Advanced Cardiac Resynchronisation Therapy
Methods of Improving Outcome

Shetty, Anoop

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Advanced Cardiac Resynchronisation Therapy: Methods of Improving Outcome

A thesis presented for the degree of Doctor of Medicine

Dr Anoop Shetty
MBChB BSc MRCP (UK)
King’s College
University of London
2012
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<td>6 minute walk test</td>
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<tr>
<td>AHR</td>
<td>Acute haemodynamic response</td>
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<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme</td>
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<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>ARB</td>
<td>Angiotensin receptor blocker</td>
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<td>AV</td>
<td>Atrioventricular</td>
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<tr>
<td>BIV</td>
<td>Biventricular</td>
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<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
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<td>CMR</td>
<td>Cardiac magnetic resonance</td>
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<td>CM</td>
<td>Cardiomyopathy</td>
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<td>CPET</td>
<td>Cardio-pulmonary exercise testing</td>
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<td>CRT</td>
<td>Cardiac Resynchronization Therapy</td>
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<tr>
<td>CS</td>
<td>Coronary sinus</td>
</tr>
<tr>
<td>DCM</td>
<td>Dilated cardiomyopathy</td>
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<td>DE</td>
<td>Delayed enhancement</td>
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<td>DSM</td>
<td>Dynamic substrate mapping</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EDD</td>
<td>End diastolic dimension</td>
</tr>
<tr>
<td>EDV</td>
<td>End diastolic volume</td>
</tr>
<tr>
<td>EF</td>
<td>Ejection fraction</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated Glomerular filtration rate</td>
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<tr>
<td>EGM</td>
<td>Electrogram</td>
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<tr>
<td>EN</td>
<td>Endocardial</td>
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<tr>
<td>EP</td>
<td>Electrophysiological</td>
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<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
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<tr>
<td>ESD</td>
<td>End systolic dimension</td>
</tr>
<tr>
<td>ESV</td>
<td>End systolic volume</td>
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<tr>
<td>HF</td>
<td>Heart failure</td>
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<tr>
<td>HRA</td>
<td>High right atrium</td>
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<tr>
<td>ICD</td>
<td>Implantable cardioverter defibrillator</td>
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<tr>
<td>ICM</td>
<td>Ischaemic cardiomyopathy</td>
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<tr>
<td>IVMD</td>
<td>Inter-ventricular mechanical delay</td>
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<tr>
<td>LAO</td>
<td>Left anterior oblique</td>
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<tr>
<td>LBBB</td>
<td>Left bundle branch block</td>
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<td>LGE</td>
<td>Late gadolinium enhancement</td>
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LV  Left ventricle
LVTAT  Left ventricular total activation time
MACE  Major adverse cardiac event
MCRT  Multi-polar cardiac resynchronisation therapy
MEA  Multi-electrode array
MLWHFQ  Minnesota living with heart failure questionnaire
MRI  Magnetic resonance imaging
MSP  Multi-Site Pacing
MV02  Maximal myocardial oxygen consumption
NCM  Non-contact mapping
NICE  National Institute for Clinical Excellence
NYHA  New York Heart Association
PA  Postero-anterior
QRSd  QRS duration
QOL  Quality of life
RAO  Right anterior oblique
RBBB  Right bundle branch block
RF  Radio-frequency
RVA  Right ventricular apex
SDI  Systolic dyssynchrony index
SR   Sinus rhythm
SSFP Steady state free precession
TDI  Tissue Doppler imaging
TE   Echo time
TRIV Simultaneous endocardial pacing in conjunction with CRT
TTE  Trans-thoracic echocardiography
VTI  Velocity time integral
VV   Inter-ventricular
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Above all I would like to thank my wife Eli and children, Anna and Ahan, for their longstanding patience and for making everything worthwhile.
Chapter 1. Summary of Thesis

Abstract

Aims
To determine whether new pacing lead technology can be used to overcome problems with left ventricular (LV) lead placement during cardiac resynchronisation therapy (CRT). To establish whether cardiac magnetic resonance (CMR) data can be used to guide LV lead placement in real-time at CRT implant. To establish the best method of multi-site pacing.

Methods
We investigated the incidence of problems with phrenic nerve stimulation (PNS) and high capture thresholds at implant and at 4 and 6 month follow-up periods in 40 patients who underwent CRT with a new quadripolar lead. In 20 patients we used a pressure wire to assess the acute haemodynamic response (AHR) to pacing within different regions of the coronary sinus (CS) to determine whether problems with poor AHR can be overcome with electronic repositioning. In 23 patients we used CMR acquisition, processing, overlay and registration tools to guide LV lead placement in real-time during CRT. In 12 patients we turned on the multi-site function of a quadripolar lead, implanted temporary endocardial and epicardial pacing leads and measured the AHR whilst pacing in multiple different ways.

Results
Quadripolar lead technology successfully overcame problems with PNS and high capture thresholds at implant and at follow-up but not poor AHR. A CMR dyssynchrony-guided approach to LV lead placement gave an AHR comparable to the best that can be achieved anywhere and was associated with improved reverse
remodelling at 6 months. Endocardial pacing gave the best overall AHR but in different patients different methods of multi-site pacing were best.

Conclusions

New lead technology can be used to overcome some LV lead problems but not poor AHR. Real-time CMR dyssynchrony guided CRT may be better than conventional empirical LV lead placement. Endocardial pacing gives excellent overall AHR but different methods of pacing (including multi-site) may be better in individual patients.

Key Words

Cardiac Resynchronisation Therapy (CRT); cardiac magnetic resonance (CMR); acute hemodynamic response (AHR); quadripolar leads; multi-site pacing
Thesis Aims

In this thesis I aim to look at methods of improving implant success rates using novel quadripolar lead and cardiac magnetic resonance (CMR) imaging technology. I will investigate whether there is a difference in acute haemodynamic response (AHR) to pacing in different regions of a patient’s coronary venous system and thus elucidate whether quadripolar lead technology can be used to overcome problems with poor AHR by simple ‘electronic repositioning’. I aim to see if CRT acute and chronic outcome can be improved using advanced CMR acquisition, processing, overlay and registration techniques. I will show that biophysical computer modelling can be used to predict AHR changes in silico when a heart is multi-site paced. Finally I will compare, in vivo, multiple different methods of pacing the heart from multiple sites simultaneously to see if this improves AHR compared to conventional CRT and if so determine the best method.
Chapter Overview

Chapter 2 gives an overview of the size of the heart failure problem, its current medical and device management and guidelines for treatment. This chapter also looks at how improvements to device therapy may be made and the methods of assessing this.

Chapter 3 describes patient selection and the general echo, CMR and AHR assessment methods used for the experimental work in this thesis.

Chapter 4 describes the use of a novel quadripolar left ventricular lead, our initial experience with it and its potential advantages in overcoming common CRT problems.

Chapter 5 describes a study of the acute haemodynamic response (AHR) when pacing within different areas of the same CS vein and comparing this to the AHR achieved when pacing in different veins.

Chapter 6 describes a study involving the use of CMR anatomical, dyssynchrony and scar data at time of implant to guide LV lead placement.

Chapter 7 describes the use of biophysical computer modelling to predict the effect of multi-site pacing the heart using the multi-site pacing function of a quadripolar lead.

Chapter 8 describes an acute haemodynamic and electro-anatomic mapping study of the benefits of different ways of multi-site pacing and determining the best method.

Chapter 9 discusses the main findings of my studies.

Chapter 10 is the conclusion of my thesis
**Contribution of Candidate and Colleagues**

I designed the studies described in this thesis in conjunction with my first supervisor Dr Rinaldi. I submitted the ethics applications for the studies and took them through the process of Research and Development approval. When approved I recruited the patients into the studies, performed the CMR imaging and ran the CRT assessment clinic where I performed 6 minute walk tests (6MWT) and supervised the cardio-pulmonary exercise tests (CPET) and dyssynchrony echo scans. I segmented the CMR anatomical data and helped to create the 3D anatomical cardiac models. I processed the CMR dyssynchrony data and thus helped to identify the left ventricular (LV) target segments for the PRISM pilot image guidance study. During CRT implant I operated the pressure-wire machines and supervised the overlay and registration of CMR data on to fluoroscopy. For the non-contact mapping studies I recruited the patients, co-ordinated the pressure wire and EnSite data collection during the procedures. For all studies I analysed the data collected and wrote the resulting manuscripts. The exception to this was chapter 7 (Biophysical Modelling of Multi-Site Pacing Using a Quadripolar Lead) on which I was second author on the resulting paper. This was a computer modelling study for which I provided the technical data with regards to lead specifications, location and pacing options, performed CMR data analysis and critically reviewed the manuscript.

Dr Matthew Ginks was responsible for submitting the original application to perform the CMR overlay pilot study and provided invaluable advice on how to conduct and analyse the data resulting from the pressure wire and non-contact-mapping studies.
Dr Simon Duckett performed the CMR scans and ran the CRT optimisation clinic with myself. He also performed echo and CMR analysis.

Dr Yinglaing Ma produced the computer models from the CMR data that I collected and segmented and was responsible for overlaying and registering the data at the time of CRT implant.

Dr Steven Niederer was responsible for the computer modelling simulations described in Chapter 7 and wrote the original manuscript.

Eliane Cunliffe and Sarah Arnold performed the echo and CPET studies respectively in the CRT pre-assessment clinic

Julian Bostock helped me design the pacing protocols for each of the studies and gave essential trouble-shooting advice during the invasive haemodynamic and electro-anatomic pacing studies. Julian also assisted with the interpretation of the data acquired.

Stephen Sinclair was the radiographer with whom we performed the vast majority of our CMR scans and whose experience was critical for the acquisition of quality data.

Dr Gerry Carr-White supervised the CRT pre-assessment clinic and helped with analysis of CMR and echo data.
Dr Kapetanakis has provided much statistical assistance required for these studies and also performed some of the 3D echo acquisition and analysis.

St Jude Medical UK provided technical assistance in the studies using their devices and non-contact mapping system. They also provided assistance in analysis of the electro-anatomic mapping data.

Dr C Aldo Rinaldi, Professor Reza Razavi and Dr Kawal Rhode supervised the CMR overlay project to ensure the project proceeded as planned.
Chapter 2. Introduction

Heart Failure - the Size of the Problem

Cardiovascular disease (CVD) is the main cause of death in the UK accounting for nearly 198,000 deaths or around a third of all mortality (1). 900,000 people live with definite or probable heart failure (HF) in the UK and the incidence of new HF is estimated at around 60 000 cases per year (2) or 1 in 100 in those over the age of 65 in the USA (figure 1). Survival after a HF diagnosis has improved over recent years but the death rate remains high with 50% of people diagnosed with HF dying within 5 years. As life expectancy increases and heart failure treatments improve, the prevalence of heart failure is expected to increase by 25% by 2030 (3).

Figure 1. Incidence of Heart Failure
Incidence of heart failure (diagnosis of heart failure based on physician review of medical records and strict diagnostic criteria) by age and sex (Framingham Heart Study: 1980–2003) (3)

Pathophysiology

Heart failure is a clinical syndrome that describes a constellation of symptoms that result from impaired cardiac pump function. The causes are multiple (table 1) (4) but generally patients are divided into ischaemic (HF secondary to coronary artery disease) and non-ischaemic groups depending on the results of clinical history and examination, 12 lead ECG, echocardiography, coronary angiography and, more recently, cardiac magnetic resonance (CMR) imaging.

LV systolic dysfunction because of adverse remodelling of the ventricles occurs as a result of the loss of myocytes and maladaptive changes in the surviving myocytes and extracellular matrix. The mechanism is twofold. One is because of intercurrent cardiac events such as myocardial infarction and the other is because of local processes (e.g. the autocrine pathway and molecular adaptations) and systemic processes (e.g. neurohumoral pathways) that are activated as a result of reduced systolic function. These systemic processes have detrimental effects on the functioning of the lungs, blood vessels, kidneys, bone marrow and muscles and contribute to a pathophysiological vicious cycle (figure 2). The molecular, structural, and functional changes in the heart and these systemic processes, coupled with electrolyte imbalances, result in electrical as well as mechanical dysfunction of the heart (4).
Myocardial disease
- coronary artery disease
- hypertension
- immune/inflammatory
  - viral myocarditis
  - Chagas’ disease
- metabolic/infiltrative
  - thiamine deficiency
  - haemochromatosis
  - amyloidosis
  - sarcoidosis
- endocrine
  - hypothyroidism
  - phaeochromocytoma
  - thyrotoxicosis
- toxic
  - alcohol
  - cytotoxics (e.g. trastuzumab)
  - negatively inotropic drugs (e.g. calcium-channel blockers)
- idiopathic
  - cardiomyopathy (dilated, hypertrophic, restrictive, peri-partum)

Valvular disease
- mitral stenosis/regurgitation
- aortic stenosis/regurgitation
- pulmonary stenosis/regurgitation
- tricuspid stenosis/regurgitation

Pericardial disease
- effusion
- constriction

Endocardial/endomyocardial disease
- Löffler endocarditis
- endomyocardial fibrosis

Congenital heart disease
- e.g. atrial or ventricular septal defect

Genetic
- e.g. familial dilated cardiomyopathy

Arrhythmias (brady- or tachy-)
- atrial
- ventricular

Conduction disorders
- sinus node dysfunction
- second-degree atrioventricular block
- third-degree atrioventricular block

High output states
- anaemia
- sepsis
- thyrotoxicosis
- Paget’s disease
- arteriovenous fistula

Volume overload
- renal failure
- iatrogenic

Table 1. Aetiology of Heart Failure
Figure 2. Pathophysiology of Heart Failure as a Result of Left-Ventricular Systolic Dysfunction

Damage to the myocytes and extracellular matrix leads to changes in the size, shape, and function of the left ventricle and heart more generally (‘remodelling’). These changes, in turn, lead to electrical instability, systemic processes resulting in many effects on other organs and tissues, and further damage to the heart. These vicious cycles, along with intercurrent events, such as myocardial infarction may cause progressive worsening of the heart-failure syndrome over time (5).
Medical Therapy

Medical therapy for CHF targets the pathophysiological mechanisms above. Good evidence for pharmacotherapy has accumulated over the past 20 years. Prognostic benefits in HF have been demonstrated for beta-blockers (6-8), ACE inhibitors (9-11), angiotensin receptor antagonists (12, 13), aldosterone antagonists (14, 15) and, more recently, ivabradine (16). With increased prescribing of such medication over the past 15-20 years, hospitalisation and fatality rates of HF patients has improved but the prognosis remains poor with pharmacotherapy alone (17).

Device Therapy

Rationale

Heart failure patients often have abnormal ventricular electrical conduction that may be manifest on the surface ECG as a prolonged QRS duration. Typically the QRS prolongation has a left bundle branch block (LBBB) morphology and results in the LV free wall being activated and contracting later than the inter-ventricular septum (18). Such asynchronous contraction may then disrupt mechanical efficiency causing a further reduction in cardiac output. Indeed, LBBB is an unfavourable prognostic marker in HF with a negative effect independent of age, HF severity and medication (19).

The aim of cardiac resynchronisation therapy (CRT) is to make the LV and right ventricle (RV) contract simultaneously using cardiac pacing to change the timing of electrical activity in asynchronous hearts. In patients who are in sinus rhythm this is usually done in conjunction with atrial pacing to ensure there is sequential atrial and ventricular contraction.
CRT Evidence Base

CRT has been shown to improve exercise capacity, quality of life, NYHA class and reverse remodelling (20-23). The hypothesis that prophylactic cardiac resynchronization therapy with (CRT-D) or without (CRT-P) a defibrillator would reduce the risk of death or hospitalization in patients with heart failure (HF) and intraventricular conduction delay was tested in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial (24). 1520 HF patients (NYHA class III/IV), with both ischaemic and non-ischaemic cardiomyopathy (CM) and a QRS duration greater than 120 ms, were randomly assigned to optimal medical therapy alone or with either CRT-P or CRT-D. The study found that at 12 months the risk of death or hospitalization was reduced by 34% in the CRT-P group (P<0.002) and 40% in the CRT-D group (P<0.001). Although the 24% reduction in risk of death from any cause seen in the CRT-P arm did not quite reach statistical significance (p=0.06), the 36% reduction in the CRT-D arm was significant (p=0.003).

The positive effect on mortality of a biventricular pacemaker without defibrillator (CRT-P) did reach statistical significance in the Cardiac Resynchronisation-Heart Failure (CARE-HF) study (25). This study of 813 patients followed for a mean of 29.4 months showed a 36% decrease in mortality (p<0.002) in NYHA class III/IV patients with evidence of ventricular dyssynchrony who received CRT-P compared to medical therapy alone. Thus it was established that cardiac resynchronisation therapy reduces mortality independent of concurrent ICD use in patients with NYHA class III and IV HF.
More recent studies have shown that the benefit from CRT seen in NYHA class III-IV patients in earlier studies can be extended to less symptomatic HF patients in NYHA class I and II. In MADIT-CRT (26), 1820 patients with ischaemic or non-ischaemic CM, LVEF \( \leq 30\% \), a QRSd \( \geq 130 \) ms and NYHA class I or II symptoms were randomly assigned to receive a CRT-D or an ICD alone. The primary end point was death from any cause or a non-fatal HF event. During an average follow-up of 2.4 years, the primary end point occurred in 187 of 1089 patients in the CRT-ICD group (17.2\%) and 185 of 731 patients in the ICD-only group (25.3\%) (p=0.001). It should be noted, however, that the significant reduction in the combined primary endpoint for CRT-D versus an ICD alone was driven by a 41\% reduction in the risk of heart-failure events and there was no significant difference between the two groups in the overall risk of death (3\% annual mortality in both groups).

In the RAFT study (27), patients with NYHA class II or III HF, LVEF \( \leq 30\% \) and an intrinsic QRSd \( \geq 120 \) ms or a paced QRSd \( \geq 200 \) were randomly assigned to receive either an ICD alone or a CRT-D. The primary outcome was death from any cause or hospitalization for HF. 1798 patients were followed for a mean of 40 months. The primary outcome occurred in 297 of 894 patients (33.2\%) in the CRT-D group and 364 of 904 patients (40.3\%) in the ICD group. In the CRT-D group, 186 patients died, compared with 236 in the ICD group (hazard ratio, 0.75; 95\% CI, 0.62 to 0.91; \( P = 0.003 \)), and 174 patients were hospitalized for HF, as compared with 236 in the ICD group (hazard ratio, 0.68 95\% CI, 0.56 to 0.83; \( P<0.001 \)). As in MADIT-CRT, RAFT therefore showed a reduction in HF hospitalisation in patients with mild heart failure but, unlike MADIT-CRT, RAFT showed a significant reduction in mortality in the
CRT-D group albeit with an increased risk of adverse events (haemo/pneumothorax, CS dissection, wound haematoma, pocket infection and lead displacement).

**Guidelines**

As a result of the above studies, numerous guidelines are available to help determine whom we should implant with a CRT device. One of the most recently published guidelines comes from the European Society of Cardiology (ESC) (28) and a summary of this guidance is given in table 2.

The British NICE guidelines (29) from 2007 do not specifically address the issue of patients with a concomitant class I pacing indication or those in atrial fibrillation and excludes those in NYHA class I or II heart failure from receiving a CRT. Another key difference between the ESC and NICE guidelines is that NICE specifies that patients should not only be NYHA class III-IV and have an EF ≤ 35% but the QRSd should be ≥ 150ms. If the QRSd is between 120 and 149ms a CRT should only be implanted if the patient has evidence of mechanical dyssynchrony on echocardiography. Although it is clear that patients with a very broad QRS (>150ms) are more likely to improve with CRT (26, 30), as we shall see, the NICE recommendation that mechanical dyssynchrony should be seen on echocardiography for those patients with a QRSd of 120-149ms appears outdated.
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Patient Population</th>
<th>Class</th>
<th>Level</th>
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<tr>
<td>CRT-P/CRT-D recommended to reduce morbidity and mortality*</td>
<td>-NYHA III/IV&lt;br&gt;-LVEF ≤35%&lt;br&gt;-QRS ≥120 ms&lt;br&gt;-Sinus rhythm&lt;br&gt;-Optimal medical therapy (Class IV patients should be Ambulatory†)</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>CRT preferentially by CRT-D recommended to reduce morbidity or prevent disease progression</td>
<td>-NYHA II&lt;br&gt;-LVEF ≤35%&lt;br&gt;-QRS ≥150 ms&lt;br&gt;-Sinus rhythm&lt;br&gt;-Optimal medical therapy</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>CRT-P/CRT-D should be considered to reduce morbidity*†</td>
<td>-NYHA III-IV&lt;br&gt;-LVEF ≤35%&lt;br&gt;-Permanent atrial fibrillation&lt;br&gt;-Pacemaker dependency induced by AV nodal ablation</td>
<td>IIA</td>
<td>B</td>
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<tr>
<td>CRT-P/CRT-D should be considered to reduce morbidity*†</td>
<td>-NYHA III-IV&lt;br&gt;-LVEF ≤35%&lt;br&gt;-Permanent atrial fibrillation&lt;br&gt;-Slow ventricular rate and frequent pacing (≥95% pacemaker dependence)</td>
<td>IIA</td>
<td>C</td>
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<tr>
<td>CRT-P/CRT-D recommended to reduce morbidity*‡</td>
<td>-NYHA III/IV&lt;br&gt;-LVEF ≤35%&lt;br&gt;-QRS ≥120 ms&lt;br&gt;-Concomitant class I pacemaker indication</td>
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<td>CRT-P/CRT-D is recommended to reduce morbidity*‡</td>
<td>-NYHA III/IV&lt;br&gt;-LVEF ≤35%&lt;br&gt;-QRS &lt;120 ms&lt;br&gt;-Concomitant class I pacemaker indication</td>
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<td>CRT-P/CRT-D is recommended to reduce morbidity*‡</td>
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<td>IIb</td>
<td>C</td>
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Table 2. 2010 Update of ESC Guidelines on Device Therapy in Heart Failure

*Class=class of evidence. Recommendation=Level of Evidence (28)

*Reasonable expectation of survival with good functional status for 1 year for CRT-D. Patients with a secondary prevention indication for an ICD should receive a CRT-D.
‡No admissions for HF during the last month and a reasonable expectation of survival 6 months

CRT Implant Failure and ‘Non-response’

In 5-15% of patients undergoing CRT, it is not possible to implant an LV lead (31-33). This may because of an inability to cannulate the coronary sinus (CS) ostium, an inability to pass the LV lead into a CS branch, unsatisfactory pacing parameters, or phrenic nerve stimulation (PNS). In a study of 197 consecutive patients undergoing CRT, Biffi et al (34) showed that clinically relevant PNS occurred in 22% of patients at CRT implant or follow-up and that its occurrence was highest in those patients for whom the LV lead was placed at pacing sites most associated with reverse remodelling. In the aforementioned study, 7% of patients required an LV lead revision or CRT to be turned off.

We have seen that when a CRT device is successfully implanted, it can improve heart failure symptoms, exercise capacity and quality of life as well as causing reverse remodelling and reducing hospitalizations and risk of death in patient populations with LV dysfunction and a broad QRS. Around 30% of patients do not respond to CRT, however, in terms of improvement in symptoms, reverse LV remodelling, freedom from hospitalisation or indeed death (25, 35). This may be because the LV is not paced optimally (36) or because the patient will not respond to CRT no matter where the LV lead is placed.
Thus strategies to improve CRT outcome include:

- Developing better methods of identifying patients who will respond to CRT
- Reducing CRT implant failure
- Selecting and pacing the regions of the LV most likely to improve electrical and mechanical dyssynchrony
- Optimisation of device settings
- Pacing the heart in novel ways

Patient Selection

Although there is good evidence that the patients most likely to respond to CRT have a QRSd $\geq$ 150ms, a recent meta-analysis(37) of 5 CRT RCTs reporting clinical events according to different QRS ranges suggests that, regardless of NYHA class, only those patients with a QRS duration greater than 150ms have a significant reduction in clinical events (death/ hospitalizations). The NICE guideline requirement that patients should have mechanical dyssynchrony on echo (see Chapter 2 General Methods) if they have a QRSd of 120-149ms reflects the fact that this patient cohort is less likely to respond to CRT than those with a QRSd $\geq$ 150ms. Nonetheless, this requirement appears outdated since the 2008 PROSPECT multi-centre study (38) was published. In this study of 498 patients undergoing CRT, 12 conventional and tissue doppler echo parameters were assessed as to their usefulness in predicting response to CRT. Despite site training in acquisition methods and central analysis, there was large variability in the analysis of the dyssynchrony parameters and no single echocardiographic measure of dyssynchrony could be recommended to improve patient selection.
Given the poor predictive value of standard and tissue doppler echo parameters in determining who will benefit from CRT, attention has turned to other methods of identifying likely responders. These include strain imaging (39) and scar burden as assessed by myocardial perfusion imaging (40) and CMR(41).

**Reducing Implant Failure**

Failure to cannulate the CS ostium or an inability to pass the LV lead into a CS branch can sometimes be predicted by pre-procedure imaging with cardiac magnetic resonance (CMR) imaging or CT. If the requisite sequences have been performed, the implanter may simply view the CMR or CT images prior to the implant to gain an idea of what to expect during the procedure. It is also possible for the CS anatomy to be overlaid on to fluoroscopic images in real-time during the implant itself to guide the operator (**Figure 3**) (42).

![Figure 3. Overlay of CS Anatomy on to Fluoroscopy](image)

**(A)** An occlusive venogram. **(B)** The overlay of 3D coronary sinus (CS) segmentation from CMR imaging with a centre line for both the venogram and the overlaid coronary veins. This is used to determine the registration error. **(C)** How the overlaid coronary veins appear to the operator during an implant. This image was taken during the occlusive venogram to show the close correspondence with anatomy (42)
Imaging may be particularly helpful for inexperienced operators who have difficulty in locating the CS os using radiological landmarks alone. Perhaps more importantly, however, imaging may identify a thebesian valve or small CS os that may make CS intubation difficult for implanters of all ability. Such imaging can also identify unusual CS anatomy such as a persistent left sided vena cava (43). Even if these imaging modalities are not available at implant, in cases where there has been failure to gain CS access at first attempt, imaging can be used to guide any reattempt.

Figure 4. CMR Image Overlay to Guide Implant in a Patient with Persistent Left-Sided Vena Cava

*Image showing how CMR data can be used to create an anatomical model of the cardiac chambers and CS (connected to persistent left sided vena cava) which is then overlaid at implant. The hand injection venogram shows that the CS and great cardiac vein are massively dilated with no obvious target vessels for LV lead placement seen. The overlay depicted in blue shows the position of the branches and selective occlusive venogram of the posterior vein of the LV (PVLV) corresponds with the overlaid anatomy. The LV lead seen in its final position in the distal PVLV. LSVC= left subclavian vein; LMV=left marginal vein (43)*
Other reasons for CRT implant failure are high lead capture thresholds or PNS at implant or follow-up. PNS and high capture thresholds are a particular problem with the LV lead because of the anatomy of the phrenic nerve and the relative technical difficulty in manipulating the LV lead into different positions if an initial site is unsatisfactory. One potential solution to this problem is ‘electronic repositioning’. This involves changing the pacing vector used to stimulate the LV and at least 4 different pacing configurations are usually possible with current LV leads. Quadripolar left ventricular leads currently allow the greatest number (10) of possible pacing configurations because of the two extra ring electrodes located on the LV lead compared to conventional bipolar leads (44). Chapter 3 will look in detail at quadripolar lead technology as a method of overcoming CRT implant failure and describes our experience of using this lead.

**Targeted LV Lead Placement**

The LV lead is often placed in a postero-lateral or lateral position in the CS as early studies suggested that this position generally produced the best haemodynamic response (45, 46). Patients may not respond to such empirical lead placement if they have postero-lateral scar (36, 47), however, and more recent large scale studies have shown no overall difference in CRT response when an LV lead is placed in an anterior, posterior or lateral position (though a mid or basal location appears superior to an apical position) (48-50).

Thus, although LV lead positioning appears to be critical to the likelihood of CRT response, the ideal target region for an individual patient is not clear. Derval et al (51) systematically assessed the haemodynamic response to LV pacing from 10 endocardial
and 1 epicardial (CS) predetermined LV sites in a random order: basal and mid-cavity (septal, anterior, lateral, inferior), apex, coronary sinus (CS), and the endocardial site facing the CS pacing site. They found major inter-individual and intra-individual variations in haemodynamic response depending on the LV pacing site but concluded that an optimal LV pacing site cannot be defined a priori and is specific to each individual (Figure 4). Thus although there do not appear to be large group differences in general anatomical site of LV lead placement, there are large differences within patients and we need to develop methods of identifying and targeting the region of the LV that will give the best response to LV pacing within an individual patient.

**Figure 5. Best and Worst Pacing Sites.**

*Distribution of best (A) and worst (B) left ventricular pacing site among the 11 tested sites demonstrates that no one site is consistently best (or worst) (51).*

Recently Khan et al (52) have used strain imaging to identify the most delayed segment of contraction and absence of scar. The authors conducted an RCT in which they targeted LV lead placement in the most delayed viable segment defined by speckle-
tracking echocardiography compared with usual care. They found that compared with standard CRT treatment, the use of speckle-tracking echocardiography to target LV lead placement significantly improved clinical status and reduced the combined endpoint of death and heart failure-related hospitalization.

CMR dyssynchrony data can be used as an alternative to echo indices and Chapter 5 describes its use in conjunction with CMR-derived anatomical information to guide LV lead placement during CRT implant. Although the temporal resolution of CMR is lower than echo it has the advantage of better spatial resolution and the availability of scar data if delayed enhancement (DE) imaging is used. Chapter 5 details how CMR dyssynchrony can be used not only to identify patients likely to respond to CRT but, in conjunction with overlay technology, how CMR scar and dyssynchrony data can be used in real-time to guide LV lead placement at implant to the region most likely to respond to pacing.

**CRT Optimisation**

The optimal outcome from CRT may be dependent on optimal programming of the pacemaker device. The atrio-ventricular (AV) timing of the device can be programmed such that it allows adequate time for passive filling of the ventricles but not so much time that the ventricles have a chance to beat on their own. The LV-RV (VV) delay can be programmed such that both ventricles contract in the most synchronised way. The AV and VV delay settings are usually optimised using echocardiography derived indices although other methods (e.g. using a pressure wire, impedance cardiography,
pulse pressure) can be used to choose the timings that appear to give the best cardiac output.

Echo assessment of AV dyssynchrony can be measured using a pulsed wave doppler recording of trans-mitral inflow (Figure 6), which requires the sample volume to be placed at the tips of the mitral leaflets (53).

Figure 6. Optimisation of AV Delay after CRT

The pulsed doppler mitral inflow pattern is seen. At a programmed AV delay of 180 ms (left panel) the closure of mitral valve occurs before the onset of ECG QRS. Optimizing AV delay at 120 ms (right panel), the diastolic filling time is much longer and the duration of atrial filling is preserved (53).
VV interval optimisation probably has less of an effect on overall cardiac output but may have a small additive benefit (53). The ideal VV interval is usually determined by the delay that gives the best aortic or LVOT VTI measurement (a surrogate for cardiac output) (figure 7).

Figure 7. VV Interval Optimisation.

Interventricular interval delay using left ventricular outflow tract (LVOT) measurements of blood flow velocities for estimation of stroke volume (SV). Stroke volume is exponentially related to the left ventricular outflow tract diameter and directly to the velocity–time integral (VTI) of the left ventricular outflow tract. Variation of the interventricular interval (VV) interval affects the stroke volume as evidenced by varying volume–time integral measurements that can serve as surrogate markers for resynchronization. The optimal interventricular interval in this example is derived from pacing the right ventricle (RV) 40 ms before the left ventricle (LV). (54)
Although some centres expend considerable time and resources optimising CRT timings at implant and/or follow-up device checks, the evidence that this makes a difference to outcome is equivocal. The RHYTHM II ICD study (55) single-blind randomized trial of 121 CRT patients found no difference in outcome (freedom from CRT-D system–related complications/NYHA class/6 minute walk distance (6MWD)/quality of life) at 6 months between those patients randomised to an echo optimised VV delay versus those whose devices were programmed to pace both ventricles simultaneously. Similarly, the DECREASE-HF multicentre randomized trial (56) evaluated 306 CRT patients after 6 months and found no significant difference in reduction in LV end-systolic and end-diastolic dimensions in those patients randomised to sequential BiV (optimised VV delay) pacing versus simultaneous BiV or LV only pacing. Indeed there was a trend toward greater echocardiographic improvement in the BiV simultaneous group.

More recently Ellenbogen et al’s SMART-AV study (57) randomised 980 patients who received a CRT-D in a 1:1:1 ratio to a fixed empirical AV delay (120 ms), echocardiographically optimized AV delay or AV delay optimized with SmartDelay (a proprietary electrogram-based algorithm). At six months, no significant difference in the primary endpoint of reduction in ESV or the secondary endpoints of change in LVEDV, LVEF, 6MWD, quality of life, and NYHA class were seen between arms. The authors thus concluded that the routine use of the AV optimization techniques assessed in that trial were not warranted. It was conceded, however, that in certain patients who do not respond to CRT, AV delay optimisation may be useful.
Acute Haemodynamic Response

The maximum rate of rise of intra-ventricular pressure (dP/dt max) has been used as a marker of global myocardial contractility for many years (58). dP/dt max correlates with event-free survival (59, 60) and can be derived in a reproducible manner by invasive measurement. This can be performed using a pressure wire passed to the LV cavity, giving haemodynamic data in real-time which can be used to assess baseline LV contractility and the acute haemodynamic response (AHR) to pacing in different ways (61, 62). More recently data from our own centre has shown that AHR is a useful predictor of reverse remodelling at 6 months in patients with both ischaemic and non-ischaemic aetiologies (63).

For our studies we used a fine calibre (0.014 inch) high fidelity Certus pressure wire (RADI Medical Systems, Uppsala, Sweden) with a torque similar to an angioplasty wire. There is a pressure sensor located 30mm from its tip (Figure 8) that records intraventricular pressure with a frequency of 600Hz.

![Figure 8. RADI Pressure Wire Structure.](image)

When making measurements with the pressure wire is important to maintain a constant heart rate as dP/dt max is influenced by heart rate through the force-frequency response. dP/dt max is also to some degree dependent upon the loading conditions of the heart being increased by factors causing an increase in pre-load or afterload. The changes in
loading conditions during the time-frame of an acute haemodynamic assessment, however, are likely to be small, with changes in afterload predominating due to changes in vascular tone. The maximum rise in pressure probably occurs during the isovolumetric phase of ventricular contraction and this is less influenced by afterload than parameters derived from the ejection phase of ventricular systole. Nonetheless it is important during studies to try to keep intra-vascular volumes stable and minimise changes in sympathetic drive (avoiding over and under-sedation).

Multi-site and Endocardial Pacing

Although many studies are underway investigating the possible advantages of pacing from two or more left ventricular sites rather than the conventional one for cardiac resynchronisation therapy (CRT), no large studies have yet been published. What follows is a summary of the small studies performed thus far.

In 2000, Pappone et al (64) hypothesized that pacing two left ventricular sites simultaneously would produce faster activation and better systolic function than single-site pacing. 14 heart failure patients (NYHA III or IV) in normal sinus rhythm with left bundle branch block and a QRS duration greater than 150 ms were studied. Pacing leads were positioned via the coronary veins at the posterior base and lateral wall. Patients were acutely paced VDD at the posterior base, lateral wall, and both sites (dual-site) with 5 atrio-ventricular delays (from 8 ms to PR -30 ms) in a random order. Dual-site pacing increased peak dP/dt max significantly more than posterior base and lateral wall pacing (figure 9). Dual-site and posterior base pacing raised aortic pulse pressure significantly more than lateral wall pacing. Dual-site pacing shortened QRS duration by 22 %, whereas posterior base and lateral wall pacing increased it by 2 and 12%,
respectively (p = 0.006). The authors therefore concluded that in heart failure patients with left bundle branch block, dual-left ventricular site pacing improves systolic function more than single-site stimulation. The authors suggested that improved ventricular activation synchrony (narrowing of the paced QRS) may have accounted for the additional benefit of dual vs single-site pacing in enhancing contractility.

Figure 9. Pappone et al Multi-site Pacing Study

Bar graph comparing haemodynamic changes produced by single-site pacing from the posterior base or lateral wall and by dual-site pacing. For each of the three pacing strategies, haemodynamic effects were not significantly different in patients grouped by aetiology of heart failure (ischaemic, n = 4; idiopathic, n =10). DCM = dilated cardiomyopathy LVEDP = left ventricular end-diastolic pressure; PP = pulse pressure(64)

In 2008 Padeletti et al (65) reported a small study of acute haemodynamic response to simultaneous stimulation of 2 LV sites. Two LV pacing leads were successfully implanted in 12 CRT candidates (NYHA class III-IV, QRS duration greater than
120ms). Target positions were the lateral or posterolateral vein (site A) and anterior or anterolateral vein (site B). Tested CRT configurations were alternated by atrial overdrive pacing at a fixed rate and included site A and B single-site CRT and dual-site LV CRT (2 LV sites plus right ventricular apex) at 4 atrioventricular intervals. Overall, single-site LV CRT significantly enhanced stroke volume, stroke work, maximum pressure derivative and conductance-derived indexes of LV synchrony when delivered in site A whereas no significant changes were noticed with pacing in site B. Specifically, site-A pacing resulted in a higher stroke volume increase. Indeed, site-A LV pacing was associated with the best hemodynamic response in 8 patients, and site-B in 4 patients. At intermediate atrioventricular intervals, dual-site LV CRT resulted in improved stroke volume, stroke work, maximum pressure derivative, and LV synchrony with respect to single-site CRT delivered at the best-LV site (all p <0.05). However, single-site CRT at the best-LV site produced results similar to dual-site LV CRT when the atrioventricular interval was optimized in each patient. The authors thus concluded that adding a second LV lead did not result in further improvement in acute haemodynamic response with respect to standard CRT when the single LV pacing site and atrioventricular interval are optimal.

The TRIP-HF (66) (TRIPle Resynchronization in Paced Heart Failure Patients) trial was designed to examine whether biventricular stimulation with 1 right ventricular (RV) and 2 LV leads increases the response to CRT and produces a greater improvement in cardiac performance and LV reverse remodelling than standard biventricular stimulation in patients with permanent atrial fibrillation. This multicenter, single-blind, crossover study enrolled 40 patients (mean age 70+/−9 years) with moderate-to severe heart failure despite optimal drug treatment, a mean LVEF of 26+/−11%, and permanent atrial fibrillation requiring cardiac pacing for slow ventricular rate. A CRT device connected
to 1 RV and 2 LV leads (inserted in 2 separate coronary sinus tributaries spaced as widely apart as possible), was successfully implanted in 34 patients.

After 3 months of biventricular stimulation, the patients were randomly assigned to stimulation for 3 months with either 1 RV and 2 LV leads (3-V) or to conventional stimulation with 1 RV and 1 LV lead (2-V), then crossed over for 3 months to the alternate configuration. The primary study end point was quality of ventricular resynchronization (Z ratio). Secondary end points included reverse LV remodelling, quality of life, 6MWD and procedure-related morbidity and mortality. Data from the 6 and 9 month visits were combined to compare end points associated with 2-V versus 3-V. Data eligible for protocol-defined analyses were available in 26 patients (table 3). No significant difference in Z ratio, quality of life and 6-min hall walk was observed between 2-V and 3-V. However, a significantly higher LV ejection fraction (27 +/-11% vs 35+-11%; p=0.001) and smaller LV end-systolic volume (157+/− 69 cm3 vs 134+/−75 cm3; p=0.02) and diameter (57+/−12 mm vs 54+/−10 mm; p=0.02) were observed with 3-V than with 2-V. There was a single minor procedure-related complication. The conclusion of the study was that cardiac resynchronization therapy with 1 RV and 2 LV leads was safe and associated with significantly more LV reverse remodelling than conventional biventricular stimulation.
Lenarczyk published a further study of triple-site (dual LV site, single RV site) pacing versus conventional CRT. Fifty-four patients in NYHA class III–IV, EF ≤35% and QRS ≥120 ms were included. 27 received triple-site pacemakers (TRIV group) and 27 conventional CRT devices (BIV group). The procedure duration was higher in the TRIV than in the BIV group (197.6 vs. 137.6 min, P=0.001), fluoroscopy exposure and complication-rates were similar. After 3 months of CRT, triple-site pacing was associated with a more significant (P=0.05) NYHA class reduction (by 1.4 vs. 1.0 class), increase in VO2 max (2.9 vs. 1.1 mL/kg/min) and 6MWD (98.7 vs. 51.6 m) than conventional CRT. A higher EF and more improved intraventricular synchrony were observed in the TRIV than in the BIV group. The response rate in the TRIV group was 96.3% vs. 62.9% in the conventional group (P=0.002). Triple-site stimulation was an independent predictor of response to CRT (adjusted odds ratio 26.4, p=0.01). The conclusion of this study was
that triple-site resynchronization appeared to be more beneficial than conventional CRT and that an upgrade to triple-site CRT should be considered in non-responders to standard resynchronization. The authors do note, however, that this was a retrospective, non-randomized, single centre observational analysis whereby a triple-site technique was compared with an historical group of patients who had previously undergone a standard CRT implant (67).

Our own centre published a study of dual epicardial (CS) site pacing versus conventional CRT in 2011 (68). This was a single centre acute haemodynamic study on 20 patients (ischaemic and non-ischaemic aetiology). Standard RA +RV leads were used and a St Jude Medical Quickflex or Medtronic 4196 LV lead. One lead was placed in a postero-lateral vein (LV1) and a 2nd lead in a lateral, anterior or middle cardiac vein (LV2). LV $dP/dt_{max}$ was recorded using a pressure wire during stimulation at LV1, LV2 and both sites simultaneously (LV1 + LV2). Patients were deemed acute responders if the increase in LV $dP/dt_{max}$ was $\geq$10%. It was found that multi-site LV pacing increased the AHR by 16% vs. single-site pacing and was particularly beneficial in patients with postero-lateral scar identified on CMR (figure 10).
More recently, Rogers et al (69) also published a study of dual epicardial site pacing. The authors describe how 43 patients were implanted with a TRIV device (RV apical lead + 1 lateral CS LV lead + a further CS or RV lead). In all patients an attempt was made to place a 2nd epicardial CS lead and if this was not possible a 2nd RV lead (placed in the high RV septum) was implanted. Devices were programmed in a randomized order to four pre-determined pacing configurations: conventional BiV, TriV, and dual-site and single-site left biventricular (LV) or RV pacing for 3-month periods with clinical and echo assessment at the end of each period. Compared with BiV pacing, TriV pacing resulted in significant improvements in 6MWD, quality of life, reduction in LV ESV and improvement in LVEF even in the patients who received 2 RV leads rather than 2 LV leads (table 4).
Table 4. Rogers et al. Multi-Site Pacing Study

Comparison of results for baseline, and after BiV and TriV pacing (69)

Pacing the LV epicardially via the CS is limited by the distribution of the CS veins. Thus even if echo or CMR were to suggest that a particular region of the LV was the latest activated and most likely to respond to LV pacing, it may not be possible to pace there because no CS vein overlies the target area or the CS tributary is inaccessible. LV endocardial pacing is not constrained by CS vein anatomy and there is evidence to suggest that pacing from the LV endocardium is more physiological and thus results in better electrical and mechanical propagation and AHR (70, 71). Indeed there is recent evidence to suggest that not only is pacing the LV endocardium better than conventional epicardial LV pacing, but that when conventional epicardial LV pacing via the CS and RV is added to LV endocardial pacing, there is an additive effect on AHR.

In a recent study of 10 patients (7 ICM and 3 DCM) at our institution by Ginks et al (72) a temporary LV pacing lead was placed in a CS branch and an LV endocardial catheter placed in anterior, posterior and lateral positions in the LV cavity. Various combinations of LV endocardial (LVEN), RV and LVEN (BIVEN), conventional CS epicardial and RV (BIVCS) and conventional BIVCS pacing with LVEN (TRIV) pacing were assessed for AHR. TRIV pacing resulted in the greatest overall mean increase in AHR (figure 11) and reduction in QRSd. All forms of endocardial pacing
tested (LVEN, BIVEN, TRIV) were significantly better than conventional BIVCS pacing.

Figure 11. Ginks et al. TRIV Study

*The AHR to pacing using different RV, endocardial and epicardial configurations*
To summarise the findings of multi-site pacing studies thus far:

- Pappone et al found an acute haemodynamic advantage to pacing two LV sites simultaneously compared to one.

- Pedeletti found that although there was an improvement in acute haemodynamic response from dual LV site pacing, there was no significant difference between this and single site LV pacing in the optimal site and with the optimal AV delay.

- TRIP-HF looked specifically at patients with atrial fibrillation and found no difference between dual site LV pacing and conventional CRT in terms of its predefined echo-derived primary endpoint (Z ratio). It did, however, perhaps more importantly, find a significant improvement in ejection fraction and reduction in LV end systolic volume and diameter when patients were paced ‘3-V’ (dual site LV and RV pacing) than ‘2 V’ (conventional single site RV and LV CRT pacing).

- Lenarczyk’s study is the largest of the published multi-site pacing studies and appears to confirm the findings of TRIP-HF and the early work performed by Pappone i.e. pacing two left ventricular sites is better than one. Lenarczyk found significant improvements in NYHA class, VO2 Max and 6MWD in the TRIV group compared to the standard BIV group. Indeed the responder rate was an astonishing 96% in the TRIV paced group. This was, however, a retrospective non-randomised study.
• Rogers et al found that TRIV pacing (including from 2 RV sites) was associated with significant improvements in clinical and echocardiographic parameters compared with BiV pacing.

• Ginks et al found that pacing from two epicardial LV sites increased the acute response by 16% vs. single-site pacing and was particularly beneficial in patients with postero-lateral scar. In a separate study, Ginks et al found that LV endocardial pacing was better than conventional biventricular pacing and that the combination of LV endocardial, RV and LV epicardial (CS) pacing gave a particularly good AHR with significant reduction in QRSd.

Although the data regarding multi-site LV pacing is limited to small studies, some of which are non-randomised, there is evidence to suggest that pacing the ventricles form more than the usual 2 RV and LV sites may be more beneficial than conventional CRT and endocardial pacing may be associated with a particularly good AHR.

Non-Contact Mapping

The idea of reconstructing intra-cavity potentials mathematically without contact with the walls of the heart was reported by Taccardi et al. in 1987 (73). The authors described how ‘pseudoisochrone’ contour maps recorded from an array of semi-direct electrodes, regularly distributed on the surface of an intraventricular probe could provide information on the site of origin of ectopic paced beats in a normal dog heart. The derived potentials were found to be spatially averaged and of lower amplitude than the raw signal, however. Non-contact mapping (NCM) has evolved since then and is now used clinically, for recording and mapping electrical potentials particularly in
cases, for example, such as right ventricular outflow tract tachycardia where activation mapping and pace mapping may have limited use because of infrequent ventricular ectopy or non-sustained VT (NSVT) (74, 75).

For the purposes of our study (Chapter 7) the EnSite 3000 non-contact mapping system (St Jude Medical, Sylmar, USA) was used. This consists of a multi-electrode array (MEA) with 64 laser-etched electrodes mounted on a wire braid on a 8mm balloon (figure 12). This is seated on a 9F catheter, which allows introduction of the balloon into the chamber of interest (with the balloon deflated).
The geometry of a chamber can be reconstructed using a low current locator signal emitted from the tip of the MEA, at 5.68Hz. This is sensed by two ring electrodes mounted on either side of the MEA balloon. With this system, other catheters can be localised in 3D. A roving electro physiological (EP) catheter is moved around the chamber to define the location of the chamber walls in 3D. The array then records intra-cavity far-field potentials that are sampled at 1.2kHz and digitally filtered at 0.1-300Hz. The resulting signals are resolved using the inverse solution to Laplace’s equation by the boundary element method. This allows mathematical reconstruction of
over 3000 virtual unipolar electrograms, which are superimposed on the chamber geometry. Both isopotential and isochronal maps can be generated, with colour coding to allow the endocardial activation pattern to be visualised. Data can be analysed off-line in any orientation. Dynamic substrate mapping (DSM) is an algorithm that can be used to mark areas of substrate activation by observing how isopotential maps display the wavefront moving around lines of block, anatomic barriers, zones of slow conduction, or diseased tissue within a cardiac chamber.

Schilling et al (76) demonstrated that the EnSite 3000 noncontact mapping system accurately reconstructs endocardial unipolar electrograms from the human left ventricle at distances from the MEA centre to endocardium (M-E) of up to 34mm. Using NCM, Auricchio et al showed the high prevalence of functional lines of block in patients with LBBB, often with the pattern of activation taking a “U-shape” around the area of slow conduction (figure 13). Furthermore, the authors found that areas of slow conduction could be defined by low voltage or fragmented electrograms and concluded that NCM could be useful in identifying and targeting specific locations that are optimal for successful CRT.
Figure 13. Type II LV Activation Pattern

*Figure demonstrating a U-shaped activation front that rotates around the apex and activates the lateral wall late. NCM = non-contact mapping; CM=contact mapping*(77)

Lambiase et al (78) performed an NCM study to characterise the effect of CRT on left ventricular activation and to examine the electrophysiological factors influencing optimal left ventricular lead placement. The authors demonstrated that pacing the LV in an area of slow conduction was associated with a significantly reduced haemodynamic benefit from CRT when compared with pacing outside these areas. Biventricular pacing the left ventricle 32 ms before the right ventricle appeared to induce the optimal mean velocity time integral (VTI) and timing for fusion of depolarisation wavefronts from the RV and LV pacing sites. Furthermore, pacing outside regions of slow conduction was found to decrease left ventricular activation time (LVAT) and increase cardiac output.
and dP/dt_{max} significantly thus suggesting that the mechanism of improved AHR was correction of the delayed LV activation.

Fung et al (79) performed a non-contact-mapping and echo study of 23 optimally treated patients with NYHA class III HF, QRS duration ≥120 ms and LVEF≤35%. The authors’ aim was to evaluate patients’ electromechanical properties by NCM and echo tissue Doppler imaging (TDI) and determine its relationship to CRT response. The authors described two distinct types of activation pattern (as previously described by Auricchio et al (77)) in patients with intra-ventricular conduction delay and found that CRT response was higher in the patients with (type II) functional block as compared with a more homogeneous (type I) activation pattern in terms of improvement in functional status, significant LV reverse remodelling and reduction of clinical events at 3 month follow-up.

Finally, Ginks et al (71) performed a study of 15 patients (age, 63 +/- 10 years; 12 men) awaiting CRT in a combined x-ray and CMR laboratory. Patients underwent CMR DE imaging and an electrophysiological study incorporating endocardial and epicardial LV pacing. The AHR during different modes of pacing was determined using a pressure wire and NCM was used to define areas of slow conduction. The authors found a significant improvement in all LV pacing modes versus baseline (p<0.001) and that LV endocardial CRT from the best endocardial site was superior to conventional CRT (P<0.05). The haemodynamic benefits of pacing were greater when LV stimulation was performed outside of areas of slow conduction defined by NCM (p<0.001). The authors also found that CMR DE imaging was able to delineate zones of slow conduction seen with NCM in ischemic patients but was unreliable in non-ischaemic patients.
We have thus seen that since it’s development in the 1980s non-contact mapping has evolved and is now considered a useful tool not only for research purposes but also clinically in patients in whom characterisation of infrequent ectopic beats or NSVT is not possible with conventional activation or pace mapping. It has been shown that pacing outside areas of slow conduction identified by NCM is likely to lead to a better AHR and that NCM can be used to characterise the LV activation pattern in patients with heart failure and thus determine the likelihood of response to CRT. Those with a type II or ‘U shaped’ activation pattern appear to have a predominantly non-ischaemic aetiology and it is these patients who are most likely to respond to CRT both acute and chronically. NCM accuracy is reduced as the distance of the MEA from the endocardial surface increases but at distances up to 34mm is considered reliable.

**Body Surface Potential Mapping**

This is a non-invasive method of reconstructing electrical sources in the heart using an 80-channel active electrode system. As part of our Multi-Site Pacing Haemodynamic and Electro-anatomic Mapping Study (Chapter 7) we have ethical approval to use the ACTIVETWO system manufactured by BIOSEMI (figure 14). BSPM has already been used to reconstruct the location of infarcted areas of the heart and the site of simulated ventricular ectopics (80). Although body surface potential mapping has been available for many years it has not been validated against contact or non-contact mapping techniques. Although I performed pilot work to confirm that it was possible to use BSPM prior to CMR in patients pre-CRT, the logistics of placing the electrode system on our Multi-Site Pacing Haemodynamic and Electro-anatomic Mapping Study patients meant that we have not yet been able to compare this non-invasive mapping system to
the NCM. This will happen in the future and if successful BSPM may negate the need for such an invasive method of determining the electrical activation patterns of the heart.

![Body Surface Potential Mapping](image)

**Figure 14. Body Surface Potential Mapping**
Personalised Models of the Heart (‘Grand Challenge’)

We have seen from Derval et al’s (51) work that the best pacing site for individual patients cannot be determined \textit{a priori} and that the best and worst site is different in different patients. We have also seen that the best method of pacing in patients may be multi-site or endocardial. In this thesis I describe various invasive studies that I undertook to determine the AHR and electro-anatomic mechanism underlying response whilst pacing in different ways. Ideally, however, we would be able to determine whether a patient was going to respond to therapy before implanting a device and if so predict the best site and method of pacing a patient using simple, non-invasive means.

We have seen in the section above that BSPM is one non-invasive method of gaining detailed information about electrical activity in the heart. ‘The Grand Challenge Modelling’ Project (see Appendix 2) seeks to address this issue by creating biophysical models of left ventricular mechanical, electrical and haemodynamic function from data acquired from echocardiography and cardiac magnetic resonance imaging that can predict the mechanical, electrical and haemodynamic response to CRT

Using echo, CMR, CPEX, 6MWT and MLWHFQ data on patients pre-CRT and regular repeat measures at regular follow-up (CMR will only be performed pre-implant), the study aims to combine this data with invasive pressure wire and electro-anatomic mapping data to create computer models of patients’ hearts. By modeling the hearts of patients pre-CRT and the changes that occur at regular intervals after CRT, it is hoped that we will be able to use this data to create accurate models of the hearts of patients who have not yet been implanted with a device (using echo and/or CMR data as a base). Thus simulations will be created of what will happen in response to pacing patients’
hearts in different ways pre-CRT. It may then be possible in the future to decide not to implant a device in a patient that computer modeling predicts will not respond to any form of CRT. It may also be possible to determine the exact type (conventional/endocardial or multi-site) and site of pacing that will give the best response in a particular patient.

I designed the study protocol and submitted the research ethics application for this study (which has been approved). Prior to completing my 2 year research period I recruited the first patients to this multi-centre study. The Grand Challenge Modelling Project is a large on-going collaboration between various UK research institutions that will take at least 2 more years to complete. Thus although no results from this study are yet available, the potential application of the technology developed is exciting.

An example of the computer modelling that is currently available (based on historic CMR, NCM and AHR data) is described in chapter 7 (81). This chapter brings together the use of quadripolar lead technology, multi-site pacing and computer modelling. This is detailed study of 1 patient involves simulating multiple different methods of multi-site pacing the heart and thus predicts the resulting AHR and changes in electrical activation that would be seen. It is this type of model we hope to be able to create using non-invasive data pre-CRT. We would thus be able to non-invasively assess the response of an individual to different types of pacing and this would enable us to decide whether CRT is a worthwhile option in a particular patient and if so the best place to position the leads and the best pacing configurations for that individual.
Chapter 3. General Methods

Patients

St Thomas’ Hospital local ethics committee approved all of the studies described in this thesis (Appendix 2). All patients provided written informed consent. Studies were performed in compliance with the Declaration of Helsinki.

Patient Selection

Inclusion Criteria

Patients with a CRT device generally fulfilled NICE guidelines (29):

- Heart failure with New York Heart Association (NYHA) Class III-IV symptoms
- Patients should be on optimal medical therapy
- Have significantly impaired LV function (ejection fraction <35%)
- QRS duration >150ms on ECG or QRS duration between120 and 149ms with evidence of dyssynchrony on echocardiography.
- Age > 18 years

Exclusion Criteria

- Contra-indication to CMR scan
- Significant renal impairment (eGFR<30ml/min/1.73m²)
- Expected survival < 6 months
- Contra-indication to anticoagulation
- Left ventricular thrombus
- Severe peripheral vascular disease
Baseline Assessment

- History and clinical examination
- Routine blood tests including FBC, U&E, CRP
- Minnesota Living With Heart Failure Questionnaire (MLWHFQ)
- 6 Minute Hall Walk Test (6MWD)
- 12 lead electrocardiogram (ECG)
- 2D and 3D echocardiography
- CMR scan

Echocardiography

Echocardiographic assessment was performed using a VIVID 7 machine (General Electric, Milwaukee, USA) for 2D/3D imaging and an IE33 machine (Philips Medical Systems, Andover, Massachusetts) for 3D imaging. Standard views (parasternal long and short axis, apical 2,3,4 and 5 chamber and subcostal) were used. The St Thomas’ Hospital echo acquisition and analysis protocols are shown in figure 15 and figure 16 respectively.
Figure 15. St Thomas’ Hospital Echocardiographic Acquisition Protocol

LAX: long axis; SAX: short axis; 2C: 2 chamber; 3C: 3 chamber; 4C: 4 chamber; TDI: Tissue Doppler Imaging; PW: Pulsed Wave; TR: Tricuspid Regurgitation; LVOT: LV outflow tract; VTI: Velocity Time Integral; CW: Continuous Wave; RVOT: RV outflow tract; PV: pulmonary valve; MV: mitral valve
Figure 16. Echocardiographic Parameters for Analysis

TsSD: standard deviation in the time from Q wave to peak systolic contraction in the 12 segment model; SDI: systolic dyssynchrony index; CFM: colour flow mapping; t-IVT: total iso-volumic time; MPI: myocardial performance index; PASP: Pulmonary artery systolic pressure; WMSI: wall motion score index; IVC: inferior vena cava.
Echo Dyssynchrony

Echocardiographic evidence of dyssynchrony was deemed present if any of the following criteria were fulfilled:

- LV pre-ejection period (LVPEP) > 140ms
- Interventricular mechanical delay (LV minus RV pre-ejection period) > 40ms
- Septal to lateral wall motion delay (TDI) > 60ms
- 3D Systolic dyssynchrony index > 10.4% (82)

Measurement of LV and RV Pre-Ejection Periods

Pulsed wave Doppler was used with the measurement made from the LV outflow tract (LVOT) in an apical 5 chamber view. The RV outflow tract (RVOT) was viewed in a parasternal short axis view. The pre-ejection period was defined as the time from the QRS onset on the ECG to the onset of flow.

Tissue Doppler Imaging (TDI)

Figure 17 shows an example of colour-coded TDI to assess intra-ventricular dyssynchrony (septal-lateral wall delay). Once acquired this data requires post-processing to determine the wall velocities and whether dyssynchrony is present. The requirement that the basal septal to lateral wall motion delay should be ≥ 60ms is based on work by Bax et al (83, 84) suggesting that this predicts improvements in LVEF and reverse remodelling when a CRT device is implanted.
Problems with TDI include the fact that two distinct peaks of tissue velocity may be seen during systole, giving rise to difficulties in measuring intervals. Furthermore, peak velocities may occur after the end of systole, giving rise to uncertainty as to whether these should be included in analysis. The PROSPECT study (38) found that there was great inter-observer variability in taking TDI measurements and thus although it may be effective in predicting outcomes when preformed by centres with special expertise, given that only between 37% and 82% of TDI measurements were interpretable by the core labs, the authors concluded that current technology, degree of training standards and analytic methods do not allow the use of TDI in a generalized setting.

Figure 17. Tissue Doppler Imaging

Colour-coded four-chamber tissue Doppler image (upper left). Post-processing yields velocity tracings (right); severe left ventricular dyssynchrony is present as indicated by the delay in the peak systolic velocity of the septum (yellow curve) as compared to the lateral wall (blue curve)(85)
3D Echo Systolic Dyssynchrony Index

A 3D volume was acquired over multiple cardiac cycles using a single breathhold. This was analysed to give an accurate LVEF, LVEDV and stroke volume. Using TomTec software (TomTec Imaging Systems, Unterschleissheim, Germany) the 3D volume was subdivided into 16 sub-volumes (figure 18). It was then possible to derive time-volume data for the entire cardiac cycle and assess the time taken to reach the minimum systolic volume. The standard deviation of these values across 16 segments was expressed as a percentage of the cardiac cycle to give the systolic dyssynchrony index (SDI), which is a marker of LV global dyssynchrony (86).
Figure 18. Real-Time 3D Echo

Image showing a 16 segment model created from a RT3DE acquisition (87)

Real-time 3DE (RT3DE) has been shown to predict acute response to CRT (88) and, more recently, Kapetenakis et al (82) have shown that patients with a RT3DE SDI of ≥10.4% are highly likely to respond to CRT in terms of reduction in NYHA functional class, 20% relative increase in LVEF and 15% reduction in LV end-systolic volume. Interestingly, in the afore-mentioned study, RT3DE SDI appeared to be equally predictive of response in patients not fulfilling traditional selection criteria (atrial fibrillation, QRS duration <120 ms, or undergoing device upgrade).

A limitation of RT3DE is the large volume of acquisition required and this gives rise to relatively poor temporal resolution. It may also be difficult to get adequate quality acquisitions in patients with atrial fibrillation as the technique relies on regular R-R intervals. Thus, in our experience, adequate quality 3D volume acquisitions in heart failure patients can only be obtained in around 75% of patients. In contrast, it is possible to get adequate 2D datasets (sufficient to calculate ESV/EDV and LVEF) in virtually all patients (using contrast if necessary).

Cardiac Magnetic Resonance

CMR scans were performed on a Philips 1.5T scanner (Philips Medical Systems, Best, the Netherlands), using either a 32 channel or 5 channel coil (if patients were obese or claustrophobic with the 32 channel coil). Patients with renal failure (eGFR<30ml/min/1.73m²) did not receive contrast because of the possible increased risk of
nephrogenic systemic fibrosis with gadolinium based contrast agents (although this risk is low(89)).

**Interactive Planning**

Interactive imaging was performed using rapid SSFP sequences to plan the geometry to be used in subsequent sequences. Four viewing windows were used to show the active imaging plane as well as its relationship to three previously acquired images (figure 19). The line in any of the three other images could be moved in order to change the angle of the active imaging plane itself. In addition the active imaging plane could be displaced in parallel planes to that which is shown using the “pull/push” function. Geometries were stored for use later in the CMR examination.
There is marked individual variation in the coronary venous anatomy which can make implanting an LV lead via the CS challenging. The CS venous anatomy can be visualised at implant using a CS balloon occlusion venogram involving the injection of an iodine-based contrast agent during fluoroscopy. This does not, however, give any information about myocardial scar that may underlie possible target tributaries rendering them unsuitable for CRT. It may therefore be useful to have data regarding coronary venous anatomy and scar prior to device implant.

Multi-slice CT can be used to visualize the coronary venous anatomy in three dimensions but involves ionizing radiation and nephrotoxic contrast agents (90). CMR has the advantage of not using ionizing radiation and being able to give information on myocardial scar as well as coronary venous anatomy. The coronary veins can be
assessed with (91, 92) or without (93) an intravenous contrast agent by employing an MTC-prepulse.

Although CMR intravenous contrast agents may allow good visualisation of the coronary venous anatomy, they do not give useful scar information. Conversely, conventional extra-vascular contrast agents used for CMR delayed enhancement (DE) imaging give good scar information but have only been shown to give good quality coronary venous anatomy visualisation in patients with normal LV function (94). Heart failure patients are more likely to have arrhythmias and irregular breathing patterns that make standard CMR image acquisition very challenging.

Thus, until recently, if both coronary venous anatomy information and scar information were required from an MR scan, patients may have undergone two separate CMR scans to allow the injection of both intra and extra-vascular agents to gain coronary venous anatomy and scar information respectively. Duckett et al (95), however, recently described the use of the gadolinium-based contrast agent dimeglumine-gadobenate (Gd-BOPTA) to acquire both coronary venous anatomy information with delayed enhancement imaging during the same CMR acquisition.

Studies had already shown that Gd-BOPTA allowed assessment of myocardial scar and viability that is comparable with conventional extravascular contrast agents (96, 97). Using the fact that Gd-BOPTA has high relaxivity (r1=9.7(mmol/L)-1 s-1 at 1.5 Tesla) and only a weak interaction with serum albumin, Duckett et al showed in 12 heart failure patients that a whole heart CMR acquisition combined with an inversion
recovery (IR) preparation allowed excellent visualisation of the coronary venous anatomy (comparable with intra-procedure CS balloon occlusion venography) and myocardial scar in a single CMR examination (95).

Using the protocol described by Duckett et al (95), we performed cardiac synchronization with vector electrocardiography (VECG). After localization and a coil sensitivity reference scan, an interactive real-time scan was performed to determine the geometry of the SA, 4CH, 3CH and 2CH. A multiple slice (M2D) cine steady state free precession (cine-SSFP) scan was performed in SA orientation to assess the ventricular function (FA=60°, TR/TE=2.9/1.5ms, resolution 2.2x2.2x10mm, 30 heart phases). The 4CH, 3CH and 2CH views were used to assess LV function for regional wall motion abnormalities. Visual assessment of the 3CH (FA=60°, TR/TE=3.0/1.5ms, resolution 2.5x2.5x10mm, 60 heart phases) view was used to determine timing of the end systole.

For the contrast enhanced coronary vein scan 0.1 mmol/kg Gd-BOPTA TA (Multihance™, Bracco Imaging SpA, Milan, Italy) was infused at a rate of 0.3ml/sec with subsequent saline flushing. In order to determine the optimal start point of the whole heart coronary vein MR-scan, a dynamic ECG-triggered 2D-scan with inversion recovery (IR) preparation (TI=300ms) was used. For coronary vein visualization, an ECG-triggered respiratory navigated 3D IR-SSFP MR-scan was applied to acquire the whole-heart during a short interval (60-80ms) in end systole using a centric profile order and the following parameters: FA=50°, TI=300ms, TR/TE=4.25/1.44ms, SENSE=3-4 (with SENSE =2 AP direction and SENSE=1.5-2 in RL-direction), resolution 1.5 x 1.5 x 2mm (average number of slices 180±15).
Patients were told to breathe normally throughout the whole heart acquisition and not too deep or too shallow. The overall scan time for the protocol would be 3.5 min assuming a 100% respiratory gating efficacy but gating efficacy was usually around 30% and the whole heart acquisition could take over 20 minutes in patients with irregular breathing patterns or arrhythmias. After the coronary vein scan, a delayed contrast-enhanced multi-slice IR gradient echo sequence (FA=25°, TR/TE= 5.8/2.0ms) was performed at end systole to depict areas of scar. A preceding Look-Locker sequence was used to determine the optimal inversion time TI (320±22ms) to null the signal of the myocardium.

**CMR Analysis**

**Volume Analysis**

Philips Viewforum™ analysis package was used to draw endocardial contours in end-diastolic and end-systolic phases for each slice (typically 10mm thick) in the short axis stack (which covered the whole heart in a series of breath holds). Thus LV and RV volumes and LVEF were calculated (figure 20).
The endocardial border has been manually drawn in green and epicardial border in yellow

Model Creation

The endocardial surfaces of all four cardiac chambers and the epicardial surface of the LV were extracted automatically by using a model-based segmentation algorithm (98) from the 3D IR-SSFP whole heart image. The CS was manually segmented from the whole heart image using ITK-SNAP (99) to yield a highly detailed anatomical model which included the CS main branch and three sub-branches.
LV Motion Analysis

The cine MR data were analyzed using the TomTec 4D LV Analysis tool (TomTec Imaging Systems, Unterschleissheim, Germany). Much like the TomTec echo analysis tool, the LV surface was divided into 16 segments and the regional volume computed as a function of the cardiac cycle. Based on regional volume, 16 mechanical delay motion curves are generated (figure 21).

Figure 21. Regional Volume Map

*Image showing 16 segment model top left; activation front is shown top middle; 16 segment model superimposed on CMR top right; 16 segment regional volume map bottom right*
Scar

In patients with myocardial scar, the position and extent was determined from the DE CMR. These image data were registered to the whole heart MR data. The 3D myocardial scar was segmented by manual segmentation using ITK-SNAP (figure 22).

Figure 22. Manual Segmentation of Scar

*Upper panel shows short axis DE image. Lower panel shows same image with scar manually segmented in red (100)*

A fully automated approach to scar segmentation was also trialled. The tool (developed at King’s College London) (100) involves projecting scar data on to the LV epicardial surface using a maximum intensity projection. A binary image was thus generated to give a regional distribution of scar on the LV epicardial surface. Although the automatic segmentation tool is quick (typically taking around 5 seconds to generate the model),
the quality of the model produced depends on the quality of the DE imaging and some manual correction is sometimes required.

**Invasive Haemodynamic Assessment**

Femoral or radial access was attained using a 5F sheath and an exchange length (210cm) 0.035 inch diameter wire was passed retrogradely across the aortic valve into the LV cavity using a pigtail catheter. The pigtail was then exchanged for a 5F multi-purpose catheter and the exchange wire then removed. A 0.014 inch diameter Certus pressure wire (RADI Medical Systems, Uppsala, Sweden) was connected to a RADI analyser and then flushed and calibrated when placed level on the patient’s body. The pressure wire was then passed through the multi-purpose catheter into the LV cavity. The multi-purpose catheter was then removed. To minimise the risk of thromboembolic complications from the pressure wire in the systemic circulation, 2500 units of heparin was then administered. The RADI analyser was connected to a laptop equipped with PhysioMon software (figure 23).
LVdP/dt\textsubscript{max} was calculated electronically from every heartbeat for a period of at least 20 seconds to ensure steady-state conditions. The results were averaged for the complete measurement period. A waiting period of at least 20 seconds was respected after any change in pacing settings or lead position to achieve hemodynamic stabilization. This method has previously been shown to reliably measure LVdP/dt\textsubscript{max} (61, 62, 101). LVdP/dt\textsubscript{max} during atrial pacing or RV pacing (atrial fibrillation [AF] patients) at 5–10 beats above intrinsic rate (to eliminate the effect of heart rate variation) was considered baseline and was kept constant when testing different pacing modes (102). Data from
premature ventricular complexes were discarded. Results during pacing modes were expressed as a percentage change from baseline. In order to minimize the effect of baseline drift in AHR (secondary to changes in patient intravascular volume/sedation levels, etc.) on the results, the baseline was reassessed prior to and after every LV lead reposition. Thus, the AHR during LV pacing was compared to a mean of the baseline taken immediately before and after each lead position change. The mean baseline drift in intrinsic LVdP/dt\textsubscript{max} seen in a previous invasive hemodynamic study that we performed was 68 ± 17mmHg (9.4 ± 2.4% change from mean baseline) (103). Using the methods above to correct for baseline drift in LVdP/dt\textsubscript{max} the mean variability in AHR seen when repeated measurements were taken was 4.8 ± 5.2%.

**Statistical Methods**

Statistical analysis was performed on JMP (version 9.0.1, Marlow, Buckinghamshire, UK) and PASW Statistics 20 (SPSS Inc, Chicago, IL, USA). Group comparisons were performed using a t-test or an appropriate non-parametric test (Wilcoxon rank sum, Kruskall-Wallis). Pearson’s correlation coefficient was used to measure the linear relationship between two variables and Chi squared test to compare categorical variables. All results are expressed as mean ± SD. P values of < 0.05 were considered statistically significant. Where 3 or more different pacing modalities were tested within individual patients, a repeated measures ANOVA was used to compare pacing modalities. All pacing methods were compared to each other and to avoid type 1 errors, p values were corrected using the Bonferroni adjustment. To perform a Bonferroni correction for each p value, the p value was divided by the number of comparisons made.
Chapter 4. Quadripolar Leads

Abstract

Background: The Quartet model 1458Q (St. Jude Medical, Sylmar, CA, USA) lead is a quadripolar left ventricular (LV) lead with pace/sense capability from four electrodes (tip and three rings). The lead is capable of pacing in 10 different configurations rather than the three that are available in conventional bipolar pacing leads. We describe a single-centre initial experience of the use of this lead in patients undergoing cardiac resynchronization therapy (CRT).

Methods: Forty patients underwent attempted CRT-D implantation between October 2009 and October 2010 with a Quartet lead. Pacing parameters, lead position, complications and presence of PNS were collected at implant, pre-discharge and at 15 ± 8 weeks and 6 month follow-up.

Results: A quadripolar LV lead was successfully implanted in 95% (38/40) of patients. During follow-up, one patient (3%) had a lead displacement requiring reposition. LV pacing parameters remained stable at 6 months (mean threshold 1.3 V at 0.6 ms and impedance 948 ohm). PNS at the time of implant was observed in 12 patients (32%) all of which were overcome by using the additional vectors available on the quadripolar LV lead or by repositioning the lead at the time of implant. At 6 months follow-up there were five (13%) cases of PNS, all of which were successfully treated by reprogramming to a different vector. No cases required reintervention, surgical epicardial lead placement, or that lead be turned off.

Conclusion: The Quartet lead is associated with a high implant success rate, stable pacing parameters and a low displacement rate during the first 6 months after implant. The ten LV pacing vectors available with this lead allowed PNS and capture threshold
problems to be overcome at implant and at follow-up, thus obviating the need for lead reposition.
**Introduction**

**Quadripolar Leads**

Failure to implant an LV lead successfully during attempted CRT occurs in 5-15% of cases (31-33). This may be because of failure to cannulate the CS ostium, an inability to pass an LV lead into a CS branch, procedural complications such as CS dissection, unsatisfactory pacing parameters (high capture thresholds or poor R-wave sensing) or phrenic nerve stimulation (PNS).

The Quartet model 1458Q (St. Jude Medical, Sylmar, CA, USA), is a quadripolar LV pacing lead that has three ring electrodes in addition to the distal tip electrode thus allowing pace/sense capability from four LV electrodes. These electrodes are spaced 20, 30 and 47 mm from the distal tip and the lead body has a maximum 4.7-French (F) diameter (5.1F at the level of the ring electrodes). All four electrodes may act as cathode and two may act as anode (M2 and P4). The right ventricular coil of the shocking lead may also act as an anode thus giving 10 possible bipolar and unipolar pacing configurations (D1-M2, D1-P4, D1-RV coil, M2-P4, M2-RV coil, M3-M2, M3-P4, M3-RV coil, P4-M2, and P4-RV coil – **figure 24**). Conventional LV pacing leads usually have only 2 LV lead electrodes and 3 different pacing configuration options. We hypothesized that the 10 different LV pacing vectors available with the Quartet lead may allow problems with PNS and high capture thresholds to be overcome non-invasively because if the initial configuration used is unsatisfactory there are 9 other pacing options available.
Biffi et al (34) prospectively observed 197 patients undergoing CRT specifically looking for the prevalence of PNS. They found that it occurred in 37% of patients at CRT implant or 6 month follow-up and was clinically relevant in 22%. They found that PNS often was not manifest at implant (whilst supine) because in some patients it only occurred whilst lying in the left lateral position or sitting. Overall 7% of all patients in that case series required an LV lead revision (5%) or for CRT to be switched off (2%) as a result of PNS that could not be managed non-invasively.
Methods

All patients provided informed consent and fulfilled standard National Institute for Clinical Excellence (NICE) guidelines for implantation of a cardiac resynchronization device with cardioverter defibrillator (CRT-D) i.e. New York Heart Association (NYHA) class III symptoms despite optimal medical therapy, a left ventricular ejection fraction (LVEF) less than 35% and QRS duration greater than 120ms. The implantation procedure was performed with a standard technique involving cannulation of the coronary sinus, identification of a suitable target vein with a contrast agent and fluoroscopy, and placement of the quadripolar LV pacing lead using an over-the-wire technique. The target coronary sinus branch vein was usually the posterolateral vein.

Patients

We looked initially at the first 28 patients (table 5) who underwent implantation with a Quartet lead at St Thomas’ Hospital and followed them up for a mean of 15 ± 8 weeks (104). We then performed a further study of the first 40 patients (table 6) implanted with a Quartet lead and extended the follow-up to 6 months post CRT (105).
Table 5. Baseline Quartet Patient Characteristics

The baseline characteristics of the initial 28 patient cohort (104)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>28</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.9 ± 15.3</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>82/18</td>
</tr>
<tr>
<td>Ischemic/nonischemic (%)</td>
<td>50/50</td>
</tr>
<tr>
<td>New York Heart Association class (%)</td>
<td>2.9 ± 0.5</td>
</tr>
<tr>
<td>Indication—primary/secondary prevention (%)</td>
<td>75/25</td>
</tr>
<tr>
<td>Previously implanted system (%)</td>
<td>39</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25.1 ± 7.1</td>
</tr>
<tr>
<td>Sinus rhythm (%)</td>
<td>91</td>
</tr>
<tr>
<td>QRS morphology</td>
<td>68% LBBB, 14% nonspecific intraventricular conduction delay and 18% had a placed rhythm</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>151.0 ± 19.5</td>
</tr>
</tbody>
</table>

The optimal pacing vector was chosen at the operator’s discretion based upon satisfactory pacing parameters and absence of PNS at the time of implant. In cases of PNS, the initial strategy was to reprogram to a different vector with the same lead position. If this did not result in an acceptable vector without PNS and a satisfactory LV capture threshold, then the lead was repositioned either to a different site in the same vein or to an alternate vein. Evidence of PNS was sought by pacing at 10 V at a pulse width of 0.5 ms in all patients using at least one vector. Capture thresholds were tested using a pulse width of 0.5 ms or 0.4 ms. At follow-up, all capture thresholds were tested using a pulse width of 0.5 ms. The time, contrast, and radiation doses for all patients were recorded. Venous access was left to the operator’s personal preference.
Detailed assessment of the pre-implantation coronary sinus venogram and post-implantation fluoroscopy and chest radiograph images were made to ascertain the final LV lead position as categorised by coronary sinus vein branch (posterolateral, lateral, anterolateral and anterior branches or middle cardiac vein) and basal LV, mid-LV or apical LV position.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>40</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.8, SD 14 (range 24–82)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>32/40 (80)</td>
</tr>
<tr>
<td>Ischaemic aetiology (%)</td>
<td>23/40 (58)</td>
</tr>
<tr>
<td>NYHA Class 3</td>
<td>39/40 (97)</td>
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<tr>
<td>NYHA Class 4</td>
<td>1/40 (3)</td>
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<tr>
<td>Indication—primary prevention</td>
<td>28/40 (70)</td>
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<tr>
<td>Indication—secondary prevention</td>
<td>12/40 (30)</td>
</tr>
<tr>
<td>Previously implanted system (%)</td>
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<tr>
<td>LVEF (%)</td>
<td>25.8, SD 6.7</td>
</tr>
<tr>
<td>Sinus rhythm (%)</td>
<td>33/40 (83%)</td>
</tr>
<tr>
<td>QRS morphology</td>
<td></td>
</tr>
<tr>
<td>LBBB non-paced</td>
<td>29/40 (72)</td>
</tr>
<tr>
<td>LBBB paced</td>
<td>6/40 (15)</td>
</tr>
<tr>
<td>Indeterminate BBB</td>
<td>5/40 (13)</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>149.7, SD 17.2</td>
</tr>
</tbody>
</table>

SD standard deviation, NYHA New York Heart Association Class, LVEF left ventricular ejection fraction, LBBB left bundle branch block

Table 6. Baseline Quartet Patient Characteristics (40 patient cohort)

Baseline Patient Characteristics of the first 40 Quartet patients (105)
Data Analysis

This was a small descriptive observational cohort study and statistical analysis was limited. Categorical variables were described by absolute number (n) and percentage (%). Continuous variables with a normal distribution were described using mean and standard deviation (SD). Comparisons of continuous variables with a normal distribution were by Student’s t-test.

Results

Initial 28 Patient Cohort

A Quartet lead and CRT-D device (Promote Q model CD3221-36 or Promote Quadra model CD 3239-40Q generator; St Jude Medical, Sylmar, CA, USA) was successfully implanted in 27 (96%) of all patients. The conventional D1-M2 bipolar pacing configuration was used as the final pacing vector in 56% of patients. PNS was found at implant in 41% of patients. In 8 of these 11 patients PNS was successfully overcome by changing the pacing configuration and in the remaining 3 patients physical repositioning of the LV lead was required. Two patients were found to have PNS at follow-up that was successfully overcome by ‘electronic’ lead repositioning. In a further 2 patients whose capture thresholds were found to have risen at follow-up, a change in pacing configuration overcame the problem in both cases.

Follow-up data for this cohort of patients revealed 1 LV lead displacement (4%) at latest follow-up and although this is perhaps higher than the published literature (106) it
represents just one case. Major adverse cardiovascular events (MACE) were low at 4% at a mean follow-up of 15 weeks. Most cases of PNS at implant were resolved simply by changing the pacing vector and all cases at pre-discharge pacing check or latest follow-up were overcome by changing the pacing configuration or reducing the pacing output. No patients required their CRT to be switched off because of PNS. Rises in capture thresholds were also successfully overcome during follow-up simply by changing the pacing vector.

**6 month Follow-up**

A Quartet lead was successfully implanted in 38/40 patients (95%). In one unsuccessful case, we were unable to pass the quadripolar lead beyond an existing LV lead that could not be extracted with traction. There were no other viable coronary sinus branch options in this patient. The other unsuccessful case was abandoned as the patient was unable to tolerate the procedure because of frank haemoptysis and did not wish to undergo a repeated attempt at implantation.

**Implant Characteristics**

Vascular access for implantation was left subclavian/axillary vein in 29/40 (73%), left subclavian/axillary and cephalic vein in 6/40 (15%) and cephalic vein only in 5/40 (13%). The left ventricular lead was successfully placed via the coronary sinus in a posterolateral branch in 21/38 patients (55%), lateral branch in 12/38 (32%), anterolateral branch in 3/38 (8%) and middle cardiac vein in 2/38 (5%). At the time of implant the final LV lead position of D1 (distal tip electrode) was apical in 19/38 (50%) patients, mid LV in 17/38 (45%) patients and basal LV in 2/38 (5%) patients.
Of the 38 cases successfully implanted with a quadripolar LV pacing lead, the final LV lead configuration was conventional bipolar D1–M2 in 25/38 (66%) of cases. In the remaining 13/38 (34%) patients, the optimal final vector was M3–M2 in 5/38 (13%), M2–P4 in 3/38 (8%), D1–RV coil in 2/38 (5%), D1–P4 in 1/38 (3%), M3–P4 in 1/38 (3%) and P4-RV coil in 1/38 (3%). Overall we utilised a pacing vector that did not incorporate D1 (and therefore used electrodes not available in current conventional bipolar CRT systems) in 10/38 (26%) of cases. The D1 electrode was not used as part of the pacing vector in 8/19 (42%) cases where the D1 pole position was apical and in 2/19 (11%) cases where the D1 pole position was basal-mid LV.

Lead Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Implant (n=38)</th>
<th>24 h (n=38)</th>
<th>3 months (n=35)</th>
<th>6 months (n=35)</th>
</tr>
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<tbody>
<tr>
<td>Time from implant (days)</td>
<td>12.5 SD 0.71</td>
<td>1.35 SD 0.76</td>
<td>1.25 SD 0.79</td>
<td>1.30 SD 0.69</td>
</tr>
<tr>
<td>LV capture threshold (V)</td>
<td>0.5 SD 0.1</td>
<td>0.5 SD 0.1</td>
<td>0.6 SD 0.2</td>
<td>0.6 SD 0.2</td>
</tr>
<tr>
<td>Pulse width (ms)</td>
<td>891.2 SD 240.3</td>
<td>899.9 SD 265.9</td>
<td>923.5 SD 251.2</td>
<td>948.3 SD 292.4</td>
</tr>
<tr>
<td>Impedance (Ω)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD standard deviation, LV ventricular, V volts, ms milliseconds

Table 7. LV Pacing Parameters Over 6 Months

*LV pacing parameters for the Quartet LV lead over the first 6 months post implant*

Table 7 shows the LV lead pacing parameters at implant and follow-up. During the follow-up period, 2/38 (5%) patients died and 1/38 (3%) patient was lost to follow-up. Six month follow-up data were therefore available for 35/38 (92%) patients. During the first 3 months, the LV pacing parameters remained stable with satisfactory LV capture threshold and impedance (mean 1.25 V at a mean pulse width of 0.6 ms and 924Ω, respectively) (figure 25). During the first 3 months, there was one case (1/35 (3%)) of
loss of LV capture due to lead displacement. This required a lead reposition, which was carried out successfully. One patient had a significant rise in LV capture threshold from 1 V at 0.5 ms at the time of implant, 1.75 V at 0.5 ms 24 h after the procedure and subsequently 4.5 V at 1 ms at 3 months. This was successfully managed by reconfiguring the pacing vector from M3–M2 to D1–M2 leading to an LV capture threshold of 1.25 V at 0.5 ms.

![Graph showing LV capture threshold and impedance trends](image)

**Figure 25. LV Capture Threshold and Impedance Trends**

*LV capture threshold (V) and impedance trends (Ω) with the Quartet lead during the first 6 months after implant.*

Six-month follow-up data are available for 35/38 (92%) patients (table 7). The LV pacing parameters remained stable with satisfactory LV capture threshold and impedance (mean 1.30 V at a mean pulse width 0.6 ms and 948Ω, respectively) (figure 21). Compared with implant data there was no significant change in mean LV capture threshold (1.30 vs. 1.25 V; p=0.3). Lead impedance measurements demonstrated a statistically significant rise over the first 6 months (948Ω vs. 891Ω; p=0.04) but
remained acceptable. There were no further lead displacements. One patient had a notable rise in LV capture threshold from 1.5 V at 0.5 ms at the time of implant to 1.75 V at 0.5 ms 24 h post procedure, 2 V at 1 ms at 3 months and subsequently 3.75 V at 1.5 ms at 6 months. Due to previous problems with PNS in all other configurations this patient was successfully managed with prolonging the pulse width and using the D1–P4 vector.

**Phrenic Nerve Stimulation (PNS)**

See figure 26.

**PNS at Implantation**

PNS was seen at the time of implant in 12/38 patients (32%) with one or more pacing vectors. Of these 12 cases, five (42%) had ischaemic heart disease and seven (58%) cases had a dilated cardiomyopathy. In 9/12 (75%) cases PNS was successfully overcome by changing the pacing vector configuration without the need to reposition the lead. Of these nine cases with PNS, seven had PNS in the conventional bipolar configuration of D1–M2. In these seven patients, the vector was successfully changed to M2–P4 in 2/7 patients, to D1–RV coil in 2/7 patients, to M3–M2 in 1/7 patients, to M3–P4 in 1/7 patients and to D1–P4 in 1/7 patients. LV lead repositioning was required in the remaining 3/12 (25%) patients with PNS at the time of implant in whom it was not possible to overcome problems of PNS by reprogramming the pacing vector in the initial vein of choice. In all three cases PNS was overcome by repositioning ± subsequent reprogramming the quadripolar lead. The final vector in these three cases was as follows: D1–M2 in two cases and M3–M2 in the third case. No cases required
referral for surgical epicardial LV lead placement. Of the cases with PNS at implant, 9/12 (75%) had the D1 electrode positioned in an apical position and 3/12 (25%) in a basal-mid LV position. Of the nine PNS cases with an apically positioned D1 electrode, LV pacing using a more proximal vector that excluded D1 was used to successfully ameliorate PNS in 7/9 (78%) patients. In the basal-mid LV position, pacing using a more proximal pole was similarly useful in 1/3 (33%) of patients. Overall, in 8/38 (21%) cases the quadripolar lead eliminated PNS by using a proximal pacing vector that did not use D1 where a conventional bipolar lead configuration may have been unsuccessful.

**PNS during Follow-up**

Five patients (13%) developed PNS during follow-up, of which three cases had not been observed at the time of implant. All cases were successfully managed by reprogramming using vectors on the quadripolar lead which would not have been available with a standard bipolar lead. No patients required repeat intervention or for the lead to be turned off due to PNS. Four patients experienced PNS during the first 3 months of follow-up. Two of these cases had not been observed at the time of implant. At 3 months, changing the LV pacing vector from D1–M2 to M3–M2, and D1–M2 to M3–M4, respectively, successfully alleviated these cases of PNS. Of the remaining two cases observed to have PNS at the time of implant, one patient had been successfully managed with a lead reposition during the index implant and one patient with a change in pacing vector. The former case was successfully managed with changing the pacing vector from D1–M2 to M2–P4. The latter case was managed by reducing the pacing output in the same vector D1–P4. Of these four cases with PNS observed during the first 3 months follow-up, the final position of the D1 pole at implant was apical in 3/4
cases and of these 2/3 were successfully managed by pacing using a more proximal vector that did not use D1. The fifth case of PNS seen at the 6-month follow-up had not been apparent either at implant or at 3 months follow-up. The lead position was also apical and was successfully managed by changing the pacing vector from D1–P4 to the more proximal vector M2–P4. Overall, all five cases were successfully managed using a pacing vector that stimulated the LV more proximally without the need to reposition the lead.
Figure 26. PNS and Programming Changes

Flow diagram showing the occurrence of PNS and subsequent pacing vector programming changes with the Quartet lead.

Quadripolar Leads and Previous Failed Implant

Four patients, two males and two females with mean age 55+21 years, underwent re-attempt at LV lead implantation at our institution between March and May 2010 (table 8). All four patients had New York Heart Association (NYHA) class III symptoms of heart failure of a non-ischaemic aetiology. The mean left ventricular ejection fraction (LVEF) was 28 ± 8.7% prior to reattempt at LV lead implantation. Three patients were in sinus rhythm and one was in atrial fibrillation. In our institution, we aim to place the LV lead in an optimal CS vein for resynchronization and this usually means a posterolateral or lateral position. In these four difficult cases, the main determinant of LV lead position was a pacing configuration that gave the best pacing parameters (lowest capture threshold with good R-wave) without PNS.

In all four cases, a Pacesetter St. Jude Quartet lead model 1458Q and Promote Q Model CD3221-36 generator (St Jude Medical) were successfully implanted. The mean procedure time for the four cases was 157.5+42.1 min. The fluoroscopy time was 18.2+19.8 min with a radiation dose of 1178+1417.2 cGycm2. Pacing parameters were stable at pre-discharge pacing check and follow-up of 8.5+5 weeks.
Table 8. Patient Characteristics pre-Quartet lead implant.

We have already established that the advantage of the Quartet lead over other leads with cathodal programmability is the number of vectors available. Thus, if problems with PNS or high capture thresholds are encountered, it offers more pacing configurations than other CRT systems and may allow patients with previous failed attempts at LV lead implantation the potential to have a successful transvenously placed LV lead rather than the options of either an epicardial surgical approach to CRT or no CRT at all.

The M3–M2 vector used as the final configuration in two of our patients is not available with other bipolar LV leads but, interestingly, the D1-M2 (conventional bipolar LV pacing) and D1-RV coil (only available when a shocking lead is in situ i.e. CRT-D) vectors used in the other two patients can be programmed with other CRT systems. The fact that we were also successful in these cases using conventional bipolar configurations suggests that the handling characteristics and lead geometry of the Quartet lead may have allowed us to attain a position in the CS that was different from the bipolar leads previously used.
Discussion

Initial reports from our centre and others have confirmed satisfactory initial results with quadripolar LV lead technology. Our current implant and follow-up data demonstrates that the quadripolar Quartet LV lead was successfully implanted in the vast majority of patients and importantly in patients where previous attempts at LV lead implantation had been unsuccessful either due to poor LV capture threshold or PNS. During the first 6 months after implant LV capture threshold and impedance remained satisfactory. No patients were referred for a surgical epicardial LV lead or had the LV lead switched off during the follow-up period. The optimal initial implant vector was conventional bipolar (D1–M2) in 66% of cases. Of the remaining patients, ten cases (29%) were optimally programmed (to either improve capture threshold or ameliorate PNS) to pacing vectors that did not use the distal pole (D1), unavailable on conventional bipolar leads, demonstrating the potential advantages of a multipolar lead.

PNS remains a significant obstacle to the success of CRT and may only become apparent following implant when repositioning is not an immediate option. In a study of 197 CRT implants, PNS was frequent and observed in 73 (37%) patients either at implant or during a mean 2-year follow-up period and felt to be clinically relevant in 41 (22%) patients. Interestingly, mid to apical LV lead position in the lateral/posterolateral vein was the strongest predictor of PNS. Importantly, 5% of cases needed invasive reintervention and three leads displaced because of a proximal position to avoid PNS. CRT was turned off in four (2%) patients because of PNS. In comparison, we observed a similar overall incidence of PNS (39%) at implant and during the 6-month follow-up period. The majority of patients with PNS were identified at the time of implant and
PNS was observed more frequently where the LV lead tip was in the apical position. Of the patients with PNS at the time of implant, approximately two-thirds of cases were successfully overcome by stimulating the LV more proximally where a conventional LV lead may have failed or been sub-optimal. During 6-month follow-up, clinically important PNS occurred in 13% of patients. The capability of utilising additional pacing vectors, unavailable on existing bipolar LV leads was able to overcome PNS in all cases obviating the need for reintervention or for the lead to be turned off.

There has been recent interest in the optimal position of the LV pacing lead for CRT. Data from the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial demonstrated that LV pacing in the apical region were associated with a significant increased risk of death or heart failure including structural (left ventricular end-diastolic volume and left ventricular ejection fraction) and functional (6MWD, quality of life and NYHA class) measures, were not significantly different between arms. Certainly a more apical LV stimulation site would appear to be associated with more PNS, supported by our data, but it is also recognised that a more basal LV lead position may be associated with a higher rate of displacement. Several bipolar LV pacing leads currently available allow the programmability of three or four pacing vectors; however, this quadripolar lead offers ten different pacing vectors. One potential advantage of this type of lead may be the ability to achieve a stable apical position within a CS branch and to perform perhaps clinically desirable basal-mid LV rather than apical stimulation by utilising the proximal electrodes. Early follow-up in this small series suggests good stability of pacing parameters and clinical utility with regard to increased programming options. Longer follow-up experience in a
larger series is required to fully assess the stability of pacing parameters and clinical outcomes with this novel technology.

**Study limitations**

This case series is a single-centre, non-randomised study of a relatively small number of patients. The cohort includes complex patients some of whom required lead extractions and others who had previous failed attempts at LV lead implant. The LV lead displacement rate was 3% in this patient cohort but this represents just 1 case out of 40 and the study was not powered to detect a significant lead displacement rate. Satisfactory pacing parameters and encouraging PNS data in the first 6 months after implant will need to be reassessed at longer term follow-up in larger series.

**Conclusions**

We have seen that the Quartet lead is associated with a high implant success rate and a low level of complications at short-term follow-up. Cathodal programmability (the capability to program either the proximal or the distal LV lead electrode as cathode) is available with several bipolar LV pacing leads and this ability to switch pacing configuration if the initial one gives rise to unacceptable pacing parameters or PNS appears to be a significant advantage. The Quartet lead offers more pacing vectors than other LV pacing leads and thus makes it more likely that common pacing obstacles can be overcome without the need to physically reposition the lead during implantation and thus risk dislodgement from the CS. It may also mean that successful CRT is achieved
in cases where a conventional lead would fail because of PNS or high capture thresholds. Equally importantly, the availability of different pacing vectors may obviate the need for a lead revision, surgical approach to LV lead placement, or CRT to be turned off in patients who encounter pacing problems after implantation.

It is not clear what the optimal number of ring electrodes on an LV lead should be. More rings will give more programming options but at the expense of increased lead complexity. In different patients, different leads may be optimal and we await the results of further studies of the clinical effects of pacing using the additional configurations available on multipolar leads.
Chapter 5. Pacing within CS Vein Tributaries

Abstract

Background: It is not clear whether there is a large difference in acute haemodynamic response (AHR) to left ventricle (LV) pacing in different regions of the same coronary sinus (CS) vein. Using the four electrodes available on a Quartet LV lead, we evaluated the AHR to pacing within individual branches of the CS.

Methods: An acute haemodynamic study was attempted in 20 patients. In each patient, we assessed AHR in a number of CS veins and along a significant proportion of each CS branch using three different bipolar configurations. We compared the AHR achieved when pacing using each different vector and also the highest AHR achieved in any position within the same patient with the lowest achieved in that patient.

Results: Sixty-four different CS positions in 19 patients were successfully assessed. No significant difference in AHR was found overall between the three vectors tested. The mean percentage difference in AHR between the CS branch vectors with the lowest and highest dP/dtmax was $+6.5 \pm 5.4\%$ ($P < 0.001$). A much larger difference of $+16.9 \pm 6.1\%$ ($P < 0.001$) was seen when comparing the highest and lowest AHR achieved using any vector in any position within the same patient.

Conclusion: A small difference in AHR is seen when pacing within the same branch of the CS compared to pacing in different branches in the same patient. This suggests that although the site of LV lead placement is important, the position within a CS branch is less important than choosing the right vein.
Introduction

Studies have shown that there is a significant difference in acute hemodynamic response (AHR) to pacing in different branches of the CS (45, 107). CS anatomy usually means, however, that it is easier to reposition a LV pacing lead within the same CS vein rather than between different CS tributaries. Gold et al (108) have previously evaluated the AHR to LV stimulation within a CS vein by placing a pacing lead in different positions within a tributary and found no significant group differences among stimulation sites within the same coronary vein but did find significant variability among sites in individuals. In our study, rather than repositioning the LV lead each time we wished to stimulate a different site in a CS tributary, we used the cathodal programmability available with the Quartet Model 1458Q LV pacing lead and Promote-Q Model CD 3221-36 generator (St Jude Medical, Sylmar, CA, USA) to pace different bipolar configurations within each CS branch (44, 104, 109).

Recent studies suggest that an apical rather than a basal or mid position is associated with a worse outcome (48-50). Given that the Quartet lead can be placed distally but allows pacing from more proximal poles other than the distal tip electrode, this may be advantageous in that the lead can be placed in a distal (more stable position) but pacing may occur via more proximal LV electrodes in the mid or basal LV that is associated with better CRT outcomes.
Methods

The study was approved by the local Ethics committee and was conducted in compliance with the Declaration of Helsinki with all patients giving written informed consent to participate. Patients fulfilling standard criteria for CRT (NYHA class III-IV with drug-refractory heart failure, LVEF ≤35% and prolonged QRS > 120ms were recruited. The clinical characteristics of the patients are presented in table 9.

<table>
<thead>
<tr>
<th>Patient Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Male/female (%)</td>
</tr>
<tr>
<td>NYHA Class (II/III/IV)</td>
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<td>LVEF (%)</td>
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<td>PR interval (ms)</td>
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<td>QRS duration</td>
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<td>QRS morphology (LBBB/RBBB/ nonspecific IVCD)</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; RBBB = right bundle branch block.

Table 9. Patient Clinical Characteristics

Implantation of a Quartet lead was attempted in 20 patients at St Thomas’ Hospital, London, United Kingdom. An acute haemodynamic study was successfully performed during CRT implant in 19 patients. Patients were lightly sedated with midazolam and morphine as necessary. Haemodynamic evaluation was performed using a 0.014 inch diameter high fidelity Certus PressureWire and PhysioMon software (RADI Medical Systems, Uppsala, Sweden) with a 500Hz frequency response and 50Hz filter bandwidth. The pressure wire was introduced into the LV through a 5-F multipurpose

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catheter via a femoral or radial artery. The multi-purpose catheter was then withdrawn into the aorta, leaving the pressure wire in a stable position within the LV cavity. Once venous access was acquired for pacing lead implant 2,500 units of heparin was administered.

LV-dP/dt<sub>max</sub> was calculated electronically from every heartbeat for a period of at least 20 s to ensure steady-state conditions. The results were averaged for the complete measurement period. A waiting period of at least 20 s was respected after any change in pacing settings or lead position to achieve hemodynamic stabilization. This method has previously been shown to reliably measure LV dP/dt<sub>max</sub>. (61, 62)

LV dP/dt<sub>max</sub> during atrial pacing (AAI) or RV pacing (AF patients) at 5-10 beats above intrinsic rate (to eliminate the effect of heart rate variation) was considered baseline and was kept constant when testing different pacing modes (102). The AHR during DDDLV (fixed AV delay 100ms) or VVI LV (patients in AF) pacing 5-10 beats above intrinsic rate was measured in as many different CS tributaries as possible in each patient. Data from premature ventricular complexes were discarded. We tested pacing parameters and AHR along a significant proportion of each CS branch by using 3 different bipolar configurations in each position. The 3 vectors used were D1-M2 (conventional bipolar configuration), M3-M2 and M3-P4 (figure 4.1). If pacing capture without significant PNS could not be achieved using the D1-M2 vector, the LV lead was repositioned.
Results at each pacing site were expressed as a percentage change from baseline. In order to minimise the effect of baseline drift in AHR (secondary to changes in patient intra-vascular volume/sedation levels etc) on the results, the baseline was reassessed prior to and after every LV lead reposition. Thus the AHR during LV pacing was compared to a mean of the baseline taken immediately before and after each lead
position change. Each CS lead position was categorized as anterior, posterior or lateral (this position included postero-lateral and antero-lateral positions) based on a left anterior oblique 30° view (48).

**Statistical Analysis**

Statistical analysis was performed on JMP (version 8.0.2, Marlow, Buckinghamshire, UK) and PASW Statistics 18 (SPSS Inc, Chicago, IL, USA). Group comparisons were performed using a paired t-test or an appropriate non-parametric test (Wilcoxon rank sum and Kruskall-Wallis). All results are expressed as mean ± SD. P values of < 0.05 were considered statistically significant.

**Results**

The CS was successfully cannulated and AHR to LV pacing assessed in 19 patients. In 1 patient it was not possible to cannulate the CS os because of its small orifice. This patient later had a surgical epicardial LV lead placed. In another patient AHR was assessed in only 1 position as a CS dissection precluded further vein assessment and an LV lead was implanted at a later date (this patient was excluded from the analyses as inter-vein comparisons could not be made). AHR data was successfully collected from a total of 63 different CS positions in 18 patients (mean 3.5 ± 0.9 per patient).
Intra-vein Variability in AHR

See Table 10.

Table 10. Summary of Acute Haemodynamic Response (AHR) Data

The mean percentage difference in AHR compared to baseline between an individual CS branch bipole with the lowest $dP/dt_{\text{max}}$ and that with the highest was $6.5 \pm 5.4\%$ ($p<0.001$) for each of the 51 CS vein positions in which the AHR for at least 2 vectors was successfully measured i.e. pacing capture without significant PNS using at least 2 of the 3 pacing configurations tested. This was the intra-vein variability in AHR.

*Excluding two patients in whom LV lead was not permanently placed.
The overall difference in AHR between the 3 different pacing vectors was also compared (figure 24) and no significant difference in AHR found between the pairs D1-M2 and M3-M2 (n=51, p=0.78), M3-M2 and M3-P4 (n=46, p=0.80) or D1-M2 and M3-P4 (n=46, p=0.98).

Figure 28. Comparison of AHR by Vector Pair

The mean AHR of each pair of vectors in each CS vein position assessed is plotted on the x-axis against the difference in AHR between each vector pair on the y-axis. The horizontal solid red bar is the mean of the difference between all vector pairs and the horizontal dashed red bars represent the 95% confidence intervals.

Inter-vein Variability in AHR

The mean difference in change in dP/dt\textsubscript{max} between the best and worst CS vectors in any CS vein position in an individual patient was 16.9 ± 6.1% (p<0.001). This was the maximum intra-patient variability in AHR. In figure 29 the maximum AHR achieved in each CS vein tested in each patient is displayed.
Figure 29. Intervein Variation in AHR

Individual patients are represented on the x-axis. Each black circle represents the highest AHR achieved for an individual CS position for a patient. The median value and quartiles of all CS positions tested for each individual patient are represented by the horizontal red bars. The black horizontal line represents the mean of the highest dP/dt_max overall for all CS vein positions in all patients.

Although the difference in AHR seen between different bipolar configurations within the same vein was not large, we did find that in some veins no pacing capture was found with one vector but was found with another. Similarly, we found that acceptable PNS may be detected with one configuration (rendering it unusable) but not found with another bipole in the same CS position. Thus, although the difference in AHR when using different vectors within a CS position was not large, differences in ability to
achieve consistent pacing capture without PNS were seen between pacing configurations.

LBBB v non-LBBB

The difference in AHR seen in patients with LBBB and those without LBBB was similar. An LV lead could not be placed in one of the 4 patients who did not have LBBB leaving 3 non-LBBB patients (1 RBBB, 2 with non-specific intra-ventricular conduction delay) in whom the best overall AHR was 19.1 ±17.1 compared to 18.0 ± 19.4 for the 15 LBBB patients (18.2 ± 10.4 for the group as a whole). The intra-patient variability in AHR was 14.1 ± 8.1 for the non-LBBB patients and 17.5 ± 5.8 for the LBBB group (16.9 ± 6.1 for the group as a whole). The intra-vein variability in AHR was 8.5 ± 9.7 for the non-LBBB group and 6.3 ± 4.7 for the LBBB group (6.5 ± 5.4 for the group as a whole).

The overall difference in AHR between the 3 different pacing vectors was assessed with patients sub-divided into LBBB and non-LBBB groups. For LBBB patients the mean AHR seen with each configuration was 10.3 ± 12.3 (D1-M2), 10.3 ± 11.5 (M3-M2) and 10.2 ± 11.0. For patients without LBBB the AHR seen was 7.8 ± 10.4 (D1-M2), 7.3 ± 11.4 (M3-M2) and 12.2 ± 11.6 (M3-P4). No significant difference in AHR was found between the pairs D1-M2 and M3-M2 (n=45, p=0.84), M3-M2 and M3-P4 (n=42, p=0.8) or D1-M2 and M3-P4 (n=42, p=0.78) for the LBBB group. No significant difference in AHR was seen in the non-LBBB group: D1-M2 and M3-M2 (n=6, p=0.57), M3-M2 and M3-P4 (n=4, p=0.65) or D1-M2 and M3-P4 (n=4, p=0.24).
**Sinus rhythm v AF**

Whether a patient was in sinus rhythm or atrial fibrillation did not appear to make much difference to the best overall AHR achieved or to the intra-vein and intra-patient variability in AHR. For the 3 patients in atrial fibrillation the best overall AHR was 17.9 ± 6.1 compared to 18.2 ± 11.2 for the 15 sinus rhythm patients (18.2 ± 10.4 for the group as a whole). The intra-patient variability in AHR was 17.6 ± 0.5 for the AF patients and 16.8 ± 6.7 for the sinus group (16.9 ± 6.1 for the group as a whole). The intra-vein variability in AHR was 8.5 ± 9.7 for the non-LBBB group and 6.3 ± 4.7 (6.5 ± 5.4 for the group as a whole).

**Ischemia and scar**

The difference in AHR seen in patients with an ischemic aetiology of their cardiomyopathy versus those with a non-ischemic aetiology was assessed. The best overall AHR in the ischemic group was 19.8 ±12.0 compared to 16.5 ± 8.9 for the non-ischemic group. The intra-patient variability in AHR was 15.1 ± 7.1 for the ischemic patients and 18.7 ± 4.8 for the non-ischemic group. 5 of the ischemic group of patients had at least some full thickness postero-lateral scar on pre-procedure delayed enhancement MRI. The overall best AHR achieved when pacing in the postero-lateral regions of the LV in these patients gave rise to a very similar response to that seen overall in our cohort with a mean AHR of 18.4 ± 10.5. The intra-vein variability in AHR when pacing postero-laterally in this group of patients was larger, however, at 8.9 ± 9.
There is evidence to suggest that a high scar burden has an unfavourable effect on clinical and functional outcomes post CRT (40). Trans-mural postero-lateral scar in particular has previously been associated with a poor response in terms of clinical and echocardiographic response at 6 months post-CRT (36). Our data, however, suggests that pacing close to but outside scar can give rise to an AHR comparable to the best that can be achieved anywhere. The larger variability in AHR seen in those patients with poster-lateral scar perhaps suggests that although a poor AHR may be seen with one vector (placed directly in scar) another configuration within the same vein may lie close to but not actually within scar thus allowing a good hemodynamic response.

![Figure 30. Change in dP/dtmax by CS Vein Anatomical Position](image)

*Each black circle represents the highest AHR achieved using any of the three vectors assessed for that CS vein position in an individual patient. The median value and quartiles for each anatomical position are represented by the red horizontal bars. The black horizontal line represents the mean of the highest dP/dt_{max} overall for all CS vein positions in all patients.*
CS Vein Position

We analyzed the overall effect of CS vein anatomical position on AHR (figure 30). We recorded the highest AHR achieved using any of the 3 bipolar configurations in each position successfully tested. The pacing configuration that gave the largest increase in \(dP/dt_{\text{max}}\) was located in a lateral vein in 67% of patients, in an anterior vein in 22% of patients and in a posterior vein in 11% of patients. These proportions broadly corresponded with the proportion of all vectors tested in each position (61%, 29% and 10% respectively). The mean increase in \(dP/dt_{\text{max}}\) was +5.7 ± 9.8 for an anterior vein, +11.4 ±11.9 for a lateral vein and +14.4 ±9.7 for a posterior vein. There was no significant difference in AHR between anterior and lateral positions (p=0.17) or between posterior and lateral positions p=0.23). A significant difference in favour of a posterior position was seen, however, between anterior and posterior positions (p=0.03).

Figure 31. Response Versus Non-response
**Responders v Non-Responders**

For each patient we analyzed the proportion of CS positions that gave rise to a >10% increase in dP/dt_{max}. A 10% improvement in cardiac index has previously been used to define responders (107) and this cut-off for improvement in dP/dt_{max} was chosen as it has been shown to be a sensitive and specific predictor of likely reverse remodelling following CRT (103) (figure 31). 5 patients did not respond in any CS position and 4 patients responded in every CS position tested. In 9 patients (50% of patients in whom an LV lead was successfully implanted), a response was found in at least 1 vein but not in at least 1 other vein.

**Discussion**

Gold et al assessed AHR within CS veins in a similar number of patients (19 subjects) to our cohort but assessed changes in dP/dt_{max} in only 1 vein in the vast majority of these (88%) (108). In our study we managed to pace multiple sites within individual veins and were able to compare the AHR in multiple veins within individual patients in 90% of our study group. Thus we were able to assess intra and inter-vein variability in AHR in the majority of our patients.
Our data suggest that a small but significant difference in AHR is seen when pacing using different configurations within the same branch of the CS. Consistent with Gold et al, no significant group differences were seen in AHR when the different pacing configurations were compared. A large and significant difference was seen, however, when pacing in different branches of the CS within the same patient. This suggests that although the site of LV lead placement is important, position within a CS branch is less important than choosing the right branch in terms of AHR.

It has previously been shown that the cathodal programmability available on the Quartet lead can be used to overcome problems with PNS and high capture thresholds (104, 109, 110). The multiple vectors available, however, do not appear to allow optimal AHR to be achieved if the lead is not placed in the most suitable CS vein. So although the Quartet lead may allow placement in a distal (and more stable) CS vein position, there does not appear to be a significant variation in the AHR that can be achieved by pacing using the more proximal LV lead electrodes within a CS branch and thus a poor response elicited using a conventional bipolar configuration is most likely to be overcome by physical repositioning in another CS tributary rather than a change in vector.

The best CS vein is not necessarily a lateral or postero-lateral branch, as the best AHR seen in this study was in an anterior or posterior vein in one third of patients. Although a significant difference in AHR was seen between anterior and posterior positions, no difference was seen between lateral and anterior positions or lateral and posterior positions. This suggests that within individual patients large variations in AHR exist and the best and worst veins are different in different subjects. Indeed, when CS positions are divided by whether they give rise to >10% increase in \( \frac{dP}{dt_{\text{max}}} \) or not, it can be seen
that in half of all patients, whether they are likely to respond or not to CRT is critically dependent on whether the right CS vein is chosen. In the other half of patients, however, it would appear that no matter which vein is chosen the same outcome will be achieved whether that be ‘response’ or ‘non-response’.

**Conclusions**

Although cathodal programmability of the Quartet lead appears to be useful in overcoming problems with PNS and high pacing capture thresholds, changing the pacing vector does not appear to offer large acute hemodynamic advantages within a vein. Great variation in AHR is seen in different CS veins within the same patient, however, and the vein that gives the best hemodynamic response is not necessarily lateral or postero-lateral. Choosing the best CS vein for CRT remains critical to likely response and robust non-invasive methods of predicting which vein will give the best outcome need to be developed. In the mean time invasive assessment of AHR at CRT implant appears to be a useful aid to optimum LV lead positioning.

**Study Limitations**

The order of the pacing vector sequence was not altered randomly from vein to vein or patient to patient and thus we cannot rule out sustained effects from earlier pacing sequences. The patient population was relatively small and a range of AV delays could not be assessed because of time limitation. For the same reason, the study was limited to the acute hemodynamic effects of LV pacing as compared to BiV pacing. Previous studies have demonstrated the non-inferiority of DDDLV pacing compared to DDDBiV pacing (62, 111), however, and recent work suggests that a dP/dt_{max} rise of >10% using DDDLV pacing at CRT implant predicts reverse remodelling at 6 months (103).
Chapter 6. Image Guided CRT Implantation (PRISM-Pilot Study)

Abstract

Objectives
To guide left ventricular lead placement in real-time during CRT implant using CMR-derived scar and dyssynchrony data.

Background
Optimal LV lead placement via the coronary sinus (CS) is critical to CRT response. Current angiographic methods for selection of lead position are largely empirical and operator-dependent.

Methods
23 patients underwent CMR and anatomical models of the cardiac chambers, coronary veins and scar were registered to a 16-segment time-volume dyssynchrony map. The 3 latest activated segments with <50% scar were chosen as targets and overlaid onto live fluoroscopy. An intra-ventricular pressure wire was used to assess acute haemodynamic response (AHR) to DDDLV pacing and validate CMR guided LV lead placement. Chronic CRT response (end systolic volume reduction ≥15%) was assessed 6 months post implant.

Results
20/23 patients underwent successful CMR guided LV lead placement. The lead was placed in the CMR target segment in 75% (15) of patients. Mean change in dP/dt_{max} for the CMR target was +14.2 ± 12.5% versus +18.8 ± 11.8% for the best AHR anywhere,
+3.4 ± 9.0 % for the worst position and +12.0 ± 13.8% for the region identified by an expert implanter based on CS venography. The optimal AHR was anterior in 30% of patients. Using CMR guidance the acute responder rate was 60% versus 50% on the basis of angiography alone. At 6 months 60% of patients were echocardiographic responders. 92% of echocardiographic responders were successfully paced in a CMR target segment compared to only 50% of non responders (p=0.04).

**Conclusions**

CMR guidance compared well when validated against AHR. Lead placement was possible in the CMR target region in most patients with an AHR comparable to the best achieved in any CS branch. Chronic response was significantly better in those patients successfully paced in a CMR target segment. These results suggest that CMR guidance may represent a clinically useful tool for CRT.
Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure but around 30% of patients do not respond (25, 35) which may relate to sub-optimal lead positioning.(36) Pacing the postero-lateral LV generally produces the best haemodynamic response (45, 46) which is the conventional target site for LV lead placement, however patients may not respond if they have postero-lateral scar.(36) Large scale studies have shown no difference in CRT response when the lead is placed in an anterior, posterior or lateral position however a mid or basal location appears superior to an apical position (48-50). There is however great variation in acute haemodynamic response (AHR) when pacing different regions of the LV with the optimal location varying among patients (51, 112). Pacing the latest mechanically activated region of the LV is associated with better CRT outcomes (113, 114) but to date no studies have assessed real time CMR LV lead guidance based on this parameter.

We hypothesized that optimal CRT response will occur if those regions of the myocardium most delayed by electromechanical dyssynchrony can be identified using CMR and targeted for pacing. Using novel data acquisition, processing, overlay and registration software we aimed to identify the latest mechanically activated regions of myocardium without scar to allow real time CMR guided LV lead implantation.

We set out to validate CMR guidance by comparing the optimal lead position defined by CMR overlaid onto fluoroscopy to an optimal acute haemodynamic LV lead position anywhere within the CS measured with a high-fidelity pressure wire.(63) Comparison
of the optimal site was made with the site chosen by an expert CRT implanter blinded to
the CMR data based on CS angiography alone.

**Methods**

**Patients**

**Study Population (Table 11)**

Patients fulfilling standard CRT criteria (NYHA class II-IV drug refractory heart
failure, LVEF ≤35% and QRS ≥ 120ms) were included. The study was approved by the
local ethics committee and written informed consent was obtained from each patient.
Baseline assessment of NYHA class, Minnesota Living with Heart Failure
Questionnaire (MLWHFQ) score, 6 minute walk distance (6MWD), peak oxygen
uptake (VO<sub>2</sub> max) and echocardiographic assessment of LV systolic function and
volumes was performed. Patients with a contraindication to CMR or significant renal
impairment (estimated glomerular filtration rate <30 ml/min/1.73m<sup>2</sup>) were excluded.

<table>
<thead>
<tr>
<th>Patients</th>
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<tbody>
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<td>Age</td>
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<tr>
<td>Male/female (%)</td>
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<tr>
<td>NYHA Class (II/III/IV)</td>
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<td>On beta-blocker</td>
<td>78%</td>
</tr>
<tr>
<td>On ACE-I or ARB</td>
<td>100%</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------</td>
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<tr>
<td>On Aldosterone antagonist</td>
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<tr>
<td>On statin</td>
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<td>LVEF (%)*</td>
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<tr>
<td>LVESV (ml)*</td>
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<tr>
<td>Ischemic/non-ischemic (%)</td>
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<tr>
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<td>6MWD (m)</td>
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<td>Sinus rhythm/Atrial fibrillation (%)</td>
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<td>Heart Rate (bpm)</td>
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<tr>
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<tr>
<td>QRS duration</td>
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<tr>
<td>QRS morphology (LBBB/RBBB/non-specific IVCD)</td>
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</tr>
</tbody>
</table>

**Table 11. Patient Pre-CRT Clinical Characteristics**

*NYHA= New York Heart Association; LVEF=left ventricular ejection fraction; IVCD=intraventricular conduction delay; LBBB=left bundle branch block;*
RBBB=right bundle branch block. ACE-I=angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

* derived from 3D echo if available pre and post CRT (otherwise 2D echo data used)

Cardiac MR Image Acquisition and Processing

Respiratory and cardiac-gated CMR images were acquired on a Philips Achieva 1.5T MR system (Philips Healthcare, Best, The Netherlands). Two, three, four chamber and multiple slice short axis cine steady state free precession (SSFP) images were acquired. Contrast enhanced CMR images of the coronary veins and myocardial scar were acquired using previously described methods (42, 43, 95). The epicardial surface of the LV and endocardial surfaces of the right ventricle, left atrium and right atrium were extracted automatically using a model-based segmentation algorithm applied to the 3D IR-SSFP whole heart image data (98). The CS was manually segmented from the whole heart images to yield a highly detailed anatomical model including the main branches (figure 32).
Figure 32. Whole Heart Segmentation

Postero-Anterior view of a whole heart segmentation showing cardiac chambers and coronary venous system (LV in dark blue, RV in green, LA in orange, RA in light blue and CS in red)

A modified American Heart Association (AHA) 16 segment LV model (115) (figure 33; CMR dyssynchrony: panels A and B) was created using TomTec 4D analysis software (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). The same analysis tool was used to create a regional volume map showing the mechanical delay motion curves of the 16 segments (figure 33: panel C).
Figure 33. CMR Dyssynchrony

Panel A shows the modified AHA 16 segment model of the LV as a bullseye plot (Sept=septum, Ant=anterior, Lat=lateral, Inf=inferior). Panel B shows the LV model created from CMR cine imaging and labelled according to the 16 segment model shown in the bullseye plot. Panel C shows the individual regional volume curves for each LV segment during a complete cardiac cycle.

The position and extent of myocardial scar was determined from LGE CMR images and segments with >50% trans-mural LGE were considered non-viable. (116) Scar data was manually segmented from the CMR multi-slice short axis stack images using ITK-SNAP software (99) and registered to the whole heart CMR data allowing scar to be visualized directly on the anatomical model and on a 16 segment bullseye plot (figure 34).
**Figure 34. CMR Scar**

*Panel A shows full thickness scar in red overlaid on to the LV epicardial surface. Panel B shows the same patient's full thickness scar overlaid in grey on to a 16 segment bullseye plot of the LV. The cyan outline around the bullseye plot represents the CS. The white arrows indicate the same region of scar in both panels for this patient.*

**MR Target Segments**

Segments with scar affecting >50% of their area were excluded as targets. Antero-septal (segments 6, 12 and 16) were excluded as pacing these segments would result in an activation pattern similar to RV pacing. Segments were also excluded if their regional volume curve was flat (overall regional volume change < 2.5ml) suggesting akinesis (71)(figure 35). Prior to CRT implant, two independent imaging specialists agreed on the target segments for LV lead implant by choosing the three latest mechanically activated segments with less < 50% scar. The implanter was blinded to this process.
Figure 35. Regional Volume Map

Time is a percentage of the total cardiac cycle on the x-axis and volume change (ml) on the y-axis. In this example segment 11 is the latest mechanically activated segment but is excluded as a potential target because the regional volume change from peak is <2.5ml. The target segments in this patient are therefore 10, 9 and 4 (no scar seen on LGE imaging).

Image Overlay and Registration

An in house developed platform based on the Philips EP Navigator (Philips Healthcare) was used to overlay and register the CMR-derived model during CRT implant (22). Accurate registration of the CMR model to live x-ray images was achieved using PA, LAO 30 and RAO 30 views with a catheter looped in the right atrium. The EP navigator software automatically maintained alignment between the model and the live X-ray
images throughout the procedure. Respiratory motion was compensated for as published previously (117). The 3D heart roadmap was translated along the head to foot vector of the patient. We have previously shown that the above methods allow accurate overlay and registration of 3D anatomical models to live fluoroscopic images (figure 36) (42).

![CMR model overlaid on to fluoroscopic image in real-time](image)

**Figure 36.** CMR model overlaid on to fluoroscopic image in real-time

*Silver spheres indicate the previous positions of the LV electrodes in an AP view.*

**Implant and Comparison of MR Guidance with Acute Haemodynamics**

Haemodynamic evaluation was performed using a 0.014 inch diameter high fidelity Certus PressureWire and PhysioMon software (RADI Medical Systems, Uppsala, Sweden) with a 500Hz frequency response and 50Hz filter bandwidth. The pressure wire was introduced into the LV through a 5-F multipurpose catheter via a femoral or
radial artery. The LV lead was placed in as many different CS positions as possible. Pacing was performed in DDDLV mode with a fixed AV delay 100ms (VVI LV in AF patients) 5-10 beats above intrinsic rate to eliminate the effect of heart rate variation. The LVdP/dt_{max} was recorded for at least 20 s to ensure steady-state conditions. LV dP/dt_{max} during atrial pacing (AAI) or RV pacing for AF patients at 5-10 beats above intrinsic rate was considered baseline and was kept constant when testing different pacing modes. A waiting period of at least 20 s was respected after any change in pacing settings or lead position to achieve hemodynamic stabilization. These methods have previously been shown to reliably measure LV dP/dt_{max} (61, 62, 101, 102).

Results at each pacing site were expressed as a percentage change from baseline. In order to minimize the effect of drift the baseline was reassessed prior to and after every LV lead reposition and comparisons were made to a mean of these two readings. Data from premature ventricular complexes were discarded. The LV lead was finally placed in or as close as possible to one of the 3 target segments. AV and VV delays were optimized with pressure wire guidance at the end of the procedure.

**CMR Guidance v Anatomical Target Segments**

Each CS vein position in which pacing was attempted was marked on to still images of the CS balloon occlusion venogram for each patient. At least two views (PA, RAO 30 or LAO 30) for each patient were assessed by an independent CRT expert implanter (JPS). All the positions in which it was possible to obtain hemodynamic data were ranked in order of preference i.e. LV lead placement based solely on the CS venograms. The AHR achieved when pacing in the highest ranked angiographic position in which
pacing could successfully be performed without PNS was compared to the CMR and haemodynamic guided targets.

Follow-up and Response

Patients were followed-up at 6 months with repeat assessment of NYHA class, MLWHFQ, 6MWD, VO₂ max and echocardiographic parameters. Echocardiographic reduction in ESV ≥15% at 6 months was used to define reverse remodelling response (118, 119). A clinical composite score (CCS) (120) was used to assess clinical response.

Statistical Analysis

Statistical analysis was performed on JMP (version 9.0.1, Marlow, Buckinghamshire, UK). Group comparisons were performed using a t-test or an appropriate non-parametric test (Wilcoxon rank sum, Kruskall-Wallis). Pearson’s correlation coefficient was used to measure the linear relationship between two variables and Chi squared test to compare categorical variables. All results are expressed as mean ± SD. P values of < 0.05 were considered statistically significant.

Results

21/ 23 (91%) patients underwent successful CRT implantation and haemodynamic study. In one patient only the postero-lateral vein was suitable for use; this had a favourable dP/dtₑₘₐₓ response but the patient was excluded from analysis. In one patient CS intubation failed due to the presence of a valve and a further patient suffered a CS
dissection precluding LV lead placement (both patients subsequently received successful CRT). The full protocol with LV lead placement in at least two separate CS branches was successfully completed in 20 patients. AHR was successfully assessed in a mean of 4.7 ± 1.6 different LV segments in these 20 patients and successful LV pacing in at least 1 target segment was achieved in 75% (15). In 5 patients it was impossible to pace a target segment either because of failure to capture or absence of an accessible vein to the target (4 ischaemic patients with scar adjacent to the target segments). The CMR targeted dP/dt_{max} in these patients was based on the nearest position to a target segment in which successful pacing could be performed.

**CMR Guided v Conventional LV Lead Placement**

The mean increase in dP/dt_{max} with the CMR guided approach was +14.2 ± 12.5% versus +18.8 ± 11.8% (p=0.69) for the best AHR achieved in any segment for those patients and +3.4 ± 9.0% (p<0.001) for the worst AHR in any segment (figure 37). A CMR guided approach compares with an increase in dP/dt_{max} of +12.0 ± 13.8% (p=0.23) for the highest ranked region based on CS venography. The mean AHR for all segments paced in all patients was +11.6 ± 12.3%.
Figure 37. Mean Change in AHR

Best = mean of best segment overall for each patient; Worst = mean of worst segment overall for each patient; Target = mean of highest ranked CMR target segment for each patient; Expert = mean of the highest ranked angiographic segment for each patient.

At least one anterior and one lateral or postero-lateral LV segment was paced in all patients completing the protocol. A conventional lateral or postero-lateral LV lead position gave the best AHR in only 70% (14/20) of cases. In the remaining 6 patients the best AHR was anterior and in 2 of these patients at least one of the CMR defined target segments was adjacent to the site of best response (figure 38 shows the overall AHR for each segment). Mean QRS duration and LBBB morphology did not differentiate these two groups (QRS 152 ± 20ms vs 152 ± 20ms and LBBB in 12/14 patients versus 5/6 patients).
Figure 38. Mean Percentage Change in $dP/dt_{\text{max}}$

Mean percentage change in $dP/dt_{\text{max}}$ compared to baseline for each LV segment.

Mean for all patients.

A positive significant correlation between the best overall AHR achieved in each patient (figure 39) and the CMR derived systolic dyssynchrony index (SDI) was seen ($r=0.63$, $p=0.003$) supporting the hypothesis that CMR-derived dyssynchrony directly correlates with AHR. Consistent with recent work, a non-significant negative correlation between intrinsic $dP/dt_{\text{max}}$ and best $dP/dt_{\text{max}}$ achieved was also seen ($r=-0.4$, $p=0.08$) (28).
Figure 39. Correlation between dP/dtmax and CMR Dyssynchrony

*Scatter plot showing correlation between highest dP/dt<sub>max</sub> achieved in each patient and MRI systolic dyssynchrony index (SDI) (r=0.63, p<0.001)*

**Basal v Mid v Apical Pacing**

The mean change in dP/dt<sub>max</sub> achieved when pacing basally (segments 1-5) ([figure 33 panel A](#) and [figure 40](#)) was +14.7 ± 12.6% versus +11.2 ± 11.8% for mid-LV pacing (segments 7-11) and +6.8 ± 10.9% for apical pacing (segments 13-15). There was a significant difference between basal versus apical regions (p=0.04) and mid versus apical regions (p=0.05) but not basal versus mid regions (p=0.71). An apical position gave rise to the best AHR in just 3 patients but the difference in AHR between the
apical segment and the best non-apical segment in these patients was not large (+11.2 ± 14.7% versus +9.9 ± 14.3% respectively). Of these 3 patients one had extensive inferior scar but the other 2 patients had no scar.

![Graph: AHR by LV Region](image)

**Figure 40. AHR by LV Region**

* (% increase over baseline)

**Acute Responders**

An AHR of ≥10% has been shown to be a sensitive and specific predictor of long term response to CRT (63) and was seen in 70% of our patients. Of the 6 patients in whom the highest ranked target segment did not result in an AHR ≥ 10%, only one had an AHR >10% in a non-target segment, suggesting that if a patient is an acute non-responder despite pacing in a target segment, it is very unlikely pacing in another segment will improve outcome. The likelihood of acute non-response was greatly increased by the presence of scar with 5 of 6 acute non-responders having scar on CMR (postero-lateral in 3 and anterior or inferior in 2 patients). Conversely, of the 10 patients
without scar only 1 was not an acute responder. Interestingly, however, the mean overall AHR seen in ischemic and non-ischemic patients was similar, (+18.3 ± 12.2% v +19.1 ± 11.8% respectively).

Of the 15/20 patients in whom a CMR target segment was paced, the acute AHR rate was 73% (11/15) according to the best dP/dt in any CS position, 67% (10/15) were responders within the target CMR segment and 60% (9/15) on the basis of angiography alone.

**Chronic Response**

At 6 months 12/20 (60%) patients were echocardiographic responders (reduction in ESV of ≥15%). The 8 echocardiographic non-responders all had an ischaemic aetiology to their heart failure. Consistent with previous clinical trials (38), a greater proportion of patients were clinical rather than echocardiographic responders with 75% having an improvement in CCS at 6 months. 11/12 (92%) echocardiographic responders were successfully paced in a CMR target segment compared to only 4/8 (50%) echocardiographic non-responders (p=0.04). Thus only 1 of the 5 patients who was not paced in a target segment reverse remodelled. 10/14 (71%) patients with an acute AHR of ≥10% at implant were echocardiographic responders.
Discussion

We have used CMR to guide LV lead placement and compared the results acutely to an optimal haemodynamic standard and angiographic approach and chronically with reverse remodelling. We were able to accurately acquire and process CMR derived CS anatomy, scar and dyssynchrony data (derived from a single CMR scan) and fuse this with live fluoroscopy during CRT implant. We were able to pace in at least one CMR target segment in the majority of patients which gave rise to an AHR comparable to the best possible in any segment. In keeping with previous studies (51, 63, 112) we showed a marked difference in AHR dependent on LV pacing site which may explain sub-optimal CRT response if a purely anatomical approach is used. Our results suggest that if a target segment is successfully paced, it is unlikely that any other segment will give rise to a significantly better acute response.

Our chronic results show an improved reverse remodelling rate of 92% in patients that successfully had the lead positioned in a CMR target segment compared to 20% in those in which the CMR target could not be paced. Our technique of using CMR guidance may allow an implanter to individualize their approach to the patient and guide them to the optimal target segment. Whether this will lead to an improved chronic outcome against a standard approach is as yet unproven and would require a randomized study of CMR guided CRT.
Comparison with Previous Studies

2D echo speckle tracking radial strain analysis has been used to identify the latest mechanically activated LV segments and targeting these regions is associated with an improved echocardiographic response and prognosis post CRT (52, 113). Non-contrast CMR has also been used to identify the site of latest mechanical activation by radial strain analysis (121). These previous studies, however, either used dyssynchrony imaging data to retrospectively analyze whether the LV lead was placed in a concordant or discordant region of the LV or used multiple fluoroscopic views at the time of implant to approximate the actual target region suggested by radial strain analysis. We have previously shown that CMR derived data of CS anatomy and scar can be registered onto fluoroscopy during CRT implant with a good validation between CMR derived and fluoroscopic parameters and the potential to facilitate CRT in patients with previously failed implants and unusual anatomy (42, 95). These previous studies did not use CMR derived dyssynchrony data to target LV lead placement and this is the first study to use CMR derived dyssynchrony and scar analysis fused with fluoroscopy to guide LV lead placement and compare it with a haemodynamic standard.

Comparison with Angiographic Approach

The acute CMR guided response rate was greater (60%) than with an angiographic approach (50%). One might argue that using an angiographic approach gives a similar outcome to a complex CMR guided approach and may be unnecessary. It should however be stated that the choice of lead position using angiography was made by an international expert implanter and an alternative argument would be that using such a CMR guidance system may allow even a relatively inexperienced implanter to achieve
the same result as an experienced operator. The large difference in AHR between the best and worse positions in each patient highlights the fact that if the wrong target vein is chosen this may result in a sub-optimal outcome. The benefit of a CMR guided approach over a standard approach may be that CMR derived dyssynchrony and scar may predict the likelihood of a favourable response. In our patients, the greater the degree of dyssynchrony, the greater the acute response. Similarly the presence of scar was associated with a poor response. Thus a preoperative CMR may guide lead placement and also be useful in predicting which patients are likely to respond on the basis of baseline dyssynchrony and scar. This may allow physicians to target potential non-responders and consider non-standard CRT approaches such as endocardial or multi-site pacing.

In this study 92% of the patients that reverse remodelled were paced in a CMR target whereas in the chronic non responders a high proportion of patients were unable to be paced in a CMR target (only 50% were paced in a target CMR segment). All of the non-responders had an ischaemic aetiology and this may reflect the generally poor response to CRT in patients with scar. In several patients the venous anatomy precluded reaching the CMR target segment and this raises the possibility of an endocardial approach guided by CMR in such patients.

**Study Limitations**

This study is limited by its small size and lack of control group but is a proof of concept for CMR CRT guidance. A range of AV delays could not be assessed because of time limitations and, for the same reason, the study was limited to measuring the AHR to LV
rather than biventricular (BiV) pacing. It is possible that DDD-BiV pacing would be superior and more comparable to a normal CRT strategy. DDD-LV pacing was the only option, however to ensure a steady state for accurate hemodynamic measurements and previous studies have demonstrated the non-inferiority of DDD-LV compared to DDD-BiV pacing (62, 111). Data from our group has suggested a good correlation between AHR and chronic response in terms of LV reverse remodelling (≥15% reduction in ESV at 6 months) predominantly in non ischemic patients (63). Other studies, however, have shown that baseline LVdP/dt$_{max}$ rather than acute change at implant are predictive of outcome in terms of symptoms and mortality (122). Improvement in dyssynchrony rather than AHR may be a more reliable predictor of CRT response and accordingly our data show a good correlation of AHR and the degree of CMR derived LV dyssynchrony suggesting AHR is related to dyssynchrony and its correction.

**Conclusion**

It is feasible to acquire, overlay and accurately register CMR derived anatomical, scar and dyssynchrony data to guide CRT implantation. LV lead placement was possible in at least 1 target region in most patients and gave an AHR comparable to the best that could be achieved in any branch of the CS. Patients successfully paced in a CMR target had a better chronic response to CRT than those that were not. A CMR guided approach to LV lead placement may therefore increase the proportion of patients that respond to CRT and increase the level of response in ‘responders’. Whether CMR image guidance produces a reduction in procedure time, fluoroscopy time, radiation dose and improves long-term outcomes needs to be evaluated in a randomized controlled study.
Chapter 7. Biophysical Modelling of Multi Site Pacing Using a Quadripolar Lead

Abstract

Background

Response to cardiac resynchronization therapy (CRT) is reduced in patients with posterolateral scar. Multipolar pacing leads offer the ability to select desirable pacing sites and/or stimulate from multiple pacing sites concurrently using a single lead position. Despite this potential, the clinical evaluation and identification of metrics for optimization of multisite CRT (MCRT) has not been performed.

Methods

The efficacy of MCRT via a quadripolar lead with two left ventricular (LV) pacing sites in conjunction with right ventricular pacing was compared with single-site LV pacing using a coupled electromechanical biophysical model of the human heart with no, mild, or severe scar in the LV posterolateral wall.

Results

The maximum $\frac{dP}{dt_{\text{max}}}$ improvement from baseline was 21%, 23%, and 21% for standard CRT versus 22%, 24%, and 25% for MCRT for no, mild, and severe scar, respectively. In the presence of severe scar, there was an incremental benefit of multisite versus standard CRT (25% vs 21%, 19% relative improvement in response). Minimizing total activation time (analogous to QRS duration) or minimizing the activation time of short-axis slices of the heart did not correlate with CRT response. The peak electrical activation wave area in the LV corresponded with CRT response with an $R^2$ value between 0.42 and 0.75.
Conclusion

Biophysical modeling predicts that in the presence of posterolateral scar MCRT offers an improved response over conventional CRT. Maximizing the activation wave area in the LV had the most consistent correlation with CRT response, independent of pacing protocol, scar size, or lead location.
Background

The Quartet quadripolar LV lead (St Jude Medical, Sylmar, CA, USA) has the ability to perform true multisite pacing (MSP) of the LV using two different vectors with a minimum 5-ms delay between them. With the addition of RV pacing, this allows up to three ventricular sites to be paced simultaneously. Given the relative close proximity of the electrodes, increasing the number of pacing sites may not necessarily produce a significant improvement in electrical activation, however. Furthermore, the increased number of pacing sites and the corresponding increase in the temporal and spatial pacing combinations means that optimizing such a device for a specific patient is a challenge in itself. The number of potential pacing permutations greatly limits the capacity to comprehensively evaluate all combinations or optimize the lead through trial and error in a single patient, thus necessitating improved optimization algorithms. The difficulty in both testing and validating such algorithms is that while safety studies of MSP are currently being performed, there are currently no clinical data on the haemodynamic effect of multisite stimulation using the quadripolar lead. In silico biophysical models allow the possibility of testing multiple pacing parameters (123).

To provide an initial prediction of the efficacy of MSP with a quadripolar lead and to facilitate the proposal of optimization algorithms, we applied this approach to evaluate the effects of MSP in a computational coupled electromechanical human heart model (Figure 41) (81). The model simulates single or multisite LV pacing in conjunction with right ventricular (RV) pacing and can be tested in the presence of no, moderate, or severe LV transmural posterolateral scar. These simulations predict the contractile
ability of the heart for each pacing combination, measured using $dP/dt_{\text{max}}$ and provide a quantitative evaluation of the effects of MSP compared with conventional CRT.

![Figure 41. Heart Geometry and Coronary Venous Anatomy](image)

**(A) Electrode position and (B) the region of LV posterolateral scar in blue.**

Using a complete set of pacing combinations, we evaluated three potential optimisation algorithms based on total activation time, cumulative fraction of activated volume, and activation time of short axis slices, parallel to the base of the heart (figure 42).

![Figure 42. Heart Model Activation Cross Sections](image)
(A) The activation patterns, where white regions are activated and black regions inactivated for evenly spaced 10-mm slices taken from the heart model in (B). (C) The point of first activation at 15 ms in slice 3, the point (marked with a yellow x) and time where the first loop of activation is formed at 92 ms, the point when the LV is fully activated at 104 ms, and the time just prior to full slice activation at 139 ms.

Methods

The computational model is based on a coupled electromechanical human heart model developed previously using invasive data from a 60-year-old female with NYHA class III heart failure, an LVEF of 25% and LBBB (QRSd 154 ms). The mechanics and electrophysiology model were validated pre and post-CRT against endocardial activation patterns derived from non-contact mapping, CMR derived wall motion, and pressure wire measures. In this study, two simplifying assumptions were made to reduce confounding factors. The heart was assumed to have no intrinsic activation and the myocardium was treated as homogenous.

Simulations were performed using the bidomain approximation of myocardial electrical activation in the heart. Simulations were performed using CARP (124) on the UK National HPC resource HeCTOR (www.hector.ac.uk). The electrophysiology model had 35 million and 26 million extra and intracellular degrees of freedom, respectively, and 208 million elements, and took approximately 3 hours to solve using 512 cores. Mechanics simulations were performed using CMISS (www.cmiss.org) on ORAC at the Oxford e-Research Centre (www.oerc.ox.ac.uk).
Pacing Model

To simulate pacing, we manually aligned the coronary venous anatomy from 3D IR-SSFP whole heart sequences with model geometry derived from cine CMR sequences. The coronary venous anatomy provided the location for the quadripolar lead that was introduced into the model. RV septal (RVS) and apical (RVA) lead positions were introduced in the centre of the RV. All electrodes are shown in Figure 41A. LV pacing was between vector D1-M2 or M3-P4. RV pacing was between the RV tip in the septum or apex position and the RV coil. Stimulation was simulated by raising the cathodal electrode to 2 V for 0.5 ms and grounding the anodal electrode.

Scar Model

Simulations were performed using the model with no scar or in the presence of a transmural basal LV posterolateral scar with a 60-mm diameter, as shown in Figure 41B. Scar was simulated by reducing conduction and decreasing anisotropy. Conduction velocities decreased by approximately 50% between viable tissue and scar (125). From the cable equation conduction velocity is proportional to the square root of conductivity (the inverse of resistance). Hence, scar was simulated by a 50% or a 90% decrease in the conductivity value corresponding to 30% or 70% decrease in conduction velocity, for mild and severe scar, respectively. The quadripolar lead was placed across the scar with the most distal pole (D1) out of the scar, M2 on the scar border, and M3 and P4 basally within the scar.
Cardiac Function and Efficacy of CRT

The efficacy of each pacing mode was evaluated using the change in dP/dt_{max} as a metric of improvement. RV apical pacing dP/dt_{max} was used as a baseline, as the model had no intrinsic activation. We normalized all CRT responses by dP/dt_{max} calculated for an instantaneous homogenous activation pattern.

Simulations

For standard CRT (single site LV and RV stimulation), simulations were performed with the LV or RV site paced first with a 5, 15, 30 or 45 ms delay. For MSP (2 LV pacing sites and one RV), the three stimulations were separated by two delays, one delay interval was always 5 ms and the other delay interval was 5, 15, 30, or 45 ms. The sites could be paced in any order except that the RV site had to be paced either before or after the 2 LV pacing sites. Activation times for combinations of pacing sites were calculated by combining activation patterns from each individual site.

Optimization Algorithms

QRS duration has been reported to correlate with CRT response (84, 118) and to test this hypothesis, we compared CRT response with QRSd, using total activation time of both ventricles as an analogue of QRS duration. Previous studies have shown that pacing the LV only increased QRS duration, potentially due to late activation of the RV (126). To account for this effect we provide results for activation times, both for the combined LV and RV and for the LV alone. If the bulk of the heart is rapidly and
synchronously activated, then late activation of peripheral regions that prolong QRS duration may confound relationships between QRS and CRT response.

Maximizing the peak rate of volume activation may minimize bulk activation asynchrony and lead to improved cardiac function. To test this hypothesis, we calculated derivative of the cumulative activation curve and plotted this against CRT response. The length dependence of cardiac muscle combined with the circumferential fibre direction in the mid-LV wall means that effective LV contraction may be achieved when a continuous strand of activated myocardium is formed around the circumference of the LV. When all myocardium is activated in such a loop, the length dependence of the muscle will spatially regulate tension development so that during isovolumetric contraction muscle length is maintained, allowing it to generate higher tension and hence improved $dP/dt_{\text{max}}$. To test if activation loops in the LV correlate with $dP/dt_{\text{max}}$ in seven short-axis slices, we evaluated the time that the first loop of myocardium around the LV is activated, when the whole of the slice is activated in both the LV and RV, and when the whole of the slice in the LV is activated.

**Results**

**Baseline**

dP/dt$_{\text{max}}$ was calculated for a homogenous instantaneous activation of the myocardium, resulting in a theoretical maximum dP/dt$_{\text{max}}$ of 1,295 mmHg/s. Baseline dP/dt$_{\text{max}}$ (RV apical pacing) was 906, 885, and 825 mmHg/s for no, mild, and severe scar or 0.7, 0.683, and 0.64 of the maximum value.
Single-Site and Multisite LV Stimulation

Figures 43 and 44 show the fraction of the theoretical maximum $dP/dt_{\text{max}}$ reached with standard CRT and MSP in the presence of no, mild, and severe scar, for different combinations of LV and RV pacing locations and delay intervals. Standard CRT caused a 21%, 23%, and 21% change in $dP/dt_{\text{max}}$ from pacing combination D1-M2 5ms RVS, M3-P4 15ms RVA, and M3-P4 45ms RVA for no scar, mild scar, and severe scar, respectively. These changes correspond to an absolute increase of 0.150, 0.154, and 0.133 in the fraction of maximum $dP/dt_{\text{max}}$ reached for no scar, mild scar, and severe scar cases, respectively.

MSP (two LV and one RV stimulation site) caused a 22%, 24%, and 25% change in $dP/dt_{\text{max}}$ from pacing combination D1-M2 5ms M3-P4 5ms RVS, M3-P4 5ms D1-M2 5ms RVS and M3-P4 5ms D1-M2 45ms RVS for no scar, mild scar and severe scar respectively. These changes correspond to an absolute increase of 0.153, 0.164, and 0.162 in the fraction of maximum $dP/dt_{\text{max}}$ reached for no scar, mild scar and severe scar cases respectively. Thus, in the presence of severe scar, there was a benefit with MSP versus conventional CRT (25% vs 21% representing a 19% relative improvement in the change in $dP/dt_{\text{max}}$).
Figure 43. Simulated Standard CRT Pacing Response

Top panel corresponds to pacing the RV first, and bottom panel pacing the LV first with increasing intervals between the two. Red lines correspond to septal and blue lines apical RV pacing. Triangle and square symbols correspond to LV pacing from the apex or base, respectively.
Figure 44. Simulated Multisite CRT Pacing Using the Quartet Lead

Red lines correspond to septal and blue apical RV pacing, and triangle and squares symbols correspond to the variable time interval being first or second, respectively.
Figure 45 compares the optimal response from conventional CRT compared to multisite pacing.

![Figure 45](image)

**Figure 45. Simulated Conventional CRT v Multi-Site Pacing**

(A) Hemodynamic effect of standard versus MSP dependent on the presence and severity of posterolateral scar. With difference between standard versus Multi-Site CRT (MCRT) labelled. (B) Comparison of optimal pacing combinations from Figures 3 and 4, for conventional CRT (CCRT, gray lines) and multi-polar CRT (MCRT), black lines) for no (solid line), 50% (dashed line), and 90% (dash dot line) scar.

**CRT Efficacy and QRS Duration**

To test if minimizing either biventricular or LV activation time is a potential method for optimizing lead timings or positions, we plotted total and LV activation time against pacing efficacy in both the conventional and MCRT simulations in Figure 46.
Figure 46. Normalized Pressure Against LV or Biventricular Activation Time
Plot of normalized pressure against LV or biventricular activation time for conventional and MCRT in the presence of no scar, 50%, and 90% scar. Point symbols correspond to pacing from RVA (square), RVS (circle), D1-M2 (triangle), or M3-P4 (diamond) first. Solid points correspond to RVA as opposed to RVS pacing.

MCRT=Multi-polar CRT

Volume Activation

Figure 47 plots the peak rate of volume activation (the rate of change of the fraction of the myocardial volume that is activated) for each pacing and scar combination, in the whole heart or only in the LV against the normalized dP/dt\text{max}. 
Figure 47. CRT Response v Peak Rate of Cumulative Activation

Correlation between CRT response and peak rate of cumulative activation for conventional CRT and MCRT in the presence of no scar, 50%, and 90% scar.

MCRT=Multi-polar CRT

LV Activation Time

To evaluate the formation of continuous strands of activated tissue, we calculated the time taken for short-axis slices of the heart or the LV to become fully activated or the time taken for the first loop of continuous activation around the LV to form. Figure 48 shows the correlations between these times and dP/dtmax.
Figure 48. Correlation between LVTAT and dP/dt_{max}

Correlation as defined by the $R^2$ value of a linear fit between the time taken for the whole slice or the first loop to form and the normalized rate of pressure development for conventional CRT (CCRT) and MCRT with no scar, 50% scar, and 90% scar.

Discussion

This is the first human biophysical model that has tested the efficacy of MSP using a quadripolar lead. The model predicts that: (1) pre-excitation of the LV in regions of slow conduction improves haemodynamic response to CRT, (2) multisite CRT offers moderate improvements in acute haemodynamic response over conventional CRT but that this is the case only in the presence of scar, (3) minimizing QRS duration or activation times of short-axis slices provide a poor indicator of CRT response, and (4)
cumulative volume activation maps provide a potential metric of CRT response that is robust to cases with scar.

**Standard and MSP**

As shown in Figure 43, in the absence of scar, approximately 0.85 of the maximum dP/dt\textsubscript{max} could be achieved with either standard or MSP. It was only in the presence of posterolateral scar that MSP showed a benefit. As the level of scar increased, the optimal response between multisite and standard CRT diverged (25% vs 21%, representing a relative increase of 19%). As the level of scar increased, the optimal combination of poles locations in both the LV and RV changed for both standard and MSP demonstrating the impact of scar on optimal lead placement.

**Figure 43** shows that if the RV (apical or septal) is the first site to be activated then regardless of the severity of posterolateral scar, increasing the delay interval decreases CRT efficacy. In the presence of scar, pre-exciting the LV with standard CRT improves response, regardless of LV or RV pacing location, consistent with earlier studies (127) that showed an improved benefit of LV pre-excitation over simultaneous LV and RV pacing. Similarly for MSP in the absence of posterolateral scar, the model predicts no significant benefit from LV pre-excitation and limited benefit in the presence of mild scar for any pacing lead combination (figure 44). Only in the presence of severe scar was a benefit seen in pre-exciting the LV for MSP.
The effect of RV septal or apical pacing remains controversial. In standard CRT, RV septal pacing has been shown to provide no benefit over RV apical pacing (114). Consistent with these results, the model predicted no clear benefit from RV septal or apical pacing for standard CRT. Interestingly, there was a consistently better response to CRT with RV septal pacing as opposed to apical pacing in the MSP simulations.

**Figures 43 and 44** predict that in a clinical context, when temporal optimization may be unavailable or limited, MSP provides an optimal or near optimal outcome in 85% of pacing combinations for near simultaneous activation compared to 71% of pacing combinations for conventional CRT. Meaning MSP may provide a more robust outcome in the absence of temporal optimization.

**Pacing in Scar**

Consistent with canine (128) and human (129) studies, the model results predict that with optimal pacing timing and location, CRT in the presence of scar can still significantly improve pump function. Specifically, the model predicts that, with lead capture, pacing in scarred regions and thus pre-excite the scarred myocardium often results in an optimal site. Controversy remains regarding the detrimental effects of pacing in or near scar, however, and these conflicting results could be due to differences in capture of the scarred region, as if electrical activation fails to propagate from the pacing site then patients will receive no benefit. Notably lead position optimization strategies have resulted in apparently conflicting conclusions. Previous reports have suggested that pacing in or near regions of scar compromises response (36, 130).
conversely an alternate strategy proposes pacing at the point of latest mechanical contraction maximizes response.

Although not explicitly inconsistent, in many cases, slow conduction in scar will result in the last region to contract being one that is scarred or compromised; this location is then either an optimal or a poor pacing location depending on the doctrine adopted. The model predicts that if the scarred region has viable but slow conduction then pre-exciting the scarred region can result in an optimal response; thus, the optimal increase in $dP/dt_{\text{max}}$ for standard and MSP was achieved by first pacing from D1-M2 in the absence of scar but in the presence of scar, it was optimal to pace first from M3-P4, which was located in the middle of the scar region. This is in keeping with non-contact mapping data where LV pre-excitation in areas of slow conduction improved haemodynamic response (78).

**Apical versus Basal Pacing**

There has been much interest recently in the position of the LV pacing lead for CRT in terms of an apical or basal pacing site. Recent data from the MADIT-CRT trial showed that leads placed in the apical region were associated with an unfavourable outcome (48). For standard CRT simulations, with a single LV stimulation site, the optimal site was basal in models with mild or severe scar. In models without scar, there was marginal difference between apical and basal pacing. For MSP, pacing at both apical and basal sites is performed so one cannot differentiate between apical and basal LV pacing.
Optimizing Activation

Previous studies have reported that minimizing QRSd correlates with CRT response (84, 131) while other studies found no change in QRSd despite seeing a response to CRT (119, 132). To directly address this issue, we evaluated the correlation between QRSd, maximum rate of volume activation, and short-axis slice activation times in both the RV and LV and the LV alone.

We found that QRSd did not consistently correlate with CRT response. Single-site LV pacing has been reported to prolong QRS while improving CRT response (126). This could be attributable to late activation of the RV prolonging the QRS while having limited impact on LV function, yet even when the confounding effects of the RV on total activation time were removed (figure 46), the correlation between CRT response and LV activation time in the model was still poor. This relationship was similar for both standard and MSP with the relationship deteriorating further in the presence of scar.

We hypothesized that minimizing the activation time of the LV, RV and LV, or a loop in a short axis slice would correlate with CRT response by corresponding to the formation of a continuous contracting region of myocardium that would cause an effective contraction of the LV. Despite showing a strong correlation of basal activation with CRT response in the absence of scar, this relationship deteriorated rapidly in the presence of scar, particularly in the MSP simulations.
It is possible that calculating the time of formation of other continuous loops of activating myocardium would correspond to CRT response. These loops could potentially lie out of the short-axis plane or in loops of myocardium following the direction of principle stress. The only metric to show a consistent correlation with the CRT response was the peak rate of cumulative activation in the LV. Given an approximate constant conduction velocity and the continuous smoothly varying LV geometry, this metric corresponds to the peak surface area of the activation wave and maximizing its size will synchronize the bulk activation time of the heart. This metric correlated with both standard and MSP and was independent of scar, RV or LV lead location, and timing interval.

The cumulative activation of the LV is not routinely measured in CRT patients. It can be approximated by evaluating the rate of cumulative volume contracting, although the relationship between activation time and deformation is dependent on the activation pattern. It is possible that simple patient-specific activation models could provide a means to evaluate this metric and be used for the model-guided optimization of CRT lead position and timing.

**Study Limitations**

The model was based on a single patient dataset due to the need for a single comprehensive and consistent dataset. However, we cannot necessarily assume that all patients would respond in the same fashion. The patient on whom the model was based, however, was a typical candidate for CRT with a broad LBBB and LVEF<35%.
In modelling the scar, we assumed a homogenous and discrete region that may not be the case for many patients with ischaemic heart disease that may have multiple and heterogeneous areas of scar. The presence of multiple infarct regions would affect the model predictions. Specifically, the presence of scarred or compromised regions in close proximity to the RV lead could favour pre-excitation of the RV to achieve an optimal response. DE CMR shows us that scar geometry is varied and often complex. In this study, we aimed to investigate the general impact of trans-mural posterolateral scar severity on conventional CRT and MSP efficacy independently from any one individual patient’s scar geometry. This leads to the use of a defined analytical description of scar geometry; however, the model results may change for different scar locations or geometries.

MSP was delivered using a commercially available lead and it is possible that other lead designs would produce a different haemodynamic response.

**Conclusions**

This biophysical model, testing the efficacy of multisite LV pacing using a quadripolar lead, shows that MSP may offer an improvement in AHR over conventional CRT but that this benefit is only seen in the presence of scar. Posterolateral scar is a well-recognized predictor of poor CRT response and therefore MSP delivered using such lead technologies may be a potential way to improve response in the CRT population, especially in patients with ischemic cardiomyopathy. These findings will clearly require *in vivo* evaluation.
Chapter 8. Multi-site Pacing and Electro-anatomic Mapping Study

Abstract

Objectives

To determine the best method of multi-site pacing for CRT and the mechanism underlying the response.

Background

Pacing the left ventricle (LV) from more than one site simultaneously improves acute hemodynamic response (AHR) and medium term-outcome in CRT. The best method of multi-site pacing is not clear, however. By using the multi-site pacing function of a quadripolar LV lead and additional temporary endocardial and epicardial LV leads, we aimed to pace from multiple sites in multiple different ways in order to establish the best method of multi-site pacing.

Methods

A haemodynamic study was performed in 12 patients with a previously implanted St Jude Quartet lead. The generator was temporarily reprogrammed to allow true multi-site pacing from the quadripolar lead. A second temporary LV lead was placed in another branch of the CS and a temporary decapolar LV roving catheter, a RADI pressure wire and an ESI non-contact mapping balloon were placed in the LV cavity. Simultaneous pacing from up to five ventricular sites was then performed.

Results

The best mean AHR overall was found using DDDLV endocardial pacing. Conventional biventricular pacing led to a 13% increase in AHR and this was similar to
various combinations of multi-site pacing (MSP). Within individuals, however, the best pacing modality varied greatly. MSP using 2 vectors from the Quartet lead was best in 25%, endocardial pacing was best in 25% of patients, conventional single LV site pacing was best in 25%, in 1 patient a combination of 2 different epicardial leads was best and in 2 patients ‘quad-site’ pacing was best.

Conclusions

Multi-site pacing the ventricles from 3, 4 or 5 sites simultaneously does not appear to confer an overall AHR group advantage compared to conventional CRT. Within individuals, however, different methods of multi-site pacing are best and may improve response in patients who do not improve with conventional CRT. CRT thus needs to be tailored to the individual.
Background

CRT is an established treatment for heart failure (24, 25, 35) but 30-40% of patients do not respond (25, 35) and this may relate to sub-optimal lead positioning (36). Investigators have demonstrated that the region of best acute haemodynamic response to CRT varies greatly between patients and the optimal site may need to be individualised for each patient (51, 107). There is also evidence to suggest that pacing the left ventricle from more than one coronary sinus (CS) site simultaneously may improve acute hemodynamic response (AHR) and medium-term outcome (64-66, 69, 133).

Multi-site pacing (MSP) via the CS is limited by the number of vein tributaries available, however, whereas endocardial pacing is not and thus a greater number of LV sites can be accessed. Furthermore, endocardial pacing may give rise to a more physiological electrical and mechanical propagation which results in a better acute haemodynamic response (70). Recent work suggests that not only is endocardial pacing better than conventional epicardial pacing via the CS but the combination of epicardial and endocardial MSP may give the best overall AHR particularly in patients with an ischaemic cardiomyopathy (71). No studies to date, however, have compared MSP from two epicardial (CS) sites simultaneously with endocardial pacing or indeed simultaneous endocardial and epicardial pacing to dual epicardial site pacing.

We aimed to ascertain the best method of multi-site pacing by using the multi-site pacing function of the Quartet 1458Q LV lead (Jude Medical, Sylmar, CA, USA) (134) in patients with a chronically implanted CRT system and then adding further temporary CS epicardial and endocardial leads to allow multiple different combinations of MSP to
be performed. Using a Certus pressure wire (RADI Medical Systems, Uppsala, Sweden) and EnSite EC1000 non-contact mapping (NCM) balloon array (St Jude Medical, Sylmar, CA, USA) we aimed to ascertain the LVdP/dt_{max} and electrical properties underlying the changes seen when multi-site pacing in different ways.

Methods

The study was approved by the local ethics committee and informed consent was obtained from each patient. Patients fulfilling standard criteria for CRT (NYHA class II-IV drug refractory heart failure, LVEF ≤35% and QRS ≥ 120ms) who had previously been implanted with a Quartet Model 1458Q LV lead and Promote Q Model CD3221-36 or Promote Quadra CD3239-40 generator (St Jude Medical, Sylmar, CA, USA) at least 3 months prior to the invasive study were recruited. Patients with a mechanical aortic valve or significant peripheral vascular disease were excluded.

Baseline assessment included NYHA functional class, ECG and 2D echocardiography prior to original CRT implant. Each patient’s heart failure aetiology was confirmed on the basis of clinical history, coronary angiography and CMR.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD) or Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 (7)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>100</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>27 (8)</td>
</tr>
<tr>
<td>NYHA Class (II/III)</td>
<td>2/12</td>
</tr>
<tr>
<td>Ischaemic/non-ischaemic (%)</td>
<td>75/25</td>
</tr>
<tr>
<td>Sinus rhythm/Atrial fibrillation</td>
<td>11/1</td>
</tr>
<tr>
<td>QRS duration pre-CRT (ms)</td>
<td>136(25)</td>
</tr>
<tr>
<td>QRS morphology (LBBB/non-specific IVCD)</td>
<td>10/2</td>
</tr>
</tbody>
</table>

**Table 12. Multi-Site Pacing Patient Characteristics**

*IVCD = intraventricular conduction delay; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association*

**Electroanatomical Study**

The implanted CRT-D system was uploaded with investigational software enabling multi-site LV pacing for the duration of the study. Patients were lightly sedated using
diazemuls (5-10mg). Bilateral femoral venous access was used to place a 5F Supreme quadripolar electrophysiological catheter (St Jude Medical, Sylmar, CA, USA) to the high right atrium and an SL3 Fast-Cath Introducer (St Jude Medical, Sylmar, CA, USA) was used to cannulate the coronary sinus. A QuickFlex Micro 1258T/92 LV pacing lead (St Jude Medical, Sylmar, CA, USA) was then placed in a CS vein tributary as far separated from the chronically implanted Quartet lead as possible.

An NCM array was passed via 10F femoral arterial access retrogradely across the aortic valve to the LV cavity. A 0.014 inch diameter high fidelity Certus PressureWire and PhysioMon software (RADI Medical Systems, Uppsala, Sweden) with a 500Hz frequency response and 50Hz filter bandwidth were used to assess real-time mean peak LVdP/dtmax as a marker of LV contractility. The pressure wire was placed retrogradely to the LV cavity via the NCM array. Via the other femoral artery, a steerable 6F Livewire decapolar catheter (St Jude Medical, Sylmar, CA, USA) was passed retrogradely to the LV cavity to perform endocardial pacing from different sites within the LV (figure 49). The NCM array uses the inverse solution method to reconstruct endocardial potentials within the LV cavity (76) and the chamber geometry was reconstructed using a locator signal from the LV decapolar catheter. Intravenous heparin (70u/kg) was administered to achieve systemic anticoagulation (target activated clotting time 300-350s).
Figure 49. Fluoroscopic Image of Multi-Site Pacing Study Catheter Set-up

Fluoroscopic image showing the Quartet LV lead in a postero-lateral branch of the coronary sinus (CS), a second temporary epicardial lead in an anterior branch of the CS, an LV endocardial roving catheter, an ESI array balloon in the LV cavity and an RV lead at the RV apex.

LVdP/dt_{max} whilst pacing 5-10 beats above intrinsic rate (to eliminate the effect of heart rate variation) was recorded for a period of at least 20 s to ensure steady-state conditions during any pacing modality. LV dP/dt_{max} during atrial pacing (AAI) or RV pacing (AF patient) at 5-10 beats above intrinsic rate was considered baseline and was kept constant when testing different pacing modes. A waiting period of at least 20 s was respected after any change in pacing settings or lead position to achieve haemodynamic stabilisation. These methods have previously been shown to reliably measure LV dP/dt_{max} (61, 62, 101, 102, 135). Results at each pacing site were expressed as a percentage change from baseline. In order to minimize the effect of baseline drift in
AHR (secondary to changes in patient intra-vascular volume/sedation levels etc) the baseline was reassessed prior to and after every change in pacing modality and comparisons were made to a mean of these two readings. Data from premature ventricular complexes were discarded.

Two 3-channel Merlin Pacing Systems Analysers (PSA’s) (St Jude Medical, Sylmar, CA, USA) were used in order to synchronize the AV and VV delays from the implanted CRT device with the additional LV CS epicardial and endocardial leads. The temporary RA quadripolar lead was required in order to ensure reliable sensing and thus allow simultaneous multi-site pacing when LV endocardial pacing or LV epicardial pacing using the 2nd CS lead in addition to pacing from the chronically implanted CRT device. An iterative approach to optimising the AV delays led us to conclude that a paced AV delay of 80ms was required to achieve near simultaneous LV capture using the endocardial LV lead or 2nd CS LV lead when the Quartet CRT system AV paced delay was set at 100ms.

In order to achieve the greatest vector separation distance when multi-site pacing using the Quartet lead, vectors D1-RV Coil and P4-RV Coil were the first choice pacing vector pair for multi-site pacing using the Quartet lead. M2-RV coil was used if D1-RV Coil was unusable as vector 1 (V1) and M3-RV coil was used if P4-RV coil was not usable as vector 2 (V2) because of a high capture thresholds or PNS (in 1 patient M2-RV Coil was used as V2 as neither M3-RV Coil or P4 to RV coil were usable). The minimum programmable VV delay of 5ms was used between the 2 vectors used and also between V2 and RV stimulation: V1 – (5 ms delay) – V2 – (5 ms delay) – RV. A pacing protocol was performed in the following order: (Rate 5-10bpm above intrinsic
rate, paced and sensed AV delay 100ms): RV only, 1 Quartet vector only (V1), RV + V1 (RV + V1), RV + 2 Quartet Vectors i.e. V1 + V2 (RV + V1 + V2), 2nd CS lead only (EPI), RV + 2nd CS lead (RV + EPI), LV endocardial pacing only (LVEN), RV + LVEN, RV + LVEN + V1, RV + LVEN + V1 + V2, RV + LVEN + V1 + EPI, RV + V1 + V2 + EPI, RV + LVEN + V1 + V2 + EPI, RV + D1-M2 (conventional biventricular CRT pacing). LVEN and RV + LVEN were repeated with the LV rove catheter in different positions. MSP from the Quartet was also repeated using a reversal of the vector sequence to V2-V1-RV and also with the VV delays from V1-V2-RV increased to 40ms.

Capture was verified with each pacing modality by looking for a change in QRS morphology at a paper speed of 200mm/s. This was also validated with reference to LV pacing by analysis of the activation wavefront on non-contact mapping. In all modes involving LV endocardial pacing the LV rove catheter was placed in a random order in as many different endocardial positions as possible.

**Derivation of LV and Trans-Septal Activation Times**

Virtual unipolar electrograms recorded at 1200Hz (temporal resolution of 0.83ms) from the endocardial surface were used to measure activation times (figure 50). The high pass filter was set at 8Hz. The onset of LV activation was defined as the first peak negative dV/dt at any point in the LV. The end of LV activation was defined as the time of the latest peak negative unipolar electrogram on the virtual endocardial surface. The trans-septal activation time was defined as the time from QRS onset to peak negative dV/dt at any point in the LV.
Figure 50. Non-Contact Mapping Unipolar Electrograms

64 Unipolar Virtual Electrograms Recorded Whilst ‘QuinV’ Pacing (pink shading indicates excluded signal)

Definition of Regions of Slow Conduction

Dynamic substrate mapping (DSM) was performed after completion of the procedure to define areas of consistently low peak negative voltage, using a method validated previously (136). Zones of slow conduction were delineated as regions which the activation wavefront failed to enter, with the endocardial voltage amplitude threshold set at 30% of the maximum endocardial voltage recorded (figure 51).
Figure 51. Dynamic Substrate Map

*Dynamic substrate map showing an antero-lateral line of scar in red.*

**Statistical Analysis**

Statistical analysis was performed on PASW Statistics 20 (SPSS Inc, Chicago, IL, USA). Data were analysed using generalised estimating equations using an exchangeable correlation structure, to explore the extent of differences between pacing methods. All pacing methods were compared to each other and to avoid type I errors, p values were corrected using the Bonferroni adjustment. To perform a Bonferroni correction for each p value, the p value was divided by the number of comparisons made. Pearson’s correlation coefficient was used to measure the linear relationship between two variables. All results are expressed as mean ± SD.
Results

Procedural Success

An invasive haemodynamic protocol was completed in all 12 patients. In three patients it was not possible to collect electro-anatomic data because of recurrent ventricular tachycardia when placing the EnSite array in the LV cavity in one patient (it was also not possible to place the LV endocardial roving catheter in this patient). In another patient it was not possible to get satisfactory arterial access for the EnSite balloon to pass (but a full multi-site pacing study was still performed without electro-anatomical mapping data). In the third patient it was not possible to perform an electronanatomical mapping study because of failure of the EnSite mapping system (again, a full multi-site pacing protocol was followed but without electro-anatomical mapping data). There were no procedural complications.

AHR

The best overall mean AHR (figure 52 and table 13) was found using LVEN pacing (25.6% increase in LVdP/dt\text{max} at best endocardial site over baseline). This was significantly (p<0.05) better than all other non-endocardial pacing modalities. Conventional Biventricular pacing (D1-M2) led to a 13.1% increase in AHR and this was similar to the various combinations of MSP using 2 vectors of the Quartet, the 2\textsuperscript{nd} epicardial CS lead, the LV endocardial lead and the RV lead. No significant differences were found in AHR between the various different methods of MSP although all were significantly better than intrinsic rhythm and RV pacing (p<0.001).
Figure 52. AHR Achieved Using Different Pacing Modalities

AHR as % change in $LVdP/dt_{max}$ over baseline (AAI pacing) on y-axis

$V1 = Qua\text{r}t\text{e}t \text{ V}ec\text{t}o\text{r} \ 1$; $V2 = Qua\text{r}t\text{e}t \text{ V}ec\text{t}o\text{r} \ 2$; $BiV = RV \text{ and} LV \text{ Pacing}$; $BiV (D1-M2) = C\text{onventional CRT using Quartet}$; $EPI = 2^{nd} \text{ CS lead}$; $LVEN = LV \text{ endocardial pacing only}$; $BIVEN = LVEN + RV$; $TriV = \text{Multi-Site Stimulation(MSP) from 3 Ventricular Sites}$; $QuadV = MSP \text{ from 4 Ventricular Sites}$; $QuinV = MSP \text{ from 5 Ventricular Sites (RV + LVEN + V1 + V2 + EPI)}$
<table>
<thead>
<tr>
<th></th>
<th>LVAT (ms)</th>
<th>QRSd (ms)</th>
<th>Trans-Septal Activation Time (ms)</th>
<th>AHR (% change over baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic</td>
<td>120 ± 22</td>
<td>183 ± 35</td>
<td>42 ± 23</td>
<td>-8 ± 6</td>
</tr>
<tr>
<td>RV</td>
<td>113 ± 33</td>
<td>227 ± 16</td>
<td>84 ± 15</td>
<td>1.2 ± 4.1</td>
</tr>
<tr>
<td>V1</td>
<td>140 ± 54</td>
<td>216 ± 48</td>
<td>73 ± 49</td>
<td>8.9 ± 12.9</td>
</tr>
<tr>
<td>RV + V1</td>
<td>139 ± 72</td>
<td>192 ± 29</td>
<td>48 ± 48</td>
<td>13.1 ± 13.9</td>
</tr>
<tr>
<td>RV + V1 + V2</td>
<td>187 ± 30</td>
<td>200 ± 29</td>
<td>7 ± 9</td>
<td>14.7 ± 11</td>
</tr>
<tr>
<td>EPI</td>
<td>151 ± 50</td>
<td>232 ± 9</td>
<td>63 ± 44</td>
<td>10.8 ± 15.9</td>
</tr>
<tr>
<td>RV + EPI</td>
<td>114 ± 22</td>
<td>208 ± 23</td>
<td>87 ± 9</td>
<td>9.6 ± 13.5</td>
</tr>
<tr>
<td>RV + EPI + V1</td>
<td>160 ± 7</td>
<td>183 ± 35</td>
<td>24 ± 43</td>
<td>15.9 ± 11.4</td>
</tr>
<tr>
<td>Best LVEN</td>
<td>132 ± 44</td>
<td>165 ± 20</td>
<td>34 ± 32</td>
<td>25.6 ± 14.3</td>
</tr>
<tr>
<td>RV + LVEN</td>
<td>163 ± 40</td>
<td>180 ± 28</td>
<td>15 ± 22</td>
<td>21.6 ± 13.1</td>
</tr>
<tr>
<td>RV + LVEN + V1</td>
<td>145 ± 26</td>
<td>168 ± 12</td>
<td>17 ± 18</td>
<td>14.2 ± 15.8</td>
</tr>
<tr>
<td>RV + LVEN + V1 + EPI</td>
<td>153 ± 36</td>
<td>176 ± 25</td>
<td>16 ± 16</td>
<td>15.8 ± 16.7</td>
</tr>
<tr>
<td>RV + LVEN + V1 + V2</td>
<td>150 ± 28</td>
<td>168 ± 15</td>
<td>15 ± 18</td>
<td>11.9 ± 17.1</td>
</tr>
<tr>
<td>RV + EPI + V1 + V2</td>
<td>141 ± 46</td>
<td>190 ± 19</td>
<td>47 ± 51</td>
<td>13.9 ± 13.4</td>
</tr>
<tr>
<td>RV + LVEN + EPI + V1 + V2</td>
<td>143 ± 21</td>
<td>167 ± 23</td>
<td>16 ± 14</td>
<td>15.7 ± 15.4</td>
</tr>
<tr>
<td>BiV (RV + DI-M2)</td>
<td>93 ± 31</td>
<td>170 ± 3</td>
<td>73 ± 33</td>
<td>15.0 ± 16.0</td>
</tr>
</tbody>
</table>

Table 13. Summary of Activation Times and AHR
Left ventricular activation Time (LVAT); QRS duration (QRSd). Trans-septal activation time and acute haemodynamic response (AHR) for each of the pacing modes: RV =right ventricle; V1= Vector 1 (D1-RV Coil or M2-RV Coil), V2=Vector 2 (P4-RV Coil or M3-RV Coil); EPI=2nd Epicardial LV Lead; LVEN=LV endocardial lead; D1-M2 = conventional bipolar biventricular pacing

Within individuals, however, the best pacing modality varied greatly (table 14). Endocardial (LVEN or BIVEN) pacing was best in 3/12 (25%) patients, MSP using two vectors from the Quartet lead was best in 3/12 of patients, conventional biventricular pacing was best in 2/12 patients, LV epicardial pacing (using the second epicardial lead) was best in one patient (in this patient the chronically implanted Quartet lead was in a distal anterior branch and the EPI lead was placed in a proximal anterior branch as no other CS tributaries were possible) and in one patient a combination of two epicardial leads was best (TRIV – LV1 + EPI + RV). In two patients a form of ‘Quad-V’ pacing was best: (V1+ EPI + LVEN + RV) in one and (V1 + V2 + EPI + RV) in the other. Although ‘Quin-V’ pacing (V1 + V2 + EPI + LVEN + RV) gave a good overall mean AHR (15.8 ± 16.7), Quin-V pacing did not give the best AHR in any individual patients.

All four of the patients in whom a form of endocardial pacing was best (including patient 8 in whom ‘Quad-V was best) had an ischaemic aetiology to their cardiomyopathy. Of the two patients without ischaemic heart disease, in one MSP using the Quartet lead was best and in the other conventional biventricular pacing using D1-M2 was best.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Quartet Position</th>
<th>LV1</th>
<th>LV2</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; EPI</th>
<th>Best Pacing Method</th>
<th>Aetiology (Activation Pattern)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Posterolateral</td>
<td>D1-RV</td>
<td>M3-RV</td>
<td>Anterior</td>
<td>Quad V (V1 +V2 + EPI)</td>
<td>I (N/A)</td>
</tr>
<tr>
<td>2</td>
<td>Lateral</td>
<td>D1-RV</td>
<td>P4-RV</td>
<td>Anterior</td>
<td>BiV (D1-M2)</td>
<td>N (Type II)</td>
</tr>
<tr>
<td>3</td>
<td>Posterolateral</td>
<td>D1-RV</td>
<td>P4-RV</td>
<td>Anterior</td>
<td>TriV (V1+V2)</td>
<td>I (Type II)</td>
</tr>
<tr>
<td>4</td>
<td>Lateral</td>
<td>D1-RV</td>
<td>M3-RV</td>
<td>Anterior</td>
<td>TriV (V1+EPI)</td>
<td>I (Type II)</td>
</tr>
<tr>
<td>5</td>
<td>Posterolateral</td>
<td>D1-RV</td>
<td>P4-RV</td>
<td>Anterior</td>
<td>TriV (V1+V2)</td>
<td>N (indeterminate)</td>
</tr>
<tr>
<td>6</td>
<td>Posterolateral</td>
<td>D1-RV</td>
<td>P4-RV</td>
<td>Anterior</td>
<td>LVEN</td>
<td>I (N/A)</td>
</tr>
<tr>
<td>7</td>
<td>Anterior (distal)</td>
<td>D1-RV</td>
<td>P4-RV</td>
<td>Anterior (prox)</td>
<td>BiVEN</td>
<td>I (Type I)</td>
</tr>
<tr>
<td>8</td>
<td>Lateral</td>
<td>D1-RV</td>
<td>M3-RV</td>
<td>Anterior</td>
<td>QuadV (V1/EPI/END O)</td>
<td>I (Type II)</td>
</tr>
<tr>
<td>9</td>
<td>Posterolateral</td>
<td>D1-RV</td>
<td>M3-RV</td>
<td>Anterior</td>
<td>LVEN</td>
<td>I (Type II)</td>
</tr>
<tr>
<td>10</td>
<td>Lateral</td>
<td>D1-RV</td>
<td>M3-RV</td>
<td>Anterior</td>
<td>BiV (D1-M2)</td>
<td>I (II)</td>
</tr>
<tr>
<td>11</td>
<td>Anterior</td>
<td>D1-RV</td>
<td>M2-RV</td>
<td>Anterior</td>
<td>LV EPI</td>
<td>I (N/A)</td>
</tr>
<tr>
<td>12</td>
<td>Posterolateral</td>
<td>M2-RV-</td>
<td>M3-RV</td>
<td>Anterior</td>
<td>TriV (V1+V2)</td>
<td>N (Type II)</td>
</tr>
</tbody>
</table>
Table 14. Lead Positions, Vectors Used and Aetiology of Cardiomyopathy

$I = Ischaemic Aetiology; N = Non-Ischaemic Aetiology; I = Type I Activation Pattern; II = Type II Activation Pattern; N/A = Activation Data Unavailable$

Activation Patterns and Times

A reduction in QRSd was seen only with forms of endocardial pacing and this was significant when compared to RV only and EPI only pacing (p<0.01) but not with other pacing modalities. There was no significant difference in LVAT between any of the different pacing modes. A weak negative correlation was seen between AHR and QRSd ($R^2=0.22$, p<0.01) and AHR and trans-septal time ($(R^2=0.22$, p<0.01). There was no significant relationship between LVAT and AHR.

The intrinsic LV activation pattern seen (71, 77) in the 9 patients in whom non-contact mapping was possible was Type I in two patients (both ischaemic aetiology) and Type II in six patients (figure 53). The activation pattern was indeterminate in a further patient.
Figure 53. Intrinsic Activation in a Patient with a Type II Activation Pattern.

Red arrow on left hand side series of 4 images indicates U-shaped pattern of activation rotating around apex. Panel of 64 images on the right shows corresponding unipolar electrograms for intrinsic activation derived from NCM. RAO: Right
Anterior Oblique; AP: Antero-Posterior; RPO: Right Posterior Oblique; LAO: Left Anterior Oblique

Discussion

Endocardial pacing appears to give a superior overall mean AHR compared to other pacing modalities. This is consistent with previously published work from our institution (71, 72) and others (137). This may relate to activation being more physiological and thus resulting in better electrical and mechanical propagation compared to conventional epicardial pacing via the CS (70). Indeed, only LV only (LVEN) and BiV Endocardial (BIVEN) pacing lead to a significant reduction in QRSd compared to other pacing modalities. The negative correlation between QRSd and AHR seen in this study, however, was weak. Again this is consistent with previous work suggesting that the mechanism of acute haemodynamic benefit may be more effective mechanical recruitment of the LV myocardium rather than shortening of the LV electrical activation time (71).

Multi-site pacing the heart from 3, 4 or 5 sites simultaneously does not appear to confer a significant overall AHR advantage compared to conventional DDDBiV pacing from an optimal LV CS site. Within individuals, however, the best pacing modality varies and although a form of MSP was best in 50% of patients, the method of MSP varied with four different methods of MSP being best for individuals. Interestingly, MSP using the Quartet Lead was best in half of this sub-group (3/6 patients) and in a further patient, MSP using the extra CS lead (EPI) in addition to the MSP function of the Quartet Lead (Quad-V Pacing) was best.
The only patient in whom the 2nd CS lead (EPI) gave the best AHR was one in whom the original chronically implanted Quartet lead had been placed in a distal anterior branch of the CS. Given that this patient had no other CS target vessels, the EPI lead was placed in a proximal position in the same anterior CS tributary as the Quartet. This raises the possibility that an improved AHR may be achieved in this patient simply by pacing using the chronically implanted Quartet lead from a more proximal pole (e.g. P4-RV Coil alone). Gold et al (108) have shown, however, that there is not a large intra-vein variability in AHR and this was confirmed by our own study of intra-vein variability using different pacing vectors of the Quartet (135) which suggested that if a poor AHR was seen with one Quartet vector, it was unlikely that large increase in AHR would be seen without physically repositioning the lead.

Our data with regard to LV endocardial pacing giving an excellent overall AHR disguises the fact that LV endocardial pacing did not give an excellent AHR in all LV positions. The mean LVEN AHR was 16.5% better than baseline. Whilst this is very good it was not significantly better than conventional BiV CRT or the MSP configurations assessed in this study. This again emphasises the findings of Derval (51) et al who found that there is not one pacing site (or combination of pacing sites) that is best for all patients and the choice of pacing modality needs to be tailored to the individual.

Implanting a permanent endocardial pacing lead is not as straight-forward as implanting a conventional CRT device. It will probably require a trans-septal puncture, life-long anti-coagulation and may interfere with the mitral valve apparatus. MSP using two CS leads is more straight-forward but implantation is still more technically challenging than
standard CRT. In any case, MSP using 2 CS leads in this study gave the best AHR in only one patient. It is thus promising that MSP using just one (commercially available) CS lead gave a good overall AHR and the best possible AHR in 25% of our cohort. If an improved AHR can be achieved simply by switching on the MSP function of an LV lead with no further invasive procedures required this is an exciting option. While it may not make a difference in most patients, in a significant minority of patients it may make a ‘non-responder’ respond.

Although previous studies have compared dual site epicardial pacing to conventional CRT or simultaneous epicardial and endocardial pacing to single LV site pacing, this is the first study to allow comparison of both MSP modalities. It is also the first study to present invasive AHR data using the MSP function of the Quartet lead and thus allow comparison of this type of MSP with dual epicardial or epi/endocardial MSP. Not only this, we extended the MSP protocols such that we assessed the AHR from four and five ventricular sites simultaneously. Although ‘Quin-V’ pacing did not give the best AHR in any patients, two different forms of ‘Quad-V’ pacing were best in individuals and thus increasing the number of ventricular pacing sites from the three tested in other studies cannot be discounted as potentially useful in some patients.

**Study Limitations**

This study is limited by its small sample size. Given the highly invasive and time-consuming nature of the study, however, this is unavoidable. The order of the pacing vector sequence was not altered randomly and thus we cannot rule out sustained effects from earlier pacing sequences. Ideally a range of AV delays and more VV delays would
have been assessed but this was not possible because of time constraints. Indeed the number of possible LV-LV-RV or RV-LV-LV vector combinations and delays mean that an empiric approach to MSP programming may need to be taken or a computer modelling based algorithm if this function is to be made available to all CRT patients.
Chapter 9. Discussion

The prevalence of heart failure is high and the population rising as treatments improve and life expectancy increases. There are a large number of RCTs supporting the use of medication in heart failure and device therapy for patients on optimal therapy who fulfil specific criteria. Even in those patients implanted with CRT devices who fulfil guideline criteria, however, a significant proportion do not gain symptomatic benefit and an even larger proportion do not appear to undergo significant LV reverse remodelling.

A proportion of patients eligible for CRT may not get the chance to ‘respond’ to therapy because of implant failure and the reasons for this include failure to get into the CS ostium, an inability to pass the LV lead into a CS branch, unsatisfactory pacing parameters and phrenic nerve stimulation (PNS). In my introduction I suggest that methods of improving CRT success might include i) Developing better methods of identifying patients who will respond to CRT; ii) Reducing CRT implant failure; iii) Selecting and pacing the regions of the LV most likely to improve electrical and mechanical dyssynchrony; iv) Optimising device settings; v) Pacing the heart in novel ways.

My thesis specifically then describes the use of quadripolar lead technology (Chapters 4 and 5) and image guidance to overcome CRT implant failure, the use of CMR dyssynchrony and scar data to improve electrical and mechanical dyssynchrony (Chapter 6) and multi-site and endocardial pacing (Chapters 7 and 8) as novel ways of pacing the heart to improve AHR. My introduction also explains why CRT device optimisation probably does not make a difference to outcome overall in the HF
population but may be of benefit in certain individuals. Chapters 5 and 6 suggest that AHR and CMR data may be used to predict who will and will not respond to CRT.

**Quadripolar Leads**

I have shown (in Chapter 4) that the Quartet quadripolar lead is associated with a high implant success rate and a low level of complications at 6 month follow-up. I have shown that the Quartet lead offers more pacing vectors than conventional LV pacing leads and thus makes it more likely that common pacing obstacles can be overcome by ‘electronic repositioning’ and thus without the risk of dislodgement from the CS involved with physical repositioning. Successful CRT may be therefore be achieved in cases where a conventional lead would fail because of PNS or high capture thresholds. The availability of different pacing vectors may obviate the need for a lead revision, a surgical approach to LV lead placement, or CRT to be turned off in patients who encounter pacing problems after implantation. The benefit of having four LV lead electrodes rather than the usual two that has been demonstrated by the work in this thesis and publications from other centres, means that quadripolar leads from multiple device manufacturers are likely to be available in the near future and may become an industry standard.

Although I have shown that the cathodal programmability available on a quadripolar lead can be used to overcome problems with PNS and high capture thresholds, my study of acute haemodynamic response to pacing within a vein (Chapter 5) showed that the multiple vectors available do not appear to allow optimal AHR for and individual to be achieved if the lead is not placed in the most suitable CS vein. Thus although a
quadripolar lead may allow placement in a distal (and more stable) CS vein position, there does not appear to be a large variation in the AHR that can be achieved by pacing using the more proximal LV lead electrodes within a CS branch and thus a poor response elicited using a conventional bipolar configuration probably cannot be overcome by a change in pacing vector.

My study of AHR within a CS vein also showed that the best CS vein is not necessarily a lateral or postero-lateral branch, as the best AHR seen in this study was in an anterior or posterior vein in one third of patients. Although a significant difference in AHR was seen between anterior and posterior positions, no difference was seen between lateral and anterior positions or lateral and posterior positions. This suggests that within individual patients large variations in AHR exist and the best and worst veins are different in different subjects. Indeed, when CS positions are divided by whether they give rise to $\geq 10\%$ increase in $dP/dt_{max}$ (‘acute responder’) or not, it can be seen that in half of all patients, whether they are likely to respond or not to CRT is critically dependent on whether the right CS vein is chosen. In the other half of patients, however, it would appear that no matter which vein is chosen the same outcome will be achieved whether this be ‘response’ or ‘non-response’.

Chapter 7 gave a detailed analysis of computer modelling in a single patient. This chapter brought together three themes of my thesis: quadripolar lead technology, multi-site pacing and computer modelling to predict response to CRT. The study managed to non-invasively assess what would happen if a patient was conventionally or multi-site paced using a quadripolar lead. Given the multiple different pacing configurations available and the multiple different delays allowed between pacing vectors, this study
would not be possible in vivo. Interestingly the predictions made are consistent with previous studies at our own and other centres. In patients without scar, MSP probably does not confer additional haemodynamic benefit. In patients with increasing amount of scar, however, MSP does appear to improve dP/dt\textsubscript{max} compared to standard CRT. The benefit seen does not appear to result in a reduced QRS duration, however, and this is consistent with the in vivo study of multi-site pacing described in Chapter 8.

**CMR-Guided CRT (PRISM pilot study)**

I have shown that CMR can be used to guide LV lead placement and compared the results acutely to an optimal haemodynamic standard and angiographic approach and chronically with reverse remodelling. I have shown that we were able to accurately acquire and process CMR derived CS anatomy, scar and dyssynchrony data (derived from a single CMR scan) and fuse this with live fluoroscopy during CRT implant. We were able to pace in at least one CMR target segment in the majority of patients and this gave rise to an AHR comparable to the best possible in any segment. I have shown that a marked difference in AHR is seen dependent on the LV pacing site chosen and this may explain sub-optimal CRT response if a purely anatomical approach is used. The results of my PRISM pilot study suggest that if a target segment is successfully paced, it is unlikely that any other segment will give rise to a significantly better acute response.

More importantly, our chronic results show an improved reverse remodelling rate of 92% in patients that successfully had the LV lead positioned in a CMR target segment compared to just 50% in those patients in whom a CMR target could not be paced. Our technique of using CMR guidance may therefore allow an implanter to individualise
their approach to the patient and guide them to the optimal target segment. Whether this will lead to an improved chronic outcome against a standard approach is as yet unproven and requires a randomized study of CMR guided CRT. I have submitted the proposal for this RCT and the study (PRISM RCT) has been approved by our local research ethics committee. The power calculations suggest that 270 patients will need to be recruited to this study in order to show a significant difference in reverse remodelling rates (≥ 15% reduction in ESV) between an image-guided and conventionally implanted CRT group. This study will thus require multi-centre participation and will likely take a further 2 years to complete.

**Multi-Site and Endocardial Pacing**

My Multi-Site Pacing and Electro-Anatomic Mapping Study confirmed that endocardial pacing appears to give a superior overall mean AHR compared to other pacing modalities. This is consistent with previously published work and may relate to activation being more physiological and thus resulting in better electrical and mechanical propagation compared to conventional epicardial pacing via the CS. Also consistent with previous work, I have shown that only endocardial pacing leads to a significant reduction in QRSd compared to other pacing modalities but that the correlation between QRSd and LVAT reduction and improvements in AHR are not strong. This may be because more effective mechanical recruitment of the LV myocardium rather than shortening of the LV electrical activation time is the main mechanism underlying improved dP/dt_{max}. 

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I have shown that MSP from three, four or five sites simultaneously does not appear to confer a significant overall mean AHR advantage compared to conventional CRT but within individuals, the best pacing modality varies. Indeed four different forms of MSP were best in 50% of patients and MSP using the Quartet Lead was best in half of this sub-group (3/6 patients). The fact that so many different methods of pacing were best in different patients again emphasises the findings of Derval (51) et al who found that there is not one pacing site (or combination of pacing sites) that is best for all patients and the choice of pacing modality needs to be tailored to the individual.

Our study was necessarily very invasive with significant associated risks. It is thus promising that MSP using a single commercially available LV lead gave a good overall AHR and the best possible AHR in 25% of our cohort. If an improved AHR can be achieved simply by switching on the MSP function of an LV lead with no further invasive procedures required, this is an exciting option. While it may not make a difference in most patients, in a minority of patients it may make a ‘non-responder’ respond.
Chapter 10. Conclusions

In this thesis I have shown that quadripolar lead technology can improve implant success rates and reduce the need for re-intervention at follow-up. I have also shown that the electronic repositioning technology available with this lead probably will not improve the haemodynamic response of patients who do not improve with CRT.

I have shown that a CMR dyssynchrony and scar-guided approach to CRT implant is feasible and may lead to an improved acute and chronic outcome. This approach is currently very labour intensive, however, and a large randomised controlled trial is due to start imminently to determine whether a CMR-guided approach to CRT improves outcome. Developments in image processing technology mean that analysis times have been significantly reduced since I started my image-guided CRT project and semi-automated tools mean that the need for manual segmentation and analysis may soon become redundant.

My multi-site pacing study has confirmed that all patients are different and we cannot \textit{a priori} decide the best pacing modality for a patient. The fact that so many different pacing modalities were best in different patients in our small cohort of patients emphasizes the need for an individualised approach to implanting CRT especially in those patients least likely to respond (e.g. ischaemic patients with large scar burden, Type I activation pattern, narrow QRS etc). The fact that multi-site pacing using a commercially available lead gave the best acute haemodynamic response in a quarter of
our study patients is promising as all other methods of MSP tested would require a further invasive procedure.

The multiple different configurations and AV and VV delays possible when MSP is performed suggest that we need better non-invasive ways of predicting response to therapy. I have shown an example in Chapter 7 of biophysical modelling in a single patient. The results of this *in silico* study have yet to be validated *in vivo* but projects such as ‘Grand Challenge’ hopefully will lead to computer modelling programs that can reliably predict the outcome of various forms of pacing using simple, non-invasively acquired (CMR/echo) data. We may thus be able to save some patients from having CRT implants that will not improve their symptoms or outcome and in others we may be able to maximise the benefit that can be achieved with CRT.
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21. Kronborg MB, Kim WY, Mortensen PT, Nielsen JC. Non-contrast magnetic resonance imaging for guiding left ventricular lead position in cardiac resynchronization therapy. J Interv


Appendix 1. Publications arising from Thesis

Papers


Duckett SG, Ginks M, **Shetty AK** et al. “Invasive acute hemodynamic response to guide LV lead implantation predicts chronic remodelling in patients undergoing cardiac


Ma, Y.L., Duckett, S., Chinchapatnam, P., Gao, G., Shetty, A et al. MRI to X-ray fluoroscopy overlay for guidance of cardiac resynchronization therapy procedures. *Computers in Cardiology* Vol 37, 2010, Article number 5737951, Pages 229-232

Ma, Y., Duckett, S., Chinchapatnam, P., Shetty, A et al. Image and physiological data fusion for guidance and modelling of cardiac resynchronization therapy procedures. *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics) 6364 LNCS*, pp. 105
Abstracts

Shetty AK et al. Magnetic Resonance Dyssynchrony-Guided Cardiac Resynchronisation Therapy versus a Coronary Sinus Venogram Guided Approach. *Heart Rhythm Society*. Boston, USA (May 2012) *(short-listed for the Eric N. Prystowsky Clinical Research Award for the fellow with the highest scoring abstract)*

Shetty AK et al. Does Multi-Site Pacing from Five Ventricular Sites Simultaneously Improve CRT Response? *Heart Rhythm Society*. Boston, USA (May 2012)

Shetty AK et al. The acute Haemodynamic Response to pacing within a vein using a novel quadripolar lead. *Venice Arrhythmias*. Venice, Italy (October 2011)

Shetty AK et al. MR Dyssynchrony-Guided LV Lead Placement in Real Time. *Venice Arrhythmias*. Venice, Italy (October 2011)

Shetty AK et al. ‘Quin-site’ CRT pacing from the LV endocardium, RV endocardium, LV epicardium and two vectors of a quadripolar lead simultaneously. *Heart Rhythm Congress*. Birmingham, UK (October 2011)

Shetty AK et al. LV Pacing and the difference in Acute haemodynamic response within Individual Branches of the Coronary Sinus. *Heart Rhythm Congress*. Birmingham, UK (October 2011)

Shetty AK et al. Is real-time CMR Dyssynchrony a useful tool in guiding LV lead placement during crt? *Heart Rhythm Congress*. Birmingham, UK (October 2011)

Shetty AK et al. Ventricular Pacing along individual branches of the coronary sinus using a quadripolar LV pacing lead. *British Cardiovascular Society*. Manchester, UK (June 2011)
Shetty AK et al. Real-time cardiac MR anatomy and dyssynchrony overlay to guide left ventricular lead placement in CRT. *British Cardiovascular Society*. Manchester, UK (June 2011)


Shetty AK et al. Implantation of a novel quadripolar left ventricular lead and CRT-D System capable of delivering long-term multisite pacing. *International Symposium on Progress in Clinical Pacing*. Rome, Italy (Nov 2010)

Shetty AK et al. Real-time cardiac MR overlay guided left ventricular lead placement predicts acute response to CRT. *Heart Rhythm Congress*. Birmingham, UK (October 2010).

Shetty AK et al. Initial single centre experience with a novel quadripolar lead for cardiac resynchronisation therapy. *Heart Rhythm Congress*. Birmingham, UK (October 2010).

Sohal M, Shetty AK et al. The Assessment Of Septal Flash Using Cardiac Magnetic Resonance Imaging And Its Association With Response To CRT. *Heart Rhythm Society*. Boston, USA (May 2012)

Sohal M, Shetty AK et al. A type II pattern of LV activation identified by cardiac magnetic resonance imaging and its role in predicting response to CRT. *Heart Rhythm Society*. Boston, USA (May 2012)


Duckett SG, Shetty AK et al. Adverse Response to Cardiac Resynchronisation Therapy in Patients with Septal Scar on Cardiac MRI Preventing a Septal Right Ventricular Lead Position. *Heart Rhythm Congress*. Birmingham, UK (October 2011)

Mehta P, Shetty AK et al. Elimination of phrenic nerve stimulation occurring during CRT Follow-up in patients implanted with a novel quadripolar pacing lead. *Heart Rhythm Congress*. Birmingham, UK (October 2011)


Duckett SG, Ginks MR, Shetty AK et al. Systolic Dyssynchrony Index derived from cardiac magnetic resonance imaging predicts left ventricular remodeling in heart failure patients undergoing CRT. *SCMR.* Nice, France (February 2011)

Duckett SG, Koken P, Shetty AK et al. Assessment of the grey zone: a comparison of two methods in heart failure patients awaiting cardiac resynchronization therapy. *SCMR.* Nice, France (February 2011)

Duckett SG, Ginks MR, Shetty A et al. Cardiac magnetic resonance imaging and three-dimensional echo-derived systolic dyssynchrony index to predict acute haemodynamic response to left ventricular and biventricular pacing in patients awaiting cardiac resynchronization therapy. Birmingham, UK (October 2010).

Duckett SG, Ginks MR, Knowles B, Ma Y, Shetty A et al. Advanced image fusion to overlay coronary sinus anatomy and myocardial scar with real-time fluoroscopy to aid left ventricular lead implantation during cardiac resynchronization therapy. Birmingham, UK (October 2010).


Ma Y, Duckett S, Chinchaptnam P, Shetty A et al. MRI to X-ray Fluoroscopy Overlay for Guidance of Cardiac Resynchronization Therapy Procedures, workshop in Statistical Atlases and Computational Models of the Heart: Mapping Structure and Function (STACOM), MICCAI, Beijing, China (September 2010).

Duckett SG, Ginks MR, Knowles BR, Shetty A et al. Imaging fusion and overlay technology to guide LV lead implantation in CRT. *Cardiostim*. Nice, France (June 2010).

Duckett SG, Ginks MR, Knowles BR, Ma Y, Shetty A et al. CMR and 3D echo predictors of acute haemodynamic response to LV pacing. *Cardiostim*. Nice, France (June 2010).

Duckett SG, Ginks MR, Knowles BR, Ma Y, Shetty A et al. Predicting haemodynamic response to LV pacing. A comparison of systolic dyssynchrony index derived from cardiac magnetic resonance imaging and 3d echo. *Cardiostim*. Nice, France (June 2010).


Study Title

PRISM-CRT: Pilot Study

Study Code

09/H0804/37

Part 1

Invitation

We would appreciate your giving consideration to our invitation to participate in the clinical research and evaluation of a new technology which has been developed with the intention of improving and streamlining the implantation of cardiac devices. This is a Cardiac Resynchronisation Therapy (CRT) pacemaker, an advanced type of pacemaker that is used to treat patients with your symptoms. Your clinician has already recommended that this treatment may be suitable for you as part of your routine care. This device can also come with a function to assist with the treatment of potentially dangerous heart rhythm disturbances, and this defibrillator function may also be suitable for you; this is called a CRT-D device. The type of device you have will be decided by you and your clinician. Either way, you are eligible to take part in this study.

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 and discuss it with friends, relatives and your GP if you wish. Please ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part in this study.
Thank you in advance for reading this and giving consideration to our invitation to participate in this study.

**What is the purpose of this study?**

We have known for some time that some people who have heart failure benefit from having a special pacemaker implanted which will make the pumping chambers of the heart beat more efficiently. This is called Cardiac Resynchronisation Therapy or CRT. This therapy restores the timely contractions of the upper (the right atrium) and lower chambers of the heart (the right ventricle and the left ventricle) by detecting the heart's natural electrical activity and by pacing the chambers in a coordinated way. These pacemaker leads are connected to an implantable device which functions as a pacemaker (and in many patients works as a defibrillator as well).

To make the heart pump as efficiently as possible it is necessary to place the pacing leads in good positions. Of particular importance is the pacemaker lead to the left side of the heart. This is responsible for re-coordinating the heart's contraction. However this is technically the most challenging part of the procedure to put in the CRT device.

The purpose of this study is to see whether a new technology can be used to facilitate the placement of the lead to the left side of the heart. Usually when the procedure is being done to put in a pacemaker like this, it is performed using X-Ray as the method of guiding the doctor where to place the pacemaker leads. We are looking at the potential to use information derived from an MRI scan of the heart in addition to the X-Ray information. This can tell us about the veins around the heart where the left-sided lead needs to be placed, as well as about areas of scarring (if you have had a heart attack in the past). If you choose to be involved in the study, we would carry out your procedure (to put in the pacemaker) using this information from the MRI scan. This would be in addition to information from X-ray (which is how the procedure is normally done). The information from the MRI scan is superimposed on the X-ray screen that we normally used during the procedure.

So, taking part in the study will not affect the type of pacemaker you have. It will affect the way in which the procedure is performed. If you choose to take part in the study, we will do an additional MRI scan beforehand, and use this
information to guide the procedure (along with X-ray, which is the standard approach).

We will also discuss with patients taking part in the study the option of using a pressure recording wire (discussed below) to evaluate the changes in pumping function of the heart as a result of the pacemaker.

**Why have I been chosen?**

Your doctor has determined that you are a candidate for Cardiac Resynchronisation Therapy (CRT) or Cardiac Resynchronisation Therapy with a Defibrillator (CRT-D). These therapies are designed to treat and lessen the symptoms related to your heart failure. Cardiac Resynchronisation is a therapy that stimulates both the right and left side of the heart to improve the heart's ability to pump. Defibrillation delivers electrical pulses or shocks (defibrillate) if dangerous rhythms are detected.

**Do I have to take part?**

Your participation in the study is completely voluntary. You will not be paid for taking part. If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form, you will also be given a copy of the signed consent form to keep. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive, will involve no penalty or loss of benefits, will not affect your relationship to your doctor and will not be detrimental to your treatment.

**What will happen to me if I take part?**

If you choose to take part you will have many of the same baseline tests as in routine care, such as an ECG, blood tests and an ultrasound scan of your heart. In addition, we would perform one or two MRI scans of your heart on separate dates before your pacemaker procedure, depending on whether you have already had one scan done as one of the routine tests before having a CRT or CRT-D device. If so then you will only need one additional scan, otherwise you will need two scans. Each scan takes approximately one hour and is performed on a separate visit as an out-patient (i.e. you do not need to be admitted to hospital for it).

The first scan is to look for any evidence of scarring in the heart which may arise from previous heart attacks or may be due to other causes.
The second scan will try to evaluate the anatomy and distribution of the veins on the surface of the heart, which is where the left-sided pacemaker lead is placed. This needs to be done on a separate scan as a different contrast agent is used to outline the cardiac veins.

During the implantation of the pacing leads the information from the MRI scans will be used to superimpose the location of the veins in the heart onto the monitor which the cardiologist uses to position the pacemaker leads.

If there is scarring in the heart muscle from previous heart attacks, information about the area affected will also be available to the cardiologist from the MRI scan. We generally need to avoid areas of scarring when positioning the pacemaker leads as this may make the treatment work less effectively.

The technology required to superimpose this information has been developed over the last 5 years in King's College London and is not available or widely used in clinical practice. However the equipment used to perform the procedure is the same as that which is used routinely and you would have the same device whether or not you decide to take part. Dr Rinaldi, a consultant cardiologist, would be performing your procedure.

In some patients we also plan to record the pressure within the heart by passing a fine calibre pressure recording wire up to the heart via the artery at the top of the leg. This is done in a similar way to a coronary angiogram, but the tube in the artery at the top of the leg is a bit smaller. The wire is passed into the left ventricle (the main pumping chamber) and the information it provides tells us about the blood pressure response to stimulating the heart with the pacemaker. Putting this wire in will add about 20 minutes to the procedure.

After the pacemaker / defibrillator has been implanted, you will need to have routine checkups, just as you would have if you had not been in the study.

**What are the alternatives for treatment?**

The alternative to taking part in this study is to have the procedure performed in a routine way.
What are the side effects of any treatment received when taking part?

The main additional component if you decide to take part is the additional 1 or 2 MRI scans. This does not involve ionising radiation (such as X-rays or CT scans). Each scan takes about an hour and involves the administration of a contrast agent. The risk of side effects with this is very low. The contrast agent should not be given to people with poor kidney function as this may be harmful. We would therefore check your kidney function is OK by doing a blood test, unless a recent result is already available.

There will be no changes to the way your device works or to your treatment as a result of your participation in the study.

What are the possible disadvantages and risks of taking part?

The other aspects of MRI scanning are that you may not be able to tolerate this if you are claustrophobic (as the scanner itself is relatively narrow and enclosed) and if you have any metal in your body then we need to check the details of this, as it can be dangerous especially if the metal is in your eyes or brain. As the scan needs to be performed on a separate day from your pacemaker procedure, this may involve a separate trip to the hospital, although we can offer you a variety of times and days for this to be performed.

It is possible that with the MRI scan we are not able to obtain images of sufficient quality to help with the pacemaker procedure. In this eventuality we would perform the procedure in a routine manner.

At the time of the procedure, the pressure wire passed to the heart poses a small risk of bleeding or bruising at the top of the leg, and an extremely small risk (less than 1 in 1000) of causing a stroke. In order to stop this from happening, we would give a small dose of a blood thinning drug (heparin) at the time of the procedure. If you would like to take part in the study but do not want to have this part of it, then please indicate that when you come to fill in the consent form, and we can still do the procedure without the pressure recording wire.

What are the possible benefits of taking part?

You may benefit from participating in this study because we will have additional information about the heart and the layout of the veins for the purpose of positioning the left sided pacemaker lead. The intention is that this new technology will allow us to see better information on the screen during the pacemaker implant procedure, thus enabling the procedure to be done more quickly and more accurately. These benefits have not been proven; this is one of the reasons that we are carrying out the research.
The information we get from this study may therefore help us with the treatment of other patients in the future.

**What happens when the research study stops?**

After the research stops your care will continue as usual. This means that your pacemaker/defibrillator device will be programmed in the usual way and you will be asked to come regularly to the hospital to have it checked.

**What happens if there is a problem?**

We are very keen to ensure that all participants in this study receive treatment and care to our usual very high standards. However, if there are complaints or you do suffer some harm these will be addressed properly in the normal way. Detailed information on this is given in Part 2.

**Will my taking part in the study be kept confidential?**

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation please read the additional information in Part 2 before making any decision.
Part 2

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available. If this happens, your doctor will tell you about it and discuss with you whether you want to continue the study. If you decide to continue in the study you will be asked to sign an updated consent form. If you decide to withdraw, your doctor will make arrangements for your care to continue.

If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?

If you withdraw from the study we will need to use the data collected up to your withdrawal and your care will continue as usual.

What will happen if I become pregnant during the study?

Candidates who are pregnant or plan to become pregnant in the next six (6) months may not be enrolled in this study. If you become pregnant after enrolment but before treatment you must immediately advise us and you will be removed from the study. However, if you become pregnant after treatment your care will continue as it would have done when having the treatment with or without the new procedure involving MRI.

What if there is a problem?

If you are harmed by taking part in this study, you should contact your doctor for further information. If you have any complaints about the way your doctor has carried out the study, you may contact the Patient Advice and Liaison Service (PALS) at your hospital. The PALS service will also be able to advise you regarding the standard NHS complaints procedure should you feel that there are any aspects of your care which have not reached your expected standards.
Will my taking part in the study be kept confidential?

Any personal information obtained about you during the course of this study will remain confidential. Information from this study will be submitted to the sponsor and your NHS Trust. During the course of the study the responsible authority, sponsor or review board may inspect and copy your records. Identifying information, such as your name, will be removed from copied records when not absolutely necessary. In recording the results of the study, you will be referred to by an alphanumeric code number. In participating in the study, you authorise the sponsoring company to use the information obtained during the study for scientific communications and publications. Should the data collected from this study be published, your identity will not be revealed and your name will not be disclosed outside the hospital at any time. If you agree, your GP will be informed of your participation in this study.

In accordance with the laws relating to data protection, you will be able to exercise your rights to access and to rectify this data at any time. If you agree to take part in the study your GP will be informed of your participation.

What will happen to the results of the research study?

The results will be analysed for the purpose of publication in scientific journals. If you would like to find out about the results of the study please ask your study doctor who will be able to provide you with this information.

Who is organizing and funding the research?

This study is organised by the Cardiology Team at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London, and sponsored by the Research & Development Department of the Hospitals’ Trust.

Are the researchers involved in this study being paid?

Your doctor and his research team will receive no payment for their involvement in this study.
**Will I be paid for my participation in this study?**

Participants in this study will not receive any payment for taking part, but you would be reimbursed for travel expenses incurred by any visits as a result of taking part.

**Who has reviewed the study?**

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed by and approved by the Guy’s Hospital Ethics Committee.

**Contact for further information**

If you have any problems, concerns or other questions about this study you should preferably contact the investigator first:

**Dr Aldo Rinaldi**

**Consultant Cardiologist**

**St Thomas' Hospital**

**Lambeth Palace Road**

**London**

**SE1 7EH**

**Tel: 020 7188 9257**

If you have any complaints about the way the investigator has carried out the study, you may contact:

**Complaints department**

**Guy's and St Thomas’ NHS Foundation Trust**

**Guy's Hospital**
Thank you for taking the time to read parts one and two of this patient information sheet and to think about taking part in this study.

If you agree to take part in this study, please complete and sign the attached consent forms.
Patient Information Sheet

Study Title
Multi-Site Pacing Haemodynamic and Electroanatomic Mapping Study

Study Code
10/H0802/29
Invitation

We would like to invite you to take part in a research study.

Outline explanation

Your heart doctor has recommended that you have a special pacemaker called a Cardiac Resynchronisation Therapy (CRT) device implanted. The aim of CRT is to improve the way the heart beats. Although CRT has been shown to work in many people, around a third of patients do not improve with this type of pacemaker. We aim to see whether other ways of pacing the heart are better.

What is the purpose of the study?

CRT usually involves putting 1 pacing wire in each of three chambers of the heart. The aim of this study is to see whether patients do better if we pace the main pumping chamber of the heart from 2 places at the same time.

What does the study involve?

Most patients will undergo an MR scan of their heart as part of their usual care before their pacemaker implant. A few patients in this study will be asked if they are willing to have extra images taken during their MR scan and also to have a special new type of electrical trace (ECG) of their heart. The extra images will make the scan around 20 minutes longer. The extra ECG will take a further 20 minutes after the MR scan.

Around a week or so after the MR scan you will have your CRT implanted in the usual way but the pacemaker used will have a new type of electrical wire that will let us stimulate the heart from more than one area at the same time using just one lead. You may also be eligible for this study if you have had this special type of pacemaker implanted recently.

You will be brought back to St Thomas’ Hospital at least one week after your CRT implant for the extra study.

This extra study is not part of routine care and you would not undergo this study if you were not participating in this research.

During the study we will place two extra temporary pacing wires in your heart. One will be placed on the outer surface and one on the inner surface of your heart. The two extra pacing wires, heart pressure wire and balloon to measure electrical activity will be placed in the heart via two arteries and one vein in your groin.
We will measure the changes in blood pressure that result from pacing the main pumping chamber of the heart from two areas rather than one. We will test this by measuring the pressure changes in the heart that we get from pacing using the extra wires and also using the pacing lead from the pacemaker you will have recently had implanted. We will also measure electrical activity using a special small balloon that we will also put into the heart.

**Why have I been chosen?**

You have been chosen to take part in this study because you are eligible for a CRT pacemaker under current guidelines.

**Do I have to take part?**

No. You are under no obligation to take part. If you do not want to take part it will not affect your routine care.

**What happens if I decide not to take part?**

If you do not take part in the study you will still receive a CRT pacemaker implanted in the usual way with standard follow-up.

**What will happen to me if I take part (see Figure 1)?**

1) If you are one of the patients asked to have a special electrical tracing of your heart (ECG) during your MR scan, you will spend an extra 20 minutes during the scan having extra images taken. You will then have a special ECG (that is much more detailed than usual) that should take no more than 20 minutes.

2) Around a week or more after the heart MR scan, you will have your pacemaker implant (using a specific type of pacemaker that will allow us to do the study at a later date) in the standard way.

3) At least one week after the pacemaker implant you will undergo the study procedure under local anaesthetic and sedation. During this procedure we will measure pressure and electrical changes in the heart in response to pacing in different ways. When all the measurements have been made, we will remove the extra wires from your heart and the tubes inserted from the groin (but will not remove the pacemaker or leads that were implanted the week before).

4) **You will spend a total of around 4 hours lying flat on the operating table.**

5) Following the procedure you will need to lie flat in bed for several hours until the tubes inserted in your groin have been removed. You will usually go home the day after the study procedure.
How does this differ from “standard practice” i.e. routine care (if you were not to take part in the study)?

In addition to routine care, you would have:

1) A longer MR scan and special ECG (a few patients only).

2) You will be asked to come back to hospital for a two day stay during which you will have an extra detailed study of the pressures and electrical activity of your heart in response to pacing it in different ways. This will require two extra days in hospital after you have had your pacemaker implanted.

What are the possible disadvantages and risks of taking part in the research study?
The MR scan is safe and does not involve radiation. You will probably have this as part of your routine care even if you are not part of the study.

The risks of the pacemaker implantation are the same as if you were not part of the research study.

The invasive electrical study that we will perform at least one week after your pacemaker implant will involve lying flat on the operating table for around 4 hours and carries several significant risks:

1. There is a risk of a stroke in anyone undergoing this sort of study because of clot forming on one of the wires that we place in your heart. We reduce this risk by giving you a blood thinning agent (heparin) during the procedure.

2. The heparin does increase the risk of bruising and bleeding around the groin sites where the tubes for the study are inserted but this is not usually serious.

3. There is a risk of puncturing the heart and fluid collecting around it requiring drainage.

4. There is an additional x-ray dose on top of that of the CRT implant if you take part in this study. The extra dose is about the same as seven years of natural background radiation in the UK and carries a less than 1/1000 risk of cancer.

Over the past 10 years we have performed similar studies in around 25 patients without any serious problems.

**What are the possible benefits of taking part?**

There is no direct benefit to you. If we find that pacing your heart from multiple sites at the same time using the pacemaker lead you have had implanted improves your response to pacing, we may programme your device to act in this way in the future.

**What happens when the research study stops?**

You will still be routinely followed up in our clinic and monitored by the cardiologists who undertook the study.

**What happens if there is a problem?**

We are very keen to ensure that all participants in this study receive treatment and care to our usual very high standards. However, if there are complaints or you do suffer some harm these will be addressed properly in the normal way.

**Will my taking part in this study be kept confidential?**

Yes

**What will happen if I don't want to carry on with the study?**
If you withdraw from the study we will need to use the data collected up to your withdrawal and your care will continue as usual.

**What will happen to the results of this study?**

We plan to publish these in a research paper with the aim of advancing the knowledge of pacemaker treatment for heart failure. All patient identities are treated as strictly confidential and anonymous in any publication.

**Who is organising the research?**

This study is organised by the Cardiology Team at Guy’s and St Thomas’ NHS Foundation Trust and King’s College London and sponsored by the Research & Development Department of the Hospitals’ Trust.

**What happens if for any reason you are no longer able to take part or give ongoing consent to take part?**

We would then withdraw you from the study and you would receive the usual care that every patient would receive. If you are agreeable we will still use the research information obtained towards the analysis of results.

**Who has reviewed the study?**

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed by and approved by the St Thomas’ Hospital REC.

**Contact for further information**

If you have any problems, concerns or other questions about this study you should preferably contact the investigator first:

*Dr Aldo Rinaldi*

*Consultant Cardiologist*

*St Thomas’ Hospital*

*Lambeth Palace Road*

*London*

*SE1 7EH*

*Tel: 020 7188 9257*

If you have any complaints about the way the investigator has carried out the study, you may contact:
Complaints department

Guy's and St Thomas' NHS Foundation Trust

Guy's Hospital

St Thomas Street

London SE1 9RT

Tel: 020 7188 3514
PATIENT INFORMATION SHEET

Project: Grand Challenge Modelling Project
REC Ref: 10/H0802/71

You are being invited to take part in a research study. 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. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

PART 1

Outline explanation

It has been recommended by your heart doctor that you have a cardiac resynchronisation therapy (CRT) device implanted. This is a special kind of pacemaker that usually consists of 3 electrical leads which are placed in the heart to improve the way it beats. Although this type of pacemaker makes many people feel better, around a third of patients do not improve with this treatment in terms of their ability to exercise and quality of life.

What is the purpose of the study?

At present it is not clear which patients will get better after CRT. The aim of this study is to see if the measurements we take during heart scans can be used to make computer models of the heart which help us to predict who will improve with CRT.
Why have I been chosen?

You have been chosen to take part as you are eligible for CRT on the basis of our current guidelines.

Do I have to take part?

No. 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 be asked to sign a consent form. You are still free to withdraw at any time and do not need to give a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

You will be given a consent form to sign.

As part of your routine care before having CRT, you will be seen in the outpatient department. You will fill in a questionnaire, have a blood test, a urine test, a walking test, a bicycle test and an ultrasound scan of your heart called an echo scan. These tests are routine and take around 2 hrs in total. Some patients will be asked to raise their legs (supported by a cushion) for 5 minutes during the echo scan.

On the same day you will also have a scan called a magnetic resonance imaging (MRI) scan. This gives us further detailed information about the heart. The MRI scan involves lying still in a scanner for around an hour. The MRI does not involve X-rays and is part of the routine work-up for the type of pacemaker you are having.

Patients in Sheffield will also have the following tests performed:

1) A grip strength test. This gives us further information about the strength of your peripheral muscles e.g. forearm, in relation to your heart muscle. This involves gripping a measuring device with your hand as hard as possible, maintained for about 5 seconds, with the best of 3 attempts recorded. There will be a rest of 30 seconds between each attempt. Taking around 5 minutes.

2) A measure of the blood flow in your brachial e.g. arm artery will also be recorded, this is called flow mediated dilatation. This is performed using an ultrasound probe e.g. without X-rays, looking at the diameter of your artery.
before and after the flow is stopped using a blood pressure cuff for a maximum of 5 minutes. The whole test will take around 30 minutes.

3) An indirect measure of the force of blood ejected from the heart, using a device called a force plate. This involves, standing, sitting and lying on a fixed platform, the force is recorded by the platform and requires no invasive measurements. This will take around 5 minutes.

Once your CRT is implanted we would like to follow you up at 6 and 12 months with a repeat of the questionnaire, walking and cycling tests and echo scan of your heart. Sheffield patients will also have repeat blood and urine tests at these follow-ups. Some St Thomas’ Hospital patients will have extra echo images taken at their 6 week and 3 month device checks.

This information will be used to develop computer models that may be helpful in the future for predicting which patients will get better with CRT.

How does this differ from “standard practice” i.e. routine care (if you were not to take part in the study)?

The assessment with the blood test, questionnaire, walking test, cycling test and echo scan before the CRT implant are all routine. The MRI scan is also part of our routine assessment for CRT.

In addition to routine care:

1) The echo scan before the CRT implant may be 10 minutes longer than usual

2) You will have a repeat questionnaire, walking test, cycling test and echo scan at 6 and 12 months after the CRT implant. Some St Thomas Hospital patients will have extra echo images taken at their 6 week and 3 month device checks. You would need to attend at these times even if you were not in a study to have your CRT device checked. Sheffield patients will also have repeat blood and urine tests, grip, force plate and blood flow tests at these follow-ups,

3) The MRI scan may take slightly longer than a standard scan.

What do I have to do?

You will need to have the routine tests which include the blood test, questionnaire, walking test, cycle test, echo scan and MRI prior to your CRT. You will then have your CRT implant. We will need to see you at 6 weeks and 3 months for a standard check of your CRT (this is not part of the research). We
will also see you at 6 and 12 months after your CRT has been implanted to repeat the initial assessments (but not the MRI scan).

**What is the procedure that is being tested?**

We are looking at the electrical and mechanical function of the heart using echo and MRI. This allows us to develop computer models of the heart that we hope will help us to predict which patients are likely to get better with CRT.

**What are the contraindications of taking part?**

If carried out properly, MRI is harmless. We have safety procedures and well-trained staff to minimise any possible risks associated with the procedure. Because MRI uses a strong magnet, it is not safe for some people to be scanned. This includes people who have a heart pacemaker or some other types of metal in the body. You will be asked to fill in a screening form to make sure that you can have a MRI scan.

**What are the possible disadvantages and risks of taking part?**

The MRI scan may be uncomfortable as you need to lie flat for around an hour. Most people tolerate this procedure very well.

The test to measure the blood flow in the arm may be uncomfortable or painful when the blood pressure cuff is inflated for 5 minutes (Sheffield patients only).

You will be required to have more tests than usual at your follow-up appointments.

The radiation dose (26mSv) from having the CRT implanted is the same as if you do not take part in this research study. It is the about the same as 12 years of natural background radiation.

**What are the possible benefits of taking part?**

You will also have more detailed follow-up following your CRT implant.
What happens when the research study stops?
You will continue to have normal follow-up in clinic.

What if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

Contact Details:
St Thomas’ Hospital patients: Prof. Reza Razavi. St Thomas’ Hospital, 4th Floor Lambeth Wing.
Telephone 02071885440

Sheffield patients: Dr Paul Sheridan, CVBRU, Northern General Hospital, Sheffield
Tel: (0)114 2714950.

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.
PART 2

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the procedure that is being studied. If this happens, your research doctor will tell you about it and discuss whether you want to or should continue in the study.

What will happen if I don’t want to carry on with the study?

If you withdraw from the study, we will need to use the data collected up to your withdrawal. We will ask you to keep in contact with us to let us know your progress.

What if there is a problem?

Complaints: If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (St Thomas’ Hospital patients: contact Prof. Reza Razavi on 02071885440 and Sheffield patients: contact Dr Paul Sheridan on (0)114 2714950). Should you wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Harm: In the event that you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone’s negligence then you may have grounds for a legal action for compensation against Guy’ & St. Thomas’ 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 this study be kept confidential?

Procedures for handling, processing, storage and destruction of your data are compliant with the Data Protection Act 1998. All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. Your data will be collected from the referral letter and patient notes, as well from your oral information; Data will be automatically stored securely, in an encrypted format; Authorised persons such as researchers, regulatory authorities and Research and Development (for monitoring of the quality of the research) will have access to these data; Data will be retained for 15 years.
What will happen to the results of the research study?

We aim to publish these in a research paper so as to advance the knowledge of echo, MRI and CRT. All patient identities are treated as strictly confidential and anonymous in any publication.

Who is organising and funding the research?

The research is organised by Prof Reza Razavi, St Thomas’ Hospital, London and funded by the EPSRC Grand Challenge Project.

Who has reviewed the study?

The study has been independently reviewed by the St Thomas’ Hospital Ethics Committee (Project Ref: 10/H0802/71).

A copy of the information sheet and a signed consent form to keep will be given to you.

Thank you for considering taking part in this study.