</table>
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