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Optimal site selection & guidance during endocardial Cardiac Resynchronisation Therapy

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King's College London

Faculty of Life Science & Medicine

Division of Imaging Science & Biomedical Engineering

**Optimal Site Selection & Guidance During Endocardial Cardiac Resynchronisation
Therapy**

by

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Thesis for the degree of Doctor of Philosophy

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Abstract

Heart failure is a complex clinical syndrome associated with a significant morbidity and mortality burden. CRT has emerged as one of the few effective treatments for heart failure, however, around 30%-50% of patients fail to respond. Novel approaches to CRT have been devised and of these endocardial pacing, shows the most promise. Pacing endocardial tissue is associated with several anatomical and physiological advantages over conventional epicardial CRT and is not constrained by coronary sinus anatomy meaning there is greater potential to identify and accurately target a specific pacing site.

This thesis looks to assess the practice of biventricular endocardial CRT and evaluate which metrics can usefully identify the optimal LV endocardial pacing site. It will compare two approaches to biventricular endocardial pacing; empirical site selection during biventricular endocardial CRT and a guided approach, where the optimal site is identified and targeted using a variety of advanced image guidance techniques.

The thesis will include a brief review of the pathophysiology of heart failure and the development of LV dyssynchrony. An exploration of the causes of non-response to conventional transvenous, epicardial CRT will lead into a discussion of the physiological benefits of biventricular endocardial pacing. The thesis will also outline the different approaches to delivering biventricular endocardial CRT. A detailed evaluation of the importance of site selection including how to identify and target the optimal LV pacing site will complete the background literature review.

The thesis will then compare the efficacy of biventricular endocardial pacing in comparison to transvenous, epicardial CRT with a view to assessing the superiority of an endocardial approach. This analysis will also include an exploration of which metrics can usefully predict the optimal LV endocardial pacing site.

Further analysis will compare two opposing strategies of biventricular endocardial pacing using a novel, leadless biventricular endocardial pacing system. In the first analysis, the approach of empirical site selection will be analysed. This study will include an assessment of the safety and efficacy of the leadless, endocardial pacing system. This will be compared against a strategy of pre-procedural site selection to identify the optimal LV endocardial pacing site. Advanced image guidance technology will then be used to target the chosen location. The safety and efficacy of this approach will also be evaluated.

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Research Thesis: Declaration of Authorship

Print name:	Dr Benjamin James Sieniewicz
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Title of thesis:	Optimal site selection & guidance during endocardial cardiac resynchronisation therapy
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I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

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2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
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6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
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Definitions and Abbreviations

AHR: Acute hemodynamic response

BiV ENDO: Biventricular endocardial

BiV EPI: Biventricular epicardial

CO: Cardiac Output

CMR: Cardiac MRI

CRT: Cardiac Resynchronisation Therapy

CS: Coronary sinus

ICM: Ischemic cardiomyopathy

LBBB: Left bundle branch block

LV: Left ventricle

LVEF: Left ventricular ejection fraction

LV_{ENDO}: Left ventricular endocardial

NICM: Non-ischemic cardiomyopathy

QLV: The interval between the onset of the QRS complex on the surface ECG to the first large positive or negative peak of the LV electrogram during a cardiac cycle.

QRSd: QRS duration

RV: Right ventricle

Thesis Summary

Chapter 1 provides an introduction to heart failure and the burden of this disease worldwide. The chapter explores the neurohormonal adaptations that occur in response to heart failure which ultimately lead to maladaptive remodelling and the development of dyssynchrony at both a macroscopic and a microscopic level.

Chapter 2 describes the role of cardiac resynchronisation therapy in the management of heart failure. The chapter explores the mechanisms behind how resynchronisation pacing influences the disease process. It also evaluates how responders to CRT are both assessed and defined. The chapter also explores why some patients fail to respond to CRT.

Chapter 3 explores differing methods of identifying the optimal LV pacing site. It also explores how this information can be fused with guidance technology to inform site selection in real time, to improve responder rates amongst patients undergoing CRT.

Chapter 4 evaluates the potential benefits of stimulating the endocardial surface of the left ventricle during CRT and how these benefits translate into an enhanced rate of response. The myriad of different LV endocardial pacing methodologies are also described.

Chapter 5 reports a clinical study comparing the acute haemodynamic effects of endocardial vs epicardial LV resynchronisation pacing. By assessing acute changes in LV contractility, we assess whether indiscriminate LV endocardial pacing is superior to traditional transvenous LV epicardial CRT and thus whether site selection is required in the context of LV endocardial pacing.

Chapter 6 describes a clinical study evaluating the safety and efficacy of a novel leadless form of wireless LV endocardial pacing. The study is a multisite international registry and reflects the largest analysis of this novel pacing technology reported to date.

Chapter 7 describes a clinical study which sought to evaluate different metrics aiding identification of the optimal LV endocardial pacing site.

Chapter 8 delineates a clinical study in which we assessed the ability of site selection metrics to locate the optimal pacing site. We also investigated the accuracy and safety of utilising a targeted approach during LV endocardial pacing.

Chapter 9 outlines a sub-analysis comparing the efficacy of leadless endocardial CRT amongst various sub-groups including cohorts who frequently show evidence of poor response to CRT. This

Thesis Summary

chapter includes a head-to-head comparison comparing a strategy of guided LV endocardial pacing electrode deployment against indiscriminate electrode placement.

Chapter 10 is a synthesis and summary of the previous chapter findings and describes our conclusions. We also describe the limitations of this work as well as suggestions for future developments in this field.

Chapter 1 Heart Failure & The Pathophysiology Of

Cardiac Dyssynchrony

This section has been adapted from *Understanding non-response to cardiac resynchronisation therapy: common problems and potential solutions* (Sieniewicz, Gould, et al., 2018).

1.1 INTRODUCTION

Heart failure is a complex clinical syndrome associated with a significant morbidity and mortality burden. Reductions in LV function trigger adaptive mechanisms aimed at regulating the cardiac output however, over time these processes cause structural changes within the LV. This remodeling can result in the development of dyssynchronous ventricular activation, typically manifested by left bundle branch block on the 12 lead ECG. This is the substrate targeted during cardiac resynchronisation therapy however, between 30-40% of patients do not experience significant benefits from this treatment [1]. This chapter will explore the reasons why some patients fail to respond to traditional transvenous, epicardial CRT and how novel methods of pacing may offer a potentially better strategy.

1.2 THE EPIDEMIOLOGY OF HEART FAILURE

Cardiovascular disease (CVD) is thought to be the leading cause of death worldwide. The World Health Organization (WHO) estimate that CVD accounts for around 30% of all annual mortality [2]. Heart failure is a complex lethal syndrome representing a common 'final pathway' for sufferers of a multitude of cardiac diseases. It is characterized by a reduction in the ability of the heart to pump and/or fill with blood ultimately resulting in an inadequate cardiac output to meet metabolic requirements and accommodate venous return. Heart failure has been described as a global pandemic, affecting around 26 million people globally [3]. One in five people will suffer from HF during their life time [4]. That equates to around 900,000 people in the UK [5] with almost as many exhibiting evidence of impaired cardiac performance without symptoms [6]. Both the incidence and prevalence of heart failure increase steeply with age. Crucially once diagnosed, 40% of patients die within one year [7], a mortality figure worse than most cancers.

Caring for heart failure is associated with a high economic burden and accounts for between 1% and 3% of health expenditure in Western Europe [3]. The repeated and lengthy in-patient hospital admissions that are a sequelae of HR account for the majority of this fiscal burden. An average hospital admission usually lasts between 5-10 days [3] however, one in four patients are re-admitted within one month of discharge and two thirds experiencing readmission within a year [8]. In 2012 global expenditure on heart failure exceeded £22.5 billion and costs are predicted to increase by 127% between 2012 and 2030 [9].

1.3 PATHOPHYSIOLOGY OF HEART FAILURE AND LV DYSFUNCTION

A consequence of the reduction in LV performance associated with heart failure is a fall in cardiac output which ultimately results in global hypoperfusion. LV dysfunction also results in an increase in the amount of blood present within the ventricle. Ultimately, this additional blood forces the ventricle to enlarge, resulting in an increase in both LV end systolic and end diastolic volume and elevation of the LV end diastolic pressure (LVEDP). Higher pressures subsequently develop in the left atrium (LA) which results in pressure elevation at the capillary bed in the lungs. It is this higher capillary bed pressure which forces fluid from the pulmonary capillary bed leading to pulmonary congestion and symptoms of dyspnea, see Figure 1.

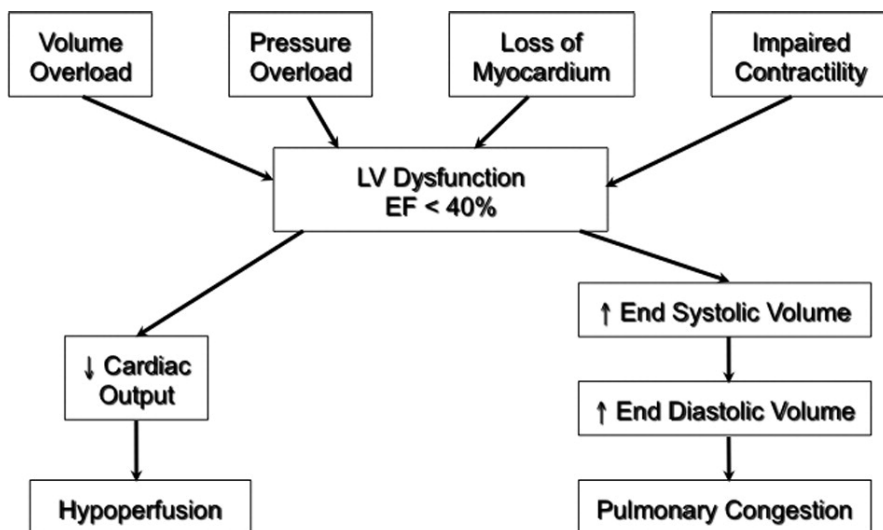


Figure 1. The pathophysiology of heart failure

1.3.1 Compensatory Mechanisms

Alterations in cardiac output have crucial sequelae on mean arterial pressure (MAP) which is the product of cardiac output and total peripheral vascular resistance (PVR). Reductions in cardiac output cause ensuing reductions in MAP and unless corrected, result in tissue hypoperfusion. Homeostatic responses to a drop in MAP include the Frank-Starling mechanism, neurohormonal activation and ventricular remodeling, see Figure 2.

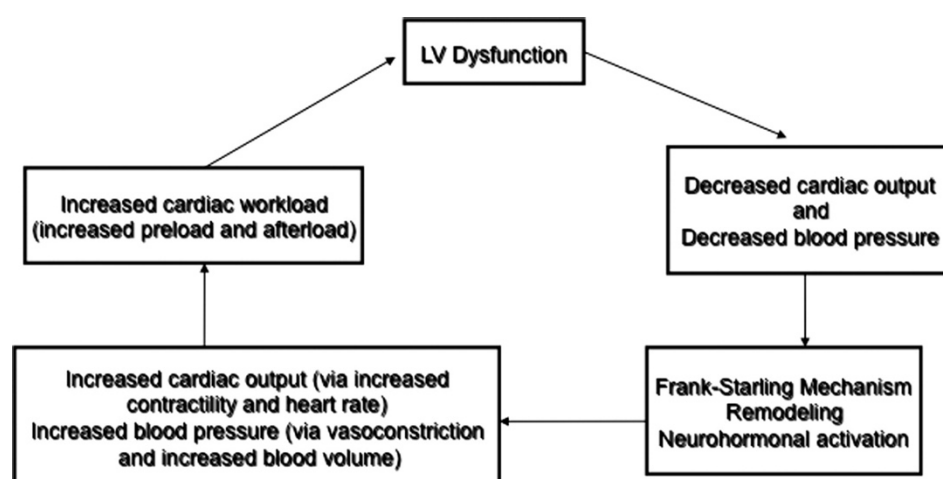


Figure 2. Compensatory mechanisms of heart failure

1.3.2 The Frank-Starling Mechanism

The Frank-Starling mechanism describes the adaptive mechanism by which as the LVEDV (also known as preload) increases, so does LVEDP, causing the LV myocardial fibres to stretch and leading to increases in CO. However, there is a limit to this increase in CO and ultimately a maximal point is reached where further increases in LVEDV do not yield improvements in ventricular performance. After this point is exceeded, the heart muscle begins to decompensate, and further increases in LVEDV and LVEDP result in pulmonary congestion and deterioration in the CO.

1.3.3 Neurohormonal Activation

Another homeostatic mechanism upregulated during the attempt to maintain MAP in the face of reductions in CO is neurohormonal activation. The predominate mechanism by which hormonal stimulation increases CO is by increasing PVR. Initial reductions in MAP lead to stimulation of the sympathetic nervous system which in turn causes the release of catecholamines (noradrenaline and adrenaline). These hormones affect both CO (increase in heart rate and contractility) and PVR (vasoconstriction), increasing MAP. MAP is also elevated by activation of the Renin-angiotensin-aldosterone system (RAAS) which also promotes vasoconstriction. Renin is secreted by the kidneys in response to sympathetic activation which ultimately leads to greater amounts of angiotensin II production ultimately causing further sympathetic stimulation and promoting sodium reabsorption as well as the release of vasopressin. Whilst these neurohormonal pathways are all initially activated in response to reductions in cardiac output, maintained activation ultimately results in ventricular remodelling and progressive myocardial dysfunction.

1.3.4 Ventricular Remodelling

In response to the progressive haemodynamic stress associated with heart failure, compensatory structural changes occur within the heart. The left ventricular myocardial mass and composition exhibit evidence of change. As this occurs the heart becomes less elliptical and more spherical as the geometry and volume of the LV change. This process is called remodelling and initially enables the heart to increase cardiac output by increasing both contractility and stroke volume. Whilst stroke volume initially increases, this process eventually becomes deleterious. A sequela of progressive ventricular enlargement is ventricular hypertrophy and this process is associated with the development of both interstitial and perivascular fibrosis. Inflammation and apoptosis result in increased wall tension and ultimately the myocardium becomes increasingly fibrotic, impairing contractility. As the left ventricle dilates and remodels, it exhibits greater contractile dyssynchrony further reducing efficiency.

1.3.5 Metabolic Remodelling

In addition to the macroscopic alterations in LV structure and function, heart failure is also associated with significant alterations at the molecular cell level as well as at the cell coupling level. Key energy metabolism processes including substrate uptake utilisation are impacted.

1.3.5.1 Modulation of Gene Expression In Heart Failure

Myocardial force is generated at the cellular level through the crossbridge cycle. During this process, the myosin crossbridge head attaches to actin and rotates forcing thick and thin filaments sliding past one another, before detaching from the actin filament to initiate another crossbridge cycle. As such, alterations to this crossbridge cycle as well as the number of crossbridges activated will significantly impact contractile function.

Crossbridge numbers can be reduced as a result of replacement by connective tissue, and this process is common in both ischaemic and non-ischaemic, dilated cardiomyopathy disease states [10]. Alterations in crossbridge cycle functionality have also been identified in animal models. Ex-vivo analysis of failing animal hearts identified changes in the expression of myocardial proteins including myosin. Two isoforms of myosin are usually expressed; α -myosin heavy chain & β -myosin heavy chain. Whilst both isoforms hydrolyse ATP. α -myosin heavy chain is associated with higher ATPase activity and more rapid shortening velocity while conversely β -myosin heavy chain is associated with slower shortening velocity and lower ATPase activity. The development of heart failure due to chronic haemodynamic overloading was associated with increased expression of the β -myosin heavy chain isoform. Ultimately these changes result in prolonged crossbridge attachment which detrimentally affects ventricular contraction by slowing myocyte relaxation and reducing shortening velocity.

1.3.5.2 Modulation of Calcium Homeostasis In Heart Failure

Regulation of cytosolic calcium concentration also appears disrupted in heart failure. Activation of the myofibrils is dependent on calcium concentrations. Altered calcium handling can therefore contribute to contractile dysfunction. Ventricular myocardium and myocytes isolated from failing human hearts displayed impaired calcium homeostasis with increased diastolic calcium concentrations and a prolonged calcium transient, resulting in action potential delay [11,12]. Changes in calcium concentration are not the result of protein channel alterations but instead reduced uptake by the sarcoplasmic reticulum [12,13].

1.3.5.3 Modulation of Cellular Signalling In Heart Failure

Alterations in G-protein mediated signal transduction pathways have also been observed in the context of heart failure. A decrease in β -adrenoreceptor number was identified in both ischaemic

Chapter 1

and non-ischaemic, dilated cardiomyopathy [14] resulting in decreased stimulation of adenylyl cyclase and intracellular cAMP levels. Other changes include increased expression of the β -adrenoreceptor kinase which results in receptor desensitisation as well as an increase in inhibitory G-proteins which both contribute to desensitisation of cardiac adenylyl cyclase functionality in impaired myocardial tissue. Crucially, the downregulation of response to catecholamines further exacerbates the calcium uptake capacity of the sarcoplasmic reticulum, disrupting cytosolic calcium homeostasis.

1.3.6 Left Ventricular Mechanics & Electrical Dyssynchrony

Structurally normal hearts display a degree of non-uniformity in contraction as a result of the complex geometric and spatial architecture. Early histological analysis confirmed the presence of variation in myocardial fibre orientation [15]. Within the epicardium and endocardium, fibres are orientated along the longitudinal axis of the heart. Midwall fibres however, follow a circumferential distribution. This complex arrangement is required given the complex pattern of mechanical activation exhibited by the ventricles, which involves both longitudinal shortening and circumferential motion.

The complex myocardial fibre architecture observed within the heart necessitates temporal activation in order to ensure efficient systolic pump function. Intrinsic activation via the His-Purkinje network initiates a wavefront of ventricular activation at the LV endocardial apex and culminates at the basal epicardium. Dyssynchronous electrical conduction can manifest as abnormal heart rate modulation, disruption to the sequence of atrial-ventricular systole and overt ventricular systolic discoordination which typically manifests as bundle branch block on the 12 lead ECG. The development of left bundle branch block is thought to occur as a result of ventricular remodelling and/or fibrogenic damage to the cardiac conduction system [16]. Progressive increases in the QRS duration herald deterioration in LV performance [17–20]. Left bundle branch block results in dyssynchronous ventricular activation causing an abnormal pattern of mechanical activation and contraction.

1.3.7 Electro-Mechanical Dyssynchrony

In the context of left bundle branch block, the right anterior septal region is initially activated via the intact right bundle in juxtaposition to the left basal posterolateral region, which slowly

propagates via cell-to-cell, intra-myocardial conduction. Contraction of the anterior right septum is imbalanced due to delayed activation of the lateral free wall and occurs unopposed. This has the effect of delaying elevation in the intra-cavity pressure gradient (dp/dt_{max}) as septal activation merely results in pre-stretch of the inactive lateral wall. When the lateral wall finally contracts, the septum is now in diastole, generating an energy sink which further reduces the overall ejection of blood via the left ventricular outflow tract. Cardiac mechano-energetic efficiency is further exacerbated by delayed activation of the posterolateral papillary muscle, causing suboptimal closure of the mitral valve and ultimately mitral regurgitation.

Myocardial strain analysis derived from tissue tracking CMR imaging can be used to illustrate mechanical dyssynchrony. An example can be seen in Figure 3A which compares regional myocardial strain during dyssynchronous activation in two phases of systole- early and late. Early activation can be observed in the septal region during which time the lateral wall is passively stretched. In late systole this pattern reverses with lateral wall systolic contraction causing the septum to stretch. Another way of visualising this phenomenon is through the use of regional elastance curves where regional cardiac stiffness is displayed with respect to activation time (Figure 3B). Dyssynchronous activation of the septum and lateral wall results in the lateral wall curve shifting to the right of the septal curve. The difference in regional cardiac stiffness between the two curves is reflective of the shift in volume from septum to lateral wall and is large in both early systole (red arrow) and even larger in late systole (blue arrow) reducing ejection and relaxation.

The net effect of dyssynchrony is a reduction in cardiac output, which can be visualised using pressure volume loops. Dyssynchronous activation of the ventricles results in a shift of end-systolic pressure-volume relationship to the right- implying LV function is compromised independent of loading, see Figure 3C. Left ventricular end diastolic volume and pressure also become elevated during dyssynchronous activation and this is represented by a reduction in stroke volume (loop width). Myocardial efficiency is also reduced alongside cardiac output as a result of dyssynchrony. Figure 3C displays regional myocardial work derived from tagged-CMR modelling. It is clear the lateral wall performs more local work than can be observed in the control model. Again, early activation of the septal region results in a lower overall workload- manifested by a low loop area. The septum stretches against a lower load in early systole due to delayed activation of the lateral wall, whilst in late systole it becomes stretched at a higher load, achieving zero net work. In contrast, workload in the late contracting lateral wall is increased due to higher initial stretch and eventual contraction against higher stress. This energy-sink further compromises myocardial energetics, further reducing efficiency in the failing heart.

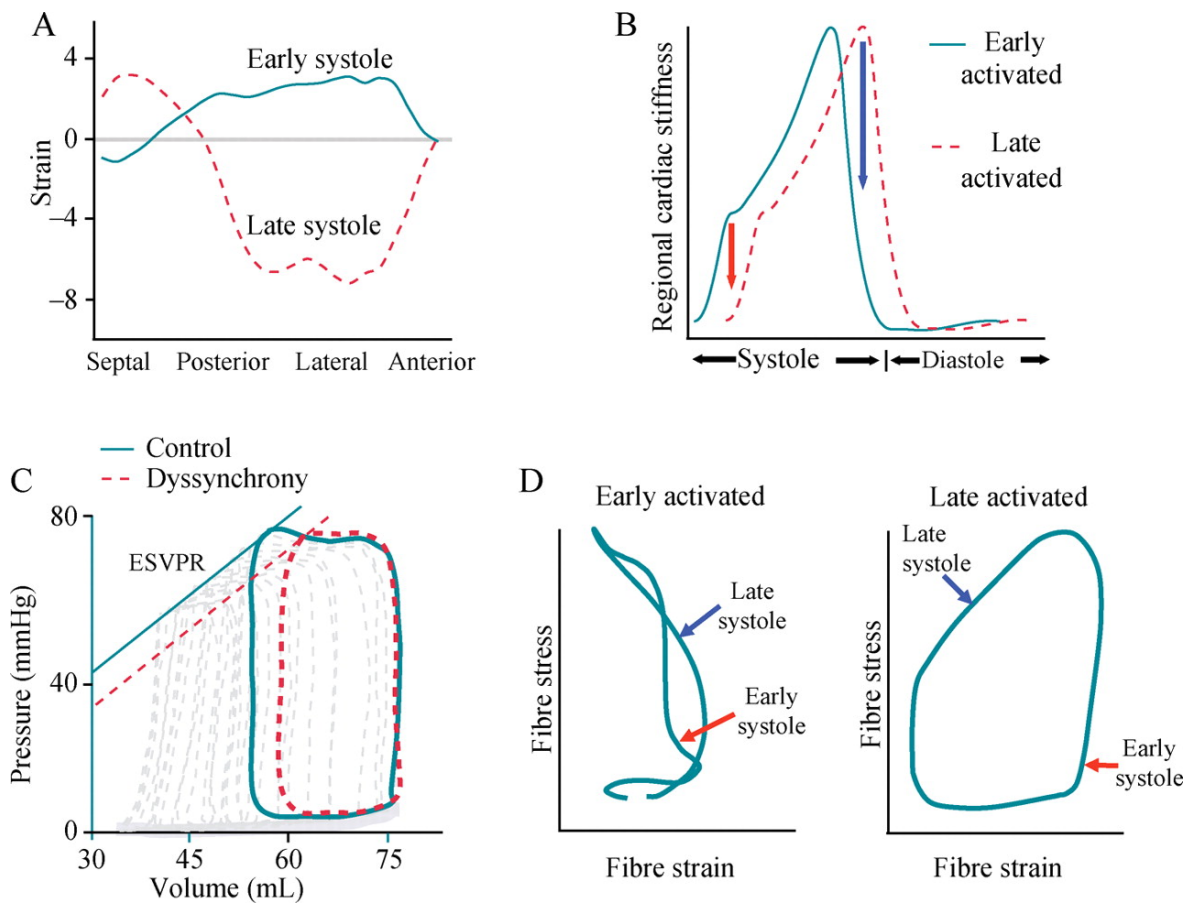


Figure 3.(A) Plot of instantaneous circumferential strain at different regions across a short-axis section of the mid-LV in a dyssynchronous heart during early (solid line) and late (dashed line) systole. At both phases, septal and lateral regions are clearly out of phase with each other. (B) Regional elastance (stiffening) plots of a dyssynchronous heart. Plots of early (solid) and late (dashed) activated myocardial regions are time-delayed. Vertical distance between the curves reflects transfer of forces from one region to the other. This difference is significant in early systole (red arrow) during isovolumic contraction reducing pressure development and this difference is even greater in late systole/early diastole (blue arrow) reducing ejection and relaxation. (C) Pressure–volume loops showing effect of dyssynchrony on ESPVR. The ESPVR shifts rightward (dashed line), end-systolic volume increases, and stroke volume and work declines. (D) Stress–strain loops from early- and late-activated regions in a dyssynchronous heart. The early-activated region initially contracts at low load and then is stretched under high load in late systole generating a figure-8-shaped loop with little area (reduced net work). The late contracting lateral wall operates at higher preload and stress, requiring greater work. In the normal synchronous heart, these loops would be similar for all regions. Reprinted with permission. Copyright © 2009 EP Europace [21].

1.3.8 The Molecular Expression of Dyssynchrony

The biomolecular changes associated with heart failure which collectively reduce force generation are further compounded by the presence of conduction delay and mechanical dyssynchrony, resulting in a pro-arrhythmic state. Regional protein expression is impacted with important consequences at both a global and cellular level. Canine modelling work has demonstrated transmural and trans-chamber gradients of stress response kinases, gap junction proteins and calcium handling [22]. Specific alterations in the lateral free wall were observed including elevation in phosphorylation of a mitogen activated protein kinase whilst expression of sarcoplasmic reticulum Ca^{2+} ATPase (SERCA), phospholambin and connexin-43 were down-regulated. Similar changes were not observed in impaired hearts displaying synchronous activation.

Dyssynchronous activation also causes molecular and cellular remodelling leading to alterations in glucose uptake, regional perfusion & calcium transport [23]. These factors can be pro-arrhythmic [24] and in combination with alterations in regional expression of gap junction proteins, may explain the increased arrhythmia susceptibility observed in this group of patients. Regional differences in action potential duration and conduction velocity have also been observed. Dyssynchrony appears to induce regional changes in K^+ & Ca^{2+} currents, prolonging action potential duration in the lateral wall. Maladaptive remodelling in the dyssynchronous heart also results in molecular changes. Stress kinase amplification including tumour necrosis factor- α have been identified in regions exhibiting late activation in dyssynchronous hearts. These factors play a key role in muscle function, fibrosis and survival.

Chapter 2 Cardiac Resynchronisation Therapy In The Management Of Heart Failure & The Issue Of Non- Response To Treatment

This section has been adapted from *Understanding non-response to cardiac resynchronisation therapy: common problems and potential solutions* (Sieniewicz, Gould, et al., 2018).

2.1 INTRODUCTION

Cardiac resynchronisation therapy (CRT) aims to eliminate the dyssynchrony which results from bundle branch block activation and restore the mechano-energetic efficiency of the heart. During CRT, both the left and right ventricles are stimulated in an attempt to re-coordinate cardiac electrical activation and produce a synchronous and efficient contraction. Several large randomised controlled trials of biventricular (BiV) pacing have been conducted which have established CRT yields both reductions in morbidity and mortality when compared to medical therapy alone.

2.2 CARDIAC RESYNCHRONISATION THERAPY

CRT is an increasingly common therapy designed to improve morbidity and mortality in patients with evidence of electrical dyssynchrony, severe LV impairment and symptomatic heart failure. Other terms including atrial-synchronised biventricular pacing or multi-site ventricular pacing better describe this treatment which involves stimulation of both ventricles in an attempt to eradicate electrical latency and restore synchronous contraction of the ventricles. In addition to a conventional right ventricular pacing lead and in some patients an atrial lead positioned in the right atrium, CRT incorporates a third lead designed to stimulate the left ventricle. This lead is commonly placed within a tributary of the coronary sinus, as this structure can be accessed from the right atrium.

2.3 MECHANISMS OF CARDIAC RESYNCHRONISATION THERAPY

CRT is an electrical therapy which seeks to eradicate the mechanical effects of altered biventricular activation. Biventricular electrical resynchronisation reduces the mechanical dyssynchrony between the left and right ventricles induced by bundle branch block as well as the intra-ventricular dyssynchrony present within the LV itself through three main mechanisms.

2.3.1 Increased LV Filling Time

LV filling is defined as the period of diastole during which blood passively flows from the atrium into the ventricle (visualised as the E wave on transmitral Doppler) and is terminated after the atrial contraction forces remaining blood into the ventricle (represented by the A wave on transmitral Doppler). In the context of interventricular conduction delay, LV activation is delayed but atrial activation occurs normally. This can lead to simultaneous passive ventricular filling and atrial activation, truncating the LV filling time and decreasing LV preload. Echocardiographically, this can be visualised through fusion of the E and A waves. By eradicating V-V dyssynchrony, CRT ensures LV activation is completed earlier, resulting in increased LV filling time.

2.3.2 Decreasing Septal Dyskinesia

CRT also reduces intra-ventricular dyssynchrony within the LV. During dyssynchronous activation paradoxical motion of the lateral wall can be observed during septal activation, with the resulting energy sink reducing the ejection of blood from the ventricle. CRT pacing ensures both septal and free walls contract simultaneously, increasing blood ejection and improving cardiac stroke volume.

2.3.3 Reducing Mitral Regurgitation

Appropriate opening and closure of the mitral valve is dependent on precise timing of the atrial and ventricular contraction. In the context of both interventricular and atrio-ventricular conduction abnormalities, complete closure of the mitral valve may not be achieved. Progressive latency can even result in diastolic mitral regurgitation. CRT restores regional activation synchrony

with respect to both the interventricular and atrio-ventricular timing, reducing and in some cases eliminating mitral regurgitation.

2.4 BIOMOLECULAR MECHANISMS OF CARDIAC RESYNCHRONISATION THERAPY

While the mechanical benefits of CRT can be easily visualised, effective resynchronisation pacing is also associated with positive biomolecular alterations. Maladaptive remodelling occurs as a result of disturbed neurohormonal balance. CRT has been associated with normalisation of plasma norepinephrine levels [25]. CRT may also improve serum natriotic peptide levels in addition to restoring autonomic balance in heart failure patients [26].

At the cellular level, CRT also reverses some of the biomolecular changes associated with dyssynchronous heart failure. Variations in regional cardiac transcriptome have been reported with down-regulation of transcripts for energy deriving functions in the anterior wall of the left ventricle in dyssynchronous hearts. Extracellular matrix components and cell signalling pathways display up-regulation within the anterior wall but conversely were downregulated in the lateral wall. These changes were effectively reversed by CRT. Resynchronisation pacing also appears to homogenise stress kinase amplification and decrease apoptosis via enhanced cell-survival signalling [21].

2.5 EVIDENCE FOR CARDIAC RESYNCHRONISATION THERAPY

Despite significant advances in the medical therapy available in the management of heart failure yielding improvements in symptoms, quality of life metrics, and survival the prognosis for patients diagnosed with heart failure has remained poor. Modes of death include pump failure and life threatening arrhythmias despite management with optimal medical therapy. CRT was first described in the early 1990s as a potential therapy for heart failure. Early trials of CRT included patients with moderate to severe heart failure including MUSTIC-SR (NYHA III, LVEF <35%, QRS > 150ms) [27], MIRACLE (NYHA III-IV, LVEF <35%, QRS > 130ms) [26], MIRACLE ICD (NYHA III-IV, LVEF <35%, QRS > 130ms) [28] and CONTAK CD (NYHA II-IV, LVEF <35%, QRS > 120ms) [29] proved CRT consistently improved NYHA functional status, exercise capacity and quality of life. CARE-HF

Chapter 2

(NYHA III-IV, LVEF <35%, QRS > 120ms) [30] was the first study to conclusively prove CRT without an ICD led to improvements in survival over optimal medical therapy, reducing both morbidity and mortality.

The above studies all recruited patients with severe heart failure (NYHA > 2) however CRT has been shown to be beneficial in patients with less severe symptoms in several studies. MADIT-CRT (NYHA I-II, LVEF <30%, QRS > 130ms) [31] showed a reduction in the primary endpoint in patients receiving CRT-D primarily driven by a decrease in heart failure events. REVERSE (NYHA I-II, LVEF <40%, QRS > 120ms) [32] similarly recruited patients with less severe symptoms and randomised them to either CRT-ON or CRT-OFF after implantation. Whilst no significant difference in the primary endpoint was observed at 12 months between, greater reverse remodelling was observed in the CRT-ON cohort and this was associated with a prolonged time to the first heart failure hospitalisation.

In both large randomised control trials as well as multiple systematic reviews, CRT has been shown to yield a significant benefit in terms of morbidity, mortality and reductions in heart failure hospitalisations [33], see Figure 4. As a result of these landmark studies, Class 1 indications exist for CRT in both European [34] and American guidelines [35] in patients with symptomatic heart failure, a severely impaired LV (LVEF < 35%) and an ECG demonstrating left bundle branch block with significant electrical delay.

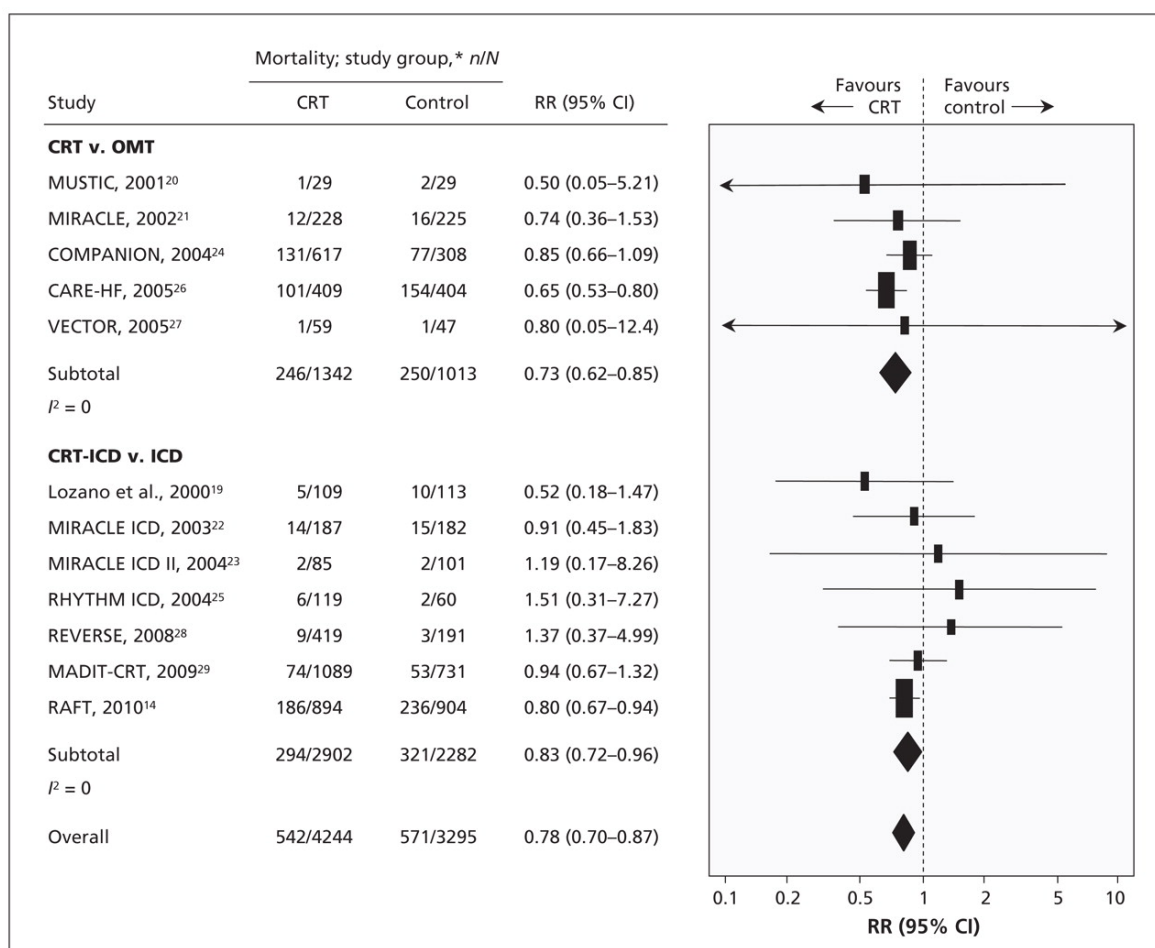


Figure 4. Results of random-effects meta-analysis of overall mortality among patients with heart failure given cardiac resynchronization therapy plus an implantable cardioverter defibrillator (CRT-ICD) versus an implantable defibrillator (ICD), by New York Heart Association (NYHA) class. Values less than 1.0 indicate a decreased risk of death with cardiac resynchronization therapy. Note CI = confidence interval, RR = relative risk. Reprinted from George Wells, PhD, Ratika Parkash, MD MSc, Jeffrey S. Healey, MD MSc, Mario Talajic, MD, J. Malcolm Arnold, MD, Shannon Sullivan, MSc, Joan Peterson, BA, Elizabeth Yetisir, MSc, Patricia Theoret-Patrick, BScRN, Marilyn Luce, BScRN, and Anthony S.L. Tang, MD. Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials. *Canadian Medical Association Journal* 2011 Mar 8; 183(4): 421–429. © Canadian Medical Association (2011). This work is protected by copyright and the making of this copy was with the permission of the Canadian Medical Association Journal (www.cmaj.ca) and Access Copyright. Any alteration of its content or further copying in any form whatsoever is strictly prohibited unless otherwise permitted by law.

2.6 DEFINING RESPONSE TO CRT

The process of defining response to CRT is challenging as no universally accepted definition of CRT response exists. Response can be measured in a variety of different clinical, functional and structural endpoints. There is also no consensus as to the optimal timeframe to re-assess patients following CRT. Response rates tend to be higher when clinical measures, such as subjective assessments of symptoms are used and the period of time between the intervention and follow up assessment is longer. Conversely, rates of response tend to be lower when remodelling or hard outcome measurements are employed, see Figure 5.

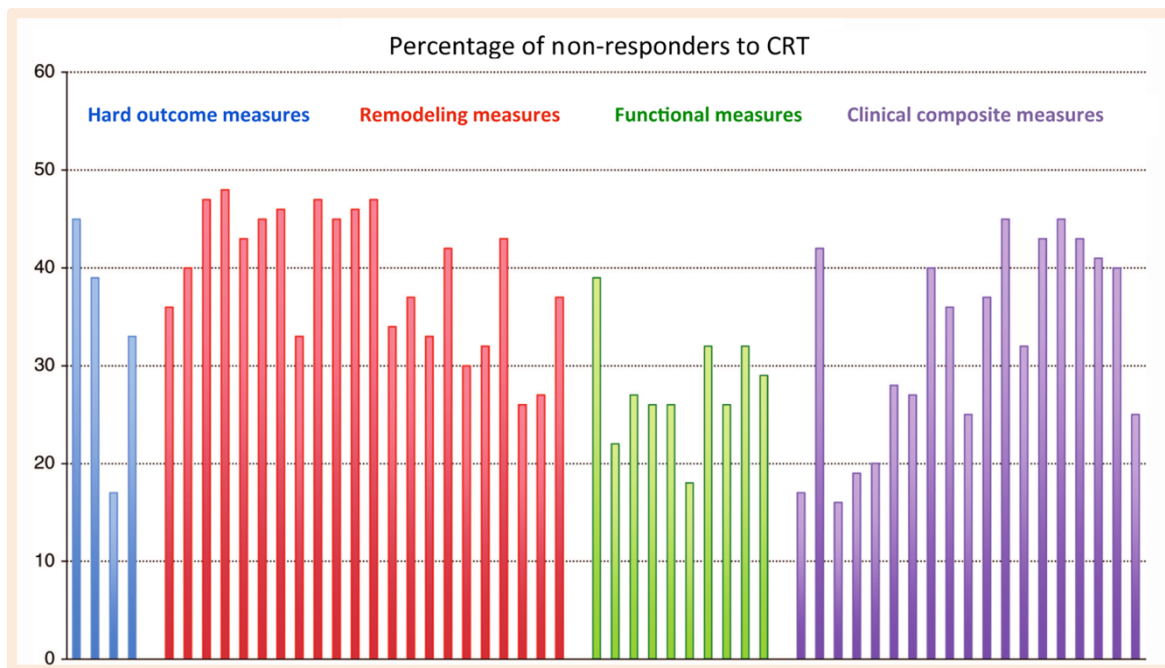


Figure 5. Rates of non-response to cardiac resynchronization therapy depending on the measure used in controlled trials and large observational studies of cardiac resynchronization therapy, each represented by a bar. Event-based measures are shown as blue, remodelling measures as red, functional and quality of life measures as green, and composite endpoints as purple bars. Reproduced with permission from Claude Daubert & Nathalie Behar. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. *European Heart Journal*. 14;38(19):1463-1472. Permission granted by Oxford University Press.

2.6.1 Event Based Endpoints To Define CRT Response

The use of all-cause mortality in the assessment of response to CRT is the most unbiased method of assessing the effect of CRT on mortality, despite the fact that events unrelated to CRT non-response are included in the analysis. Given the relative rarity of this endpoint however, it necessitates a long follow up period. An easier event based endpoint is heart failure hospitalisation, which records unplanned hospitalisation as a result of heart failure decompensations.

2.6.2 Biomolecular Endpoints To Define CRT Response

Several biomarkers have been explored due to their potential to identify patient response to CRT. One example is the use of tissue inhibitors of matrix metalloproteinases (TIMPs) which regulate the extracellular matrix which in a prospective study appeared to correlate with CRT response [36] and survival [37]. Variability exists in these results however, with other studies identifying no differences in TIMP between responders and non-responders [38]. The utility of these biomarkers has consequently remained unclear however, extracellular matrix remodelling is clearly implicated in the response to CRT.

2.6.3 LV Remodelling Endpoints To Define CRT Response

Echocardiographic assessments of CRT response benefit from being objective measures of LV size or function. As such they are less subjective than measures of clinical response. When defining response echocardiographically, a repeat study is undertaken at least 6 months after implantation in order to compare both volumetric size and left ventricular function. Several different methods of defining response have been described including an absolute increase in left ventricular ejection fraction of > 5% as well as markers of left ventricular reverse remodelling (LVRR) following device implantation. Reverse remodelling is frequently preferred as it compares two dimensions- whereas ejection fraction relies on accurately calculating both systolic and diastolic left ventricular volumes. As such a reduction in LV end-systolic volume (LVESV) of >15% is the most widely accepted echocardiographic marker of response [39,40]. Volumetric change predicts clinical response and prognosis amongst CRT patients with larger decreases in LVESV correlating to fewer heart failure hospitalisations and a lower mortality rate.

2.6.4 Acute Haemodynamic Endpoints To Define CRT Response

Finally, some metrics evaluate acute changes in LV contractility. Acute haemodynamic response (AHR) is a reproducible marker of LV contractility best expressed as the change in the maximum rate of left ventricular pressure (LV-dP/dt_{max}), from a baseline control state [41,42]. Previous work has evaluated the acute haemodynamic effects of CRT using LV-dP/dt_{max} as an outcome measure [42–45] and this metric has been used to compare the effects of biventricular pacing at different locations [41,42,46]. An improvement in LV-dP/dt_{max} of 10% during acute implantation has been shown to predict chronic LV reverse remodelling in patients receiving CRT [47].

A criticism of LV-dP/dt_{max} is that even during optimal data collection, natural variations in contractility caused by changes in heart rate, blood pressure and respiration can result in drifts in LV-dP/dt_{max} values [48]. A different method of analysing of acute haemodynamics involves the delineation of pressure-volume loops to determine changes in LV contractility. In one study, long term echocardiographic response was predicted by significant improvements in acute pump function at implant, while non-responders showed no improvement [49], see Figure 6. Various acute parameters were examined including stroke work, cardiac output, ejection fraction although acute changes in LV contractility (dP/dt_{max}) failed to achieve statistical significance.

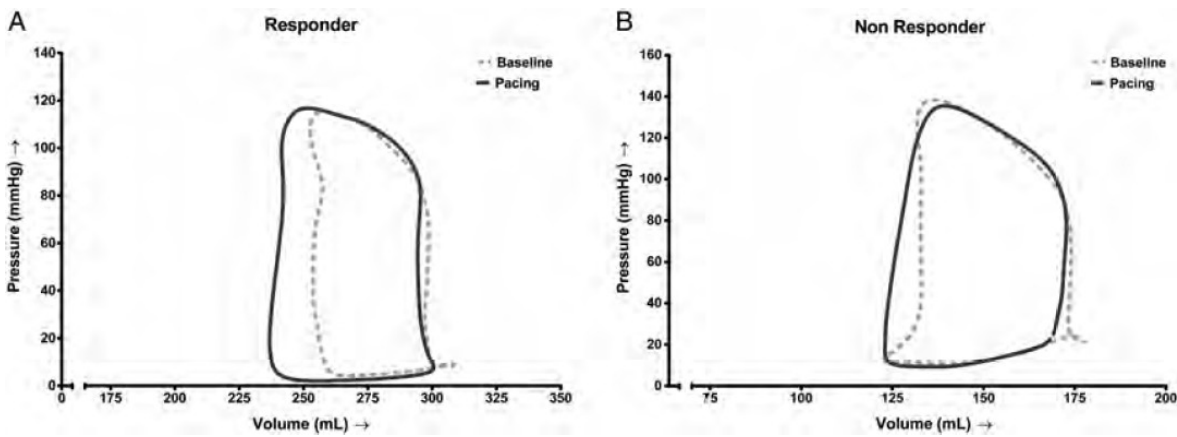


Figure 6. Pressure–volume loops of two different patients during baseline (dotted) and during biventricular pacing (dark blue). (A) Substantial acute change in a long-term responder. (B) Negligible acute change in a long-term non-responder [49].

2.6.5 Functional Endpoints To Define CRT Response

Several classification systems exist to describe symptoms of dyspnoea, the most widespread being the NYHA status. As such, one marker of response commonly used is when a patient's symptoms improve sufficiently for them to be reclassified according to their NYHA score. With only four classes, heterogeneity exists within each NYHA classification and in addition, this assessment is open to subjective bias. An assessment incorporating multiple components of well-being is thus preferred. Such assessments may describe, symptoms, quality of life as well as functional capacity in order to demonstrate reliability. Physical assessments of exercise capacity can also be undertaken including a six minute walk test. A more reliable assessment of exercise tolerance can be obtained through formal cardiopulmonary exercise testing.

2.7 CONGRUENCE BETWEEN RESPONSE METRICS

Agreement between different methods of defining response to CRT is poor. Symptomatic improvements can show poor correlation with both changes in ventricular structure and function. In a retrospective analysis of one registry 99% of patients could be classified as a responder according to one of the 15 widely used criteria to define response, while 94% also met the definition of a non-responder [50]. Agreement between these 15 widely used criteria which included echocardiographic measures of ejection fraction and volumetric remodelling, clinical measures of functional capacity or quality of life and combinations of both showed poor agreement, see Figure 7.

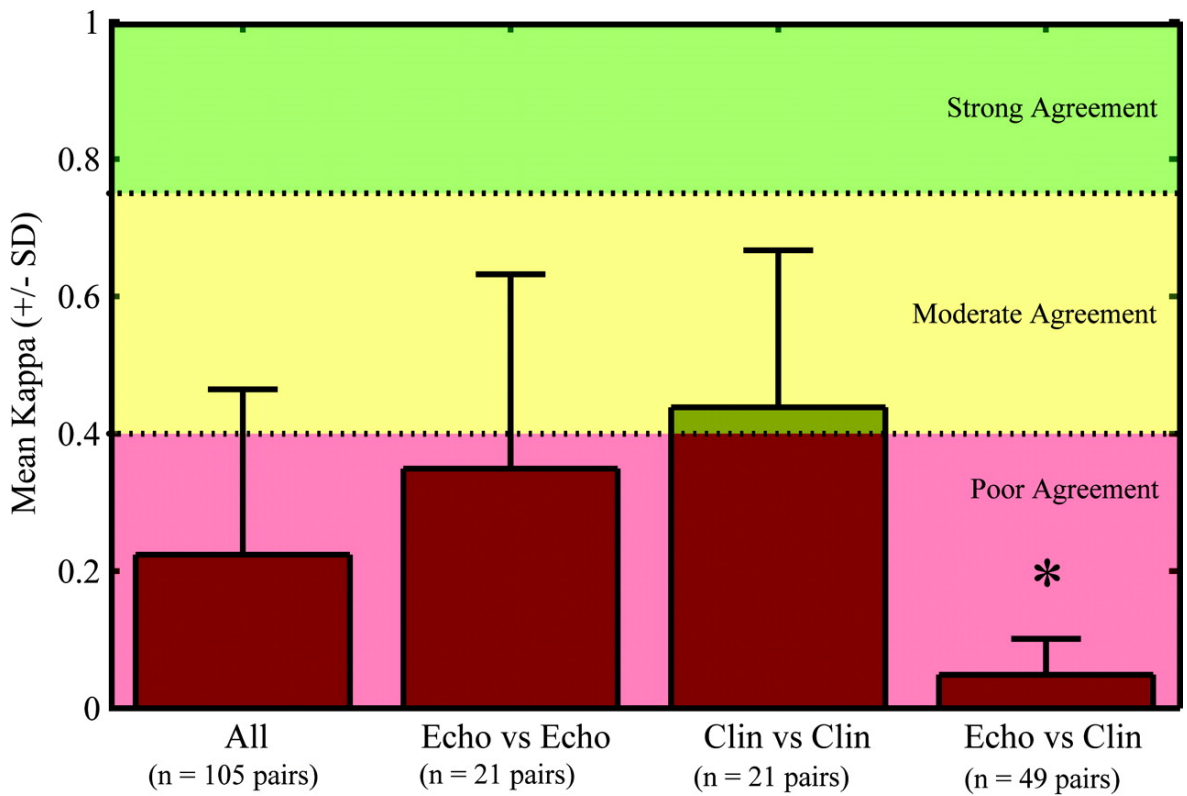


Figure 7. Agreement among the 15 response criteria was poor. The y-axis shows the following ranges delineated by dotted lines: strong agreement (0.75), moderate agreement (0.40-0.75), and poor agreement (0.0-0.40). The worst agreement was between echocardiographic (Echo) and clinical (Clin) parameters. *P<0.001 vs “Echo vs Echo” and “Clin vs Clin.” [50]

The most widely accepted definition of response involves an assessment of left ventricular reverse remodelling (LVRR) six months after implantation, with reductions in LV end-systolic volume (LVESV) frequently identified as the most useful measure [39,40]. However, agreement between different echocardiographic parameters remained similarly poor, see Figure 8. Remodelling endpoints are typically associated with non-responder rates of between 30-45% [51] although in the systematic review published by Birnie and Tang (2006), the true figure appears somewhat higher at around 40-50% [52].

	Echocardiographic							Clinical							Combined	
	↑LVEF > 5 units	↑LVEF > 15% (relative)	↓LVESV ≥ 10%, no HF death	↓LVESV > 15%	LVESV < 115% of baseline	↓LVEDV > 15%	↑Stroke Volume ≥ 15%	↓NYHA ≥ 1	↓NYHA ≥ 1, no HF death	↓NYHA ≥ 1 and ↑6MWD ≥ 25%	↓NYHA ≥ 1 and ↑6MWD ≥ 25%, no HF death	↑6MWD ≥ 10%, no HF death, no transplant	2/3 of: ↓NYHA ≥ 1, ↑6MWD ≥ 50m, ↓QOL ≥ 15	Clinical composite score improved	↑LVEF > 5 units or ↑6MWD ≥ 50m and ↓NYHA ≥ 1 or ↓QOL ≥ 10	
Echocardiographic	↑LVEF > 5 units	-	0.88	0.48	0.48	0.16	0.29	0.47	0.05	0.03	0.04	0.02	0.02	0.07	0.01	0.33
	↑LVEF > 15% (relative)	-	0.47	0.48	0.18	0.26	0.48	0.12	0.1	0.09	0.07	0.1	0.14	0.03	0.4	
	↓LVESV ≥ 10%, no HF death	-	0.82	0.28	0.62	0.03	0.11	0.16	0	0.04	0.02	0.07	0.14	0.2		
	↓LVESV > 15%	-	0.23	0.74	0	0.17	0.15	0.03	0.01	-0.01	0.11	0.13	0.22			
	LVESV < 115% of baseline	-	0.18	0	0.01	0	-0.01	-0.01	0	0.04	0	0.08				
	↓LVEDV > 15%	-	-0.2	0.07	0.05	0.04	0.02	-0.03	0.03	0.06	0.11					
	↑Stroke Volume ≥ 15%	-	-0.01	-0	0.01	-0.02	0.04	0.08	0.01	0.14						
Clinical	↓NYHA ≥ 1							-	0.97	0.32	0.3	0.14	0.6	0.61	0.52	
	↓NYHA ≥ 1, no HF death							-	0.3	0.32	0.18	0.57	0.64	0.49		
	↓NYHA ≥ 1 and ↑6MWD ≥ 25%							-	0.97	0.44	0.45	0.21	0.32			
	↓NYHA ≥ 1 and ↑6MWD ≥ 25%, no HF death							-	0.46	0.43	0.23	0.3				
	↑6MWD ≥ 10%, no HF death, no transplant							-	0.45	0.21	0.49					
	2/3 of: ↓NYHA ≥ 1, ↑6MWD ≥ 50m, ↓QOL ≥ 15							-	0.39	0.56						
Combined	Clinical composite score improved														-	0.38
↑LVEF > 5 units or ↑6MWD ≥ 50m and ↓NYHA ≥ 1 or ↓QOL ≥ 10															-	

Figure 8. Agreement among the response criteria was poor 75% of the time and strong only 4% of the time. Values are color-coded according to the following ranges: Green = strong agreement (0.75), yellow = moderate agreement (0.40.75), and red = poor agreement (0.4). LVEF indicates left ventricular ejection fraction; HF, heart failure; NYHA, New York Heart Association; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; 6MWD, distance walked in 6 minutes; and QOL, quality-of-life score [50].

2.8 NON-RESPONSE TO EPICARDIAL CRT

The reasons why some patients fail to adequately respond to transvenous, epicardial CRT are multifactorial and involve several pre, peri and post implant factors, see Figure 9.

Chapter 2

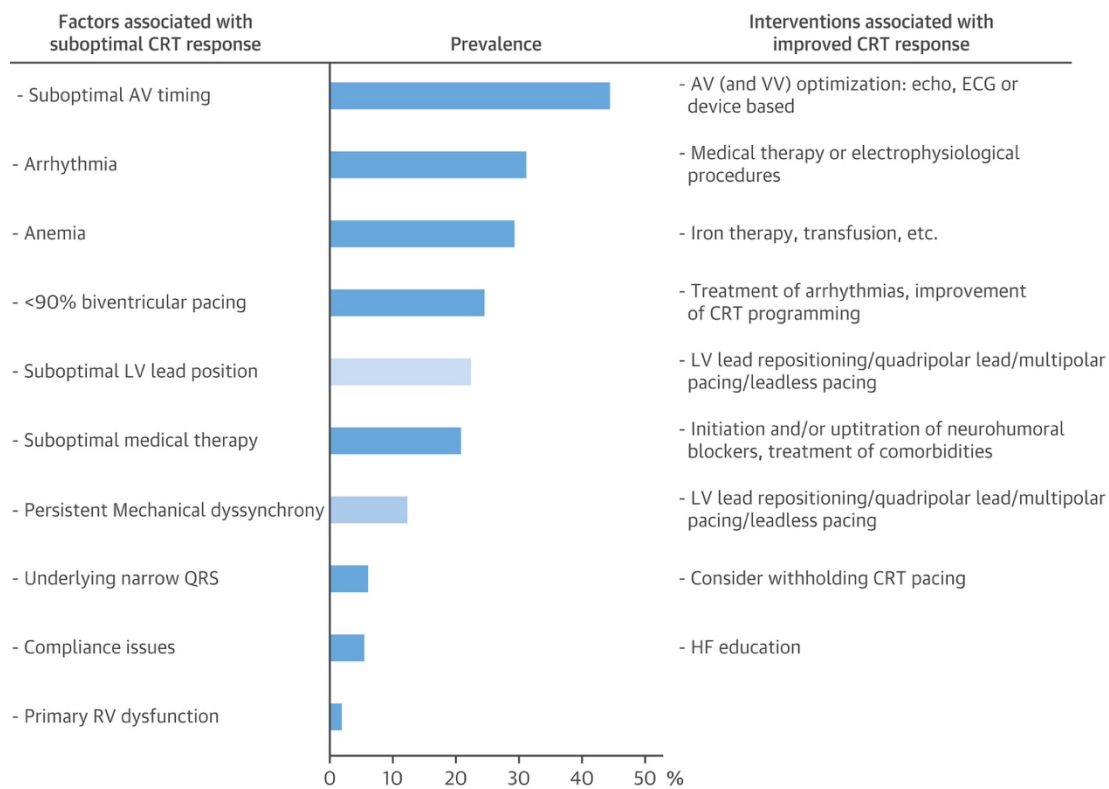


Figure 9. Factors associated with sub-optimal CRT response. Reproduced with permission from Wilfried Mullens & Petra Nijst. Understanding Non-Response to Cardiac Resynchronisation Therapy; Common Problems and Potential Solutions. Journal of the American College of Cardiology 2017 69(17):2130-2133

2.8.1 Pre-Implant

Pre-implant factors associated with non-response to CRT include; appropriate patient selection, patient aetiology, myocardial scar and disease severity.

2.8.1.1 Patient Selection

Optimal patient selection is critical when looking to maximise response to CRT. In both European [9] and American [10] guidelines CRT is indicated in patients with symptomatic heart failure who exhibit impaired LV function and display evidence of ventricular dyssynchrony. Patients must have been established on optimal tolerated medical therapy and reversible causes of heart failure should have been excluded, including ischaemia, arrhythmia or valvular heart disease. In addition, current patient selection criteria utilise the surface 12 lead ECG to identify electromechanical

delay; although recent sub-group analysis have suggested that the actual pattern of activation, may in fact be more important determinant the actual QRS width [53,54].

2.8.1.2 ECG Morphology and QRS Duration

The presence of left bundle branch block morphology is a strong predictor of response to CRT [55]. Whilst no definitive data exists evaluating CRT response in patients with RBBB, retrospective analysis suggests that this group of patients tends to do less well. One reason for this is that despite the presence of a broad QRS on the surface ECG, RBBB is associated with less global LV dyssynchrony than LBBB [56]. This disparity can be explained by evaluating the asymmetric geometry of the LV. While the lateral free wall is dependent on LV loading conditions, loading of the septum occurs due to activation of both the RV and the LV. In the context of RBBB, early activation of the lateral LV free wall occurs against an unloaded septum but RV loading can offset this, reducing ventricular dyssynchrony.

Interestingly, when patients with heart failure and RBBB were analysed using 3D non-contact mapping, some were found to exhibit significant LV activation delay in addition to the delay identified in in the RV [57]. In addition, LBBB activation is not exclusively associated with electrical conduction delay [58]. In one analysis, up to a third of patients with LBBB who underwent electromechanical or non-contact mapping demonstrated normal transseptal activation time and a near-normal LV endocardial activation time [59]. It is possible more nuanced assessments of electrical delay, such as non-invasive body surface mapping, may be able to detect remediable patterns of electrical delay with greater accuracy.

The evidence for CRT in patients with nonspecific intraventricular conduction delay (NICD) who possess a wide QRS without the appearance of left or right bundle branch block, is also sparse. This ECG abnormality is present in between 3.8% & 5.8% of patients with impaired LV function [50,60] and can be caused by a variety of pathophysiological processes, which may independently influence response. In the context of ischaemic heart disease, atypical electrical activation may occur around an area of necrotic tissue post-myocardial infarction, modifying the appearance of a classic left bundle branch block morphology. Similarly, in peri-infarct block, the trajectory of electrical activation becomes widened as it bypasses a previously infarcted area. Finally, NICD can occur in several cardiomyopathic processes as a result of increased LV myocardial mass and modifications in myofibrillar organisation.

Conflicting outcomes following the use of CRT in patients with NICD have been reported with some studies appearing to show benefits in quality of life [61], whilst others revealed no benefit in

clinical composite score, remodelling or mortality [53,54,62,63]. Morphology again appears to be the critical determinant with patients exhibiting a LBBB-like NICD morphology appearing to gain the most benefit. While reliably categorising the activation pattern on the basis of a 12 lead ECG alone can be challenging, this is possible using both invasive electroanatomical mapping or novel non-invasive body surface mapping technology.

2.8.1.3 Gender

Women have been consistently under-represented in nearly all large scale trials of CRT and yet gender appears to play a key part in determining response to CRT [64–67]. Female CRT recipients appear to achieve superior survival benefits when compared to male recipients, although lower rates of ICM confound this analysis [65,67]. Interestingly, it appears that the degree of electrical dyssynchrony required to predict response to CRT differs between the sexes. The analysis by Varma et al, identified that the peak probability of response occurred with a comparatively narrower QRS than that of men [68]. Whilst the Class 1 indication for CRT of a QRS > 150ms affords men a ~60% chance of responding to CRT, women achieved the same level of response with a QRS of just 130ms, see Figure 10.

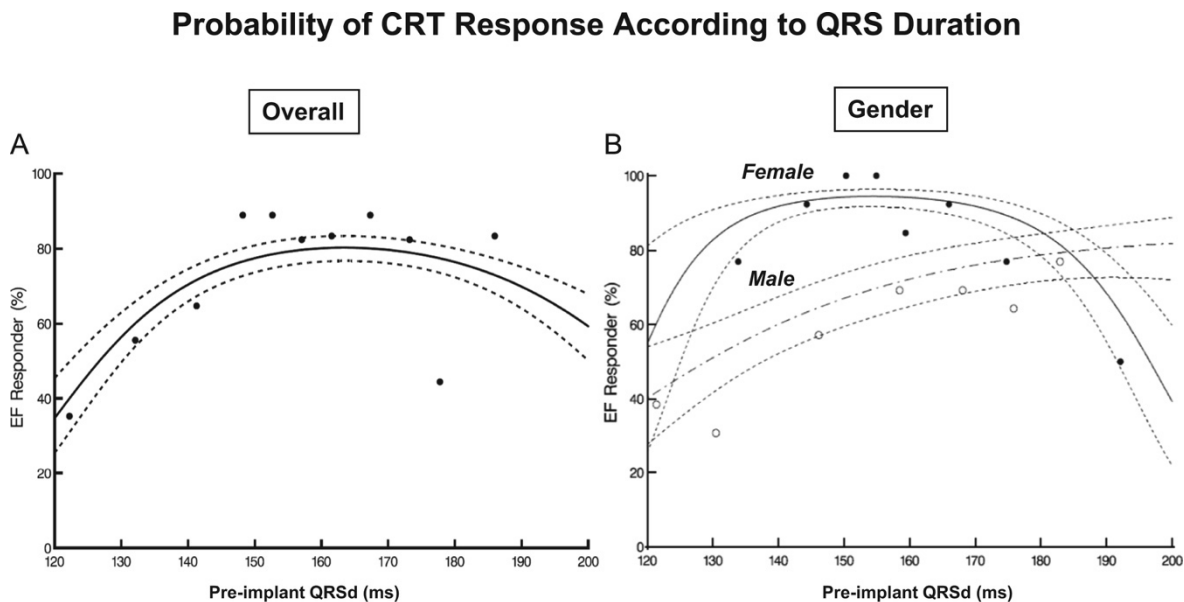


Figure 10. Probability of CRT response according to QRSd as a continuous function. Parametric model: multivariable logistic regression shown with the corresponding 68% confidence limits (comparable to ± 1 SD). The decile points representing mean percentage of responders according to the deciles of QRSd are given as a crude verification of model fit. **A:** Overall. Closed symbols represent decile points based on the equal number of patients (17 or 18 patients). **B:** Gender-specific plot is based on

a patient with baseline LVEDD 6 cm, baseline LVEF 20%, and 2 years from implant to follow-up echocardiography. Each decile point represents an average of ~10 patients (closed symbols: women; open symbols: men). Shapes were confirmed by semi- and nonparametric modelling. Reproduced with permission from Varma N, Manne M, Nguyen D, He J, Niebauer M, Tchou P. Probability and magnitude of response to cardiac resynchronization therapy according to QRS duration and gender in nonischemic cardiomyopathy and LBBB. *Heart Rhythm*. 2014 Jul;11(7):1139-47.

2.8.1.4 Aetiology & Myocardial Scar

In roughly 50% of patients receiving CRT, the aetiology of their heart failure will be ischaemic in origin [51] however, ischaemic aetiology is an independent predictor of non-response to CRT [69,70]. Other studies have shown patients with ischaemic cardiomyopathy (ICM) experience less improvement in LVEF than patients with non-ischaemic, dilated cardiomyopathy (DCM) [71,72]. The difference in remodelling has been attributed to a sequelae of the greater burden of scarred myocardium typically identified in ischaemic patients, reducing the potential for LV remodelling [73].

2.8.1.5 Atrial Arrhythmias

Around 25% of patients undergoing CRT implantation are in permanent atrial fibrillation (AF) [74]. It is common for patients with AF to concurrently exhibit older age, increased severity of heart failure and additional comorbidities than patients who present with sinus rhythm. Patients with AF are more likely to have a faster and more irregular heart than patients in sinus rhythm and the aetiology of their LV dysfunction may in some instances be a result of tachycardiomyopathy. When the presenting rhythm was analysed in a randomised trial, CRT appeared to confer no benefit to patients with coexistent AF whilst a 25% reduction in mortality was observed amongst those in sinus rhythm [75]. One explanation for this discrepancy is that amongst the group with AF, only 50% patients experienced a BiV pacing burden in excess of 90%. As such, the current European guidelines include the caveat that when contemplating CRT implantation in patients with AF, a class IIa indication exists, “provided that a BiV pacing as close to 100% as possible can be achieved” [34].

Given the importance of maximising the percentage of BiV pacing, it has been postulated that all patients with AF should undergo Atrio-Ventricular (AV) junctional ablation and this approach does

appear to enhance the effects of CRT with the same magnitude as those seen in patients with sinus rhythm [76].

2.8.1.6 Upgrades to CRT

Patients with a bradycardia pacing system in situ who go on to develop heart failure symptoms account for around 23-28% of CRT implants. The deleterious effects of chronic RV pacing have been well established [77–79] and recently reviewed [80]. As such, implantation of a BiV pacing system may be appropriate for patients with evidence of symptomatic heart failure and reduced ejection fraction who are expected to experience a high pacing burden. It is likely stricter adherence to professional practice guidelines identifying suitable patients to undergo an upgrade to a CRT system will improve the response rate to the therapy.

2.8.2 Peri-Implant

Peri-implant factors associated with non-response to CRT include utilising appropriate LV lead technology and optimisation of the LV lead stimulation site.

2.8.2.1 LV Lead Technology

Transvenous, epicardial CRT was traditionally performed by implanting a bipolar pacing lead in a tributary of the coronary sinus, facilitating depolarisation of the LV ventricle. Multi-site pacing (MSP) where stimulation is delivered from two or more sites within the LV, would intuitively appear preferable to single site stimulation. In early pilot work, MSP was associated with greater reverse remodelling [81,82] however in a larger, randomised study of prior non-responders to CRT, no clinical or echocardiographic benefit was observed [83].

MSP can also be delivered via multipoint pacing (MPP). This technique utilises quadripolar LV pacing leads which have four integrated pacing cathodes along the course of the lead, allowing greater customisation from any of the of the 10-17 MPP vectors available. The increased choice for the implanting physician means it is possible to programme around frequently occurring issues including high pacing thresholds- potentially caused by areas of scar- or phrenic nerve stimulation, where LV depolarisation causes diaphragmatic twitching. The use of MPP has been shown to yield

greater improvements in acute haemodynamic response [84] and in a small, randomised study; greater improvements in overall response [85].

2.8.2.2 Stimulation Site

The optimal LV pacing site displays large inter and intra-patient variability amongst patients with both DCM [42] & ICM [41,86,87]. Delivering stimulation from a more apical position has largely been shown to yield less favourable outcomes [88,89] and this practice is not endorsed in current guidelines [34]. In general, there is a consensus that the lateral free wall represents the most favourable target for LV lead deployment; typically within the lateral, or postero-lateral cardiac veins of the coronary sinus [26,27,90,91]. Unfortunately, the constraints of the coronary sinus anatomy mean it is occasionally impossible to even implant an LV lead, let alone target a specific site which displays desirable viability and latency [92].

An alternative strategy which eliminates the need to access the coronary sinus is to attempt to capture the His-Purkinje conduction system. This approach aims to restore physiological biventricular activation and can significantly reduce activation time when compared to conventional epicardial CRT [93,94]. Initial experience with His pacing was primarily constrained to patients with intact His-Purkinje conduction however, LBBB can be corrected by His pacing via three mechanisms. The first is described as longitudinal disassociation; and relies on the fact that fibres which form the proximal His bundle are predestined to form either the left anterior or left posterior fascicle of the left bundle or the right bundle. As such, delivering pacing to the His bundle distal to the area of block can overcome a more proximal block. Output dependence can also be observed, where greater stimulus strength can recruit fibres closely bordering an area of functional block. Finally, non-selective His capture can be achieved by stimulating myocardium within the vicinity of the His bundle, allowing capture of local myocardium before activating the His-Purkinje system and bypassing the area of block.

Despite promising electro-anatomical data, large scale clinical trials of this approach are awaited. In one feasibility study, LBBB correction proved possible in 71% of patients and capture thresholds remained largely stable during follow up [95]. At 12 months, improvements in both NYHA functional class and LVEF were observed. These findings were replicated in other work, where 88.9% of patients whose LVEF <40% at baseline improved to > 50% at 1 year following His pacing [96].

2.8.3 Post Implant

Post-implant factors associated with non-response to CRT include; remote monitoring, frequency of biventricular pacing, device programming and optimisation.

2.8.3.1 Remote Monitoring

Almost all modern cardiac implanted electronic devices (CIEDs) have the capability allow remote device follow up. Large, randomised studies have consistently shown remote device monitoring is both feasible and reduces the need for ambulatory outpatient clinic attendance [97]. The use of remote monitoring has been shown to improve clinical outcomes for patients with heart failure as well as achieving a significant reduction in mortality [98]. However, similar benefits were not observed when a more rationalised approach to remote monitoring was adopted in other work [99].

Whilst CIEDs can analyse fluid status by calculating thoracic impedance as part of a multi-parametric assessment, monitoring-only implantable technologies have also been devised. The CardioMEMS Heart Failure system (Abbott Medical Inc, Atlanta, GA, USA) is a wireless pulmonary artery haemodynamic monitor, which provides an accurate assessment of real time pulmonary artery (PA) pressure, allowing the physician to optimise pharmacotherapy. Use of this system was associated with a 33% reduction in hospitalisations when compared to standard of care [100]. Such systems appear to hold a great deal of promise, particularly if they could be integrated with the currently available CIED multiparametric assessments.

2.8.3.2 Biventricular Pacing Burden

In order for a CRT system to function effectively it is essential that it is able to deliver consistent biventricular pacing. Frequent ventricular ectopics and atrial tachyarrhythmias can reduce the frequency of biventricular pacing and were identified in up to a third of non-responders to CRT [101]. There are several mechanisms by which atrial tachyarrhythmias reduce response to CRT. Rapid atrial rates can result in loss of ventricular stimulation, but of equal significance are the detrimental haemodynamic sequelae of the irregularity of the rhythm as well as the loss of intrinsic atrial function. A strategy of attempting to maintain sinus rhythm using pharmacological

therapy in patients with heart failure, conferred no benefit over a strategy of rate control [102]. Other strategies to increase the frequency of biventricular pacing include both catheter ablation [103,104]. Recent work has suggested that this approach may even confer a survival benefit in patients with AF and heart failure [105]. AV junction ablation is an alternative strategy in patients with AF and whilst rendering the patient pacing dependant, appears highly effective when combined with biventricular pacing. As such this practice is endorsed in the most recent guidelines [34].

Ventricular extra systolic beats can similarly disrupt the efficient function of a CRT system, reducing the frequency of effective biventricular pacing and as such, contributing to non-response. Again the therapeutic target is to minimise the occurrence of such events either through the use of pharmacological therapy or catheter ablation [106].

2.8.3.3 Programming & Optimisation

Appropriate programming can increase the frequency of biventricular pacing but is also essential in order to ensure the optimal mechanical functioning of the heart, which facilitates greater response. Arguably the most important settings requiring optimisation are the pacing mode, upper and lower rate limits, the LV capture voltage, the stimulation vector and A-V and V-V intervals. Programming a high upper tracking rate ensures biventricular pacing is maintained during exercise. Similarly, the LV pacing output should include an adequate safety margin to ensure continual BiV pacing, although some modern devices can automatically adjust this parameter.

Iterative optimisation of the A-V & V-V intervals using doppler echocardiography is the established reference method of achieving optimal programming by ensuring optimal diastolic filling of the LV [107,108]. Recent large multicentre studies evaluating this practice have shown it to be largely ineffective when compared to the use of empirical programming [109,110]. A more promising technique, which optimises the A-V & V-V intervals using an integrated haemodynamic sensor, is currently undergoing further assessment [111].

Chapter 3 Strategies To Improve Response To CRT:

Optimal Site Selection & Image Fusion Guidance

Technology

This section has been adapted from *Optimal site selection & image fusion guidance technology to facilitate cardiac resynchronisation therapy* (Sieniewicz, Gould, et al., 2018).

3.1 INTRODUCTION:

One in five people will suffer from HF during their life time and once diagnosed ~40% of patients die within one year [6]. Cardiac resynchronisation therapy (CRT) by pacing the left (LV) and right (RV) ventricles to re-coordinate cardiac electrical activation and produce a synchronous contraction, has emerged as one of the few effective treatments for HF(2,3). However, at present 30% of patients fail to respond clinically through improved quality of life, exercise capacity and New York Heart Association (NYHA) functional classification of HF and up to 50% show no beneficial changes in cardiac function[1]. Suboptimal LV lead position is a common culprit when evaluating poor outcomes after CRT [88,101,112,113]. Equally, several groups have reported enhanced response rates when targeting tissue which displays evidence of favourable viability [114–117] or advantageous mechanical [118–124] or electrical [125–129] properties. This chapter will evaluate how to define the optimal LV pacing site and the mechanisms by which it is possible to selectively deploy a pacing electrode at this site.

3.2 ACUTE AND CHRONIC MARKERS OF RESPONSE

In order to identify the optimal pacing location, it is necessary to perform an examination of the available sites and preferentially select the site which possesses the most favourable characteristics. Unfortunately, in the 20 years since the first description of resynchronisation pacing for heart failure [130], no consensus has been achieved on how to define “response” to CRT [131] making comparison of the various pacing sites problematic. A multitude of different clinical and event-based definitions of response to CRT have been described with rates of

response varying from 32% to 91% depending on the criteria used. This review will predominantly focus on three indices; outcome based metrics which evaluate survival and mortality after device implantation. Markers of left ventricular reverse remodelling (LVRR) following device implantation, of a reduction in LV end-systolic volume (LVESV) is the most widely accepted marker [39,40]. Finally, some metrics evaluate acute changes in LV contractility. Acute haemodynamic response (AHR) is a reproducible marker of LV contractility best expressed as the change in the maximum rate of left ventricular pressure (LV-dP/dt_{max}), from a baseline control state [41,42]. Previous work has evaluated the acute haemodynamic effects of CRT using LV-dP/dt_{max} as an outcome measure [42–45] and this metric has been used to compare the effects of biventricular pacing at different locations [41,42,46]. An improvement in LV-dP/dt_{max} of 10% during acute implantation has been shown to predict chronic LV reverse remodelling in patients receiving CRT [47].

3.3 TISSUE CHARACTERISATION:

3.3.1 Pathophysiology of Scar in Ischemic and Non-Ischaemic Cardiomyopathy

Ischaemic scar forms as a result of permanent myocyte death following an ischaemic insult. A reparative process is initiated to rebuild the infarcted myocardium and maintain the structural integrity of the ventricle. An initial inflammatory phase of healing is followed by a fibrogenic phase that eventually results in the formation of scar tissue as dead myocytes are progressively replaced by collagenous scar. Ischaemic scar tends to display a sub-endocardial or transmural distribution affecting a specific coronary territory. Histological evidence of myocardial fibrosis has also been described in non-ischaemic presentations [132–134]. Whilst the precise mechanism behind this scar formation, which typically follows an epicardial or mid-wall distribution, is unclear, interstitial and perivascular fibrosis ultimately results in myocardial necrosis [135].

3.3.2 Impact of scar on the mechanical properties of the heart

Almost immediately following coronary artery occlusion, the subtended area of myocardium becomes passive and non-contractile. The non-viability and reduced plasticity of infarcted scar tissue is associated with a reduction in efficient and effective mechanical function during systole. Nearly all of the determinants of systolic function are negatively impacted by the presence of scar

including cardiac shape and dimensions, preload, afterload & contractility [136]. During systole, the scarred region stretches and bulges outward while the remaining myocardium contracts, causing a reduction in the mechanical efficiency of the heart as a pump. This effect is strongly dependant on the total area of scarred tissue [137].

3.3.3 Impact of scar on outcomes

The size, location and transmuralty of scar all impact LV remodelling after CRT. Global scar burden has been shown to be inversely proportional to LV reverse remodelling amongst both ischaemics [138], non-ischaemics [139] and mixed populations, [140–142]. Functional improvement [138,139,143] and survival [144] are also inversely proportional to scar burden. Retrospective analysis has confirmed that favourable markers for response include smaller scar size and fewer areas of transmural scar [142]. The location of scar is of equal importance, in particular when it is located in the postero-lateral region of the LV, a site empirically thought to be optimal for LV lead deployment. Scar in this area is associated with lower response rates following CRT [142,145].

3.3.4 Impact of scar on electrical activation

Scar prevents effective transmission of the electrical impulse, resulting in prolonged activation. Electrical activation in regions of fibrosis is characterised by localised delays and fractionated, low-amplitude extracellular electrograms [146]. This has been attributed to changes in patterns of excitation and conduction due to altered ion channel activity [147] and decreased cellular connectivity [148] compounded by tortuous conduction through areas of surviving myocytes. This delay in LV activation results in less haemodynamic improvement during biventricular pacing [149]. Electrical stimulation in regions of scar can also be pro-arrhythmic [150,151] and is associated with increased morbidity and mortality [114,152]. Significantly, the presence of myocardial scar at the site of LV stimulation during CRT is associated with non-response [114,153].

3.3.5 Scar Identification

Given the negative implications associated with stimulating scarred and fibrotic myocardial tissue, current evidence favours avoiding these areas and targeting viable tissue. , see Table 1.

Anatomical imaging involves direct visualisation of tissue defined as scarred. Functional imaging relies on surrogate markers of scar such as measures of wall motion, strain, voltage or contractile reserve. Biological imaging assesses metabolism or perfusion as a surrogate for viability.

Table 1. Techniques for assessment of viability and scar

Imaging technique	Classification	Technique	Marker of viability/scar
CMR	Anatomical imaging	LGE	Direct visualisation of scar
	Anatomical imaging	Wall thickness	EDWT as surrogate for scar
	Functional imaging	Contractile reserve	Contractile reserve
	Functional imaging	Functional assessment	Severe dysfunction as surrogate for scar
TTE	Functional imaging	Strain assessment	Severely reduced strain as surrogate marker
	Anatomical imaging	Wall thickness	EDWT as surrogate for scar
	Functional imaging	Contractile Reserve	Contractile reserve
	Functional imaging	Functional assessment	Severe dysfunction as surrogate for scar
CT	Functional imaging	Strain assessment	Severely reduced strain as surrogate marker
	Anatomical imaging	Wall thickness	EDWT as surrogate for scar
PET or SPECT	Biological Imaging	Perfusion	Perfusion as a surrogate for viability
PET or SPECT with FDG	Biological imaging	Glucose Utilisation	Glucose utilization as a surrogate for viability

3.3.6 Cardiac MRI

Late gadolinium enhancement (LGE) cardiac MRI (CMR) is the gold standard for delineating myocardial scar with high resolution, as the superior spatial resolution of LGE CMR permits differentiation between epicardial, transmural and sub-endocardial infarction. The technique relies on the fact that gadolinium washes out of the blood pool but accumulates in the extracellular space. Tissues with weak intracellular bonds and high amounts of non-cellular space, including necrotic tissue or fibrous scar, will develop higher concentrations of gadolinium than the surrounding healthy tissues. Scar detected by LGE CMR has been shown to closely match histologically-proven myocardial infarction [154].

3.3.7 Trans-thoracic echocardiography

Trans-thoracic echocardiography has the potential to identify areas of scarred or fibrotic myocardium. Early work focussed on regional wall thinning [155] and assessment of regional contractile function [156] while more recent work has focussed on the ability of speckle-tracking radial strain [157] and longitudinal strain [158] to better identify areas of regional akinesis. Other techniques include the use of 3D contrast echo [159] and pulse cancellation echocardiography [160] which have both shown some promise as tools to identify areas of scar.

3.3.8 Cardiac Computed Tomography (CT)

Tissue characterisation using cardiac CT has been used to identify areas of myocardial scarring. After an infarct, myocardial tissue replaced by fibrous scar and eventually, after several months, undergoes significant lipomatous metaplasia [161]. Using unenhanced CT, it is possible to identify the fat in infarcted myocardium. New-generation dual-source CT (DSCT) allows the integration of late-iodine enhancement (LIE) imaging and has been shown to correlate reasonably well (52% sensitivity, 88% specificity) with LGE derived CMR imaging [162].

3.3.9 Nuclear Imaging

Tracer uptake during Nuclear imaging using either positron emission tomography (PET) or single-photon emission computed tomography (SPECT) relies on adequate myocardial blood flow and myocyte viability. The finding of a fixed perfusion defect can either represent myocardial scar or viable hibernating myocardium. Differentiation between these two states can be further enhanced through an assessment of glucose uptake via Fluorine-18-labeled deoxyglucose (FDG) with hypocontractile regions exhibiting reduced perfusion but normal or increased FDG uptake representing likely hibernating myocardium. During head to head comparison, MIBI has been shown to consistently overestimate areas of myocardial scar tissue whilst FDG lacks the spatial resolution associated with LGE CMR [163].

3.3.10 Electro-Anatomical Mapping

Whilst LGE CMR has the capacity to directly visualise anatomic myocardial scar, the abnormal electrophysiological substrate extends beyond the dense anatomical scar, into regions of heterogeneous “boarder-zone” tissue [164] and may be optimally identified using electroanatomic mapping (EAM). The ability of EAM to assess myocardial viability on the basis of myocardial voltage has been validated against SPECT [165], PET imaging [166] and latterly LGE CMR [167–170] in both ischaemic and non-ischaemic cardiomyopathies. Furthermore, analysis of electrogram characteristics can also help to predict histologic properties of scar tissue [146].

3.3.11 Invasive Electroanatomical Mapping

During invasive EAM, intracardiac electrical activation is recorded in relation to anatomic locations in a particular cardiac chamber of interest, allowing the definition of 3D cardiac chamber geometry as well as delineating areas of anatomic interest such as regions of scar. Systems can be divided into contact and non-contact mapping systems. Contact mapping systems rely on recording local activation between two poles on a mapping catheter. The resulting bi-polar voltage map can be thresholded to reveal areas with a voltage outside of normal range for ventricular tissue, typically 0.5mV to 1.5mV.

Non-contact mapping systems utilise a multi-electrode array (MEA) catheter to simultaneously record endocardial activation over multiple areas [171]. The array is situated on a balloon with 64 electrodes allowing high density mapping from a single heartbeat. Advantages of this system include the ability to acquire multiple endocardial electrograms during a single cardiac cycle however this comes at the cost of greater inaccuracy in electrogram timing and morphology at greater distances from the MEA [172]. Work evaluating this system has already established that non-contact mapping can identify regions of electrically viable myocardium, which could be used to inform lead position, particularly among ischaemic patients [149].

3.3.12 Electrocardiographic Imaging

Electrocardiographic imaging (ECGI) is a novel, non-invasive 3D epicardial electrophysiology imaging modality. This technique uses 252 ECG electrodes mounted on a wearable vest to

reconstruct epicardial potentials from torso potentials, see Figure 11. These are displayed as electrograms and activation sequences (isochrones) on the epicardial surface of the heart [173].



Figure 11. The 252-lead vest records torso surface electrograms. Reproduced with permission from MEDTRONIC.

ECGI benefits from a non-invasive approach and is able to measure the activation across the whole heart simultaneously compared to the slower sequential mapping with EAM. Inverse ECG mapping technology is able to identify fibrotic tissue due to the abnormal electrical properties exhibited by scarred myocardium, specifically low-amplitude electrical potentials with broad fractionated electrograms typically in areas exhibiting delayed or slow activation [174–176]. A degree of discrepancy between CMR and EAM is expected as CMR can struggle to detect areas of homogenous microscopic diffuse fibrosis due to the low resolution of the image while inverse ECG EAM can be more sensitive at detecting zones of epicardial and transmural fibrosis but may miss sub-endocardial scar. Despite this, good correlation has been observed between areas of low voltage on ECGI and areas of scar, as identified on LGE CMR [177] with one study quoting an 89% sensitivity and 85% specificity at detecting epicardial scar [178].

3.4 DYSSYNCHRONY ASSESSMENT AND IDENTIFICATION OF THE SITE OF LATEST MECHANICAL ACTIVATION (LMA)

A paradox exists between the electrical substrate corrected by CRT, specifically dyssynchronous biventricular electrical activation and its mode of action, which is predominately mechanical and aims to enhance cardiac contractility by correcting the mechanical dyssynchrony and restoring the mechano-energetic efficiency of the heart. Intuitively, it would seem sensible to specifically assess the degree of mechanical dyssynchrony present, as this would both help patient selection and aid in the determination of the optimal LV pacing site. Dyssynchrony is the measure of dispersion in the timing of mechanical contraction of the various LV segments [179] and may be measured by a variety of different imaging techniques.

3.4.1 Trans-thoracic echocardiography

Early work assessing the utility of echocardiographic parameters of dyssynchrony to aid patient selection for CRT appeared promising. A systolic dyssynchrony index (SDI), calculated from tissue Doppler imaging (TDI) proved capable of retrospectively predicting enhanced clinical response in single centre work [180]. These benefits were also observed in a multicentre retrospective analysis where the use of baseline TDI imaging predicted not only functional and echocardiographic improvement but also identified patients who yielded prognostic benefit from CRT [181]. Speckle tracking radial strain analysis superseded TDI, as it was less dependent on the angle of incidence of the ultrasound beam and also appeared able to predict echocardiographic response in retrospective analysis [182].

Unfortunately, the utility of mechanical dyssynchrony assessment to identify CRT responders has not been reproduced in larger, prospective, randomised multicentre studies [183] and this has cast some doubt on the reproducibility of the technique. In addition, when all the various echocardiographic measures of mechanical dyssynchrony were analysed in a large, international multi-centre study, no single measure proved capable of improving patient selection for CRT [184]. Promisingly, newer techniques including longitudinal myocardial strain assessment [185] and 3D speckle tracking echo [186] appear more reliable and indicate an encouraging direction for future work.

Given the primary target of CRT is the restoration of coordinated myocardial contraction and those patients exhibiting mechanical dyssynchrony appeared to yield the most benefit from CRT, it seemed logical that the optimal site for LV lead deployment would be at the site of maximal mechanical delay. In a retrospective analysis where TDI assessment of mechanical activation was performed prior to CRT implantation, patients in whom the LV lead was situated at the site exhibiting the latest activation showed increased functional and echocardiographic improvements [121]. Superior response to CRT was also observed when the site of latest mechanical activation was targeted using tissue synchronization imaging (TSI) [187], 3D echocardiography [188], and speckle tracking [189]. The TARGET [119] and STARTER [122] trials prospectively assessed the utility of echocardiographic speckle-tracking 2-dimensional radial strain imaging to inform LV lead deployment. Echo guided lead implantation was associated with echocardiographic response rates (>15% reduction in ESV) of 70% & 57% respectively. Both studies showed increased rates of event free survival over empirical lead placement.

3.4.2 Cardiac MRI

CMR has several potential advantages when looking to characterise mechanical activation. These include greater reproducibility, less artefact secondary to patient habitus, detailed assessment of myocardial tissue characterisation as well as chamber size and volumes and greater spatial resolution. CMR can also assess strain in multiple planes allowing the assessment of both radial and longitudinal strain. A recent prospective, single-centre randomised study (CMR-CRT) showed the feasibility of performing an assessment of circumferential strain in order to identify the latest mechanically activated viable segment [190]. Several dyssynchrony assessment metrics have been proposed including myocardial tagging, displacement encoding with stimulated echoes (DENSE) and phase contrast tissue velocity mapping (TVM). Whilst myocardial tag data has been shown to predict functional improvement following CRT implantation [191], tag decay remains an issue and this led to the development of 3D volumetric change as a means of assessing both global LV dyssynchrony and assessing mechanical activation [192]. When compared to other mechanical dyssynchrony measures, volume change systolic dyssynchrony index (SDI) proved the sole predictor of chronic reverse remodelling [124].

3.4.3 Cardiac Computed Tomography (CT)

Cardiac computed tomography (CT) offers a potential benefit over CMR due to the fact that approximately 28% of patients undergoing CRT implantation have already received an implantable cardiac device rendering them unsuitable to undergo CMR scanning [193]. Cardiac CT is associated with submillimetre spatial resolution and can assess regional and global LV dyssynchrony by calculating the stretch of the endocardial surface throughout the cardiac cycle (stretch quantifier for endocardial engraved zones [SQUEEZ]) [194]. When assessed in patients undergoing an upgrade to a CRT pacing system, CT-SQUEEZ targets were associated with a similar improvement in AHR as the best achievable ($20.4\% \pm 13.7\%$ vs $24.9\% \pm 11.1\%$; $P=0.36$) [195]. In addition, delivering LV stimulation at a site identified using CT-SQUEEZ resulted in greater clinical response vs non-target segments (90% vs 60%, $P < 0.001$).

3.5 IDENTIFYING THE SITE OF LATEST ELECTRICAL ACTIVATION (LEA)

The primary substrate targeted during CRT is delayed electrical activation, typically manifest by a left bundle branch block pattern on the surface ECG. Detailed analysis of ventricular activation confirms a myriad of differing underlying conduction disturbances amongst even this group, with ischaemic patients displaying a particularly high degree of variability in activation [59]. The standard 12 lead ECG is therefore of limited use when looking to define the optimal site for LV stimulation and focus has shifted to more detailed methods of visualising electrical latency. In the context of LBBB, ventricular activation is initiated at the distal branching of the right bundle, with activation of the left endocardium occurring after a significant delay, as a result of slow conduction through the interventricular septum. Theoretically, the site of latest activation should exhibit the most dyssynchrony and as such would represent an ideal pacing site. Whilst some work appears to confirm the site of LEA is synonymous with the optimal pacing site [127], more recent analysis has shown optimal site exhibits late but not supremely delayed activation [196]. Sites demonstrating excessively delayed activity may in fact merely represent distal activation occurring within islands of non-viable tissue. A variety of different methods of identifying the site of latest activation have been described, as outlined below.

3.5.1 Q-LV & LV Lead Electrical Delay

An advantage of assessing electrical delay is that it can be performed both intra-procedurally and without the need for any additional mapping equipment. Singh et al, devised a measure of electrical latency called the Left Ventricular Lead Electrical Delay (LVLED) [126]. This marker of electrical delay was calculated during LV lead implantation by determining the onset of the surface ECG QRS complex to the onset of the sensed electrogram on the LV lead, and expressing the value (the Q-LV time) as a percentage of the baseline QRS interval. They identified that LVLED correlated with greater haemodynamic improvements (derived using transthoracic echo).

When dichotomised, patients with an LVLED of > 50% exhibited greater event free survival and reduced rates of hospitalisation. In a sub-study of the SMART AV Trial [110], patients were again dichotomised, although this time according to the median Q-LV value (95ms). Gold et al showed that implanting the LV lead at a site with a favourable Q-LV was independently associated with symptomatic improvement and greater reverse remodelling at 6 months [125].

Both of these studies retrospectively analysed the degree of electrical latency at the site of LV lead deployment however, Zanon et al evaluated whether Q-LV might be used to identify the optimal site in an individual patient by systematically screening all of the suitable coronary sinus veins [127]. A strong correlation was observed between Q-LV prolongation and improvements in acute haemodynamic response. Again a Q-LV value of greater than 95ms appeared significant, yielding an improvement in AHR of >10%, a finding which has been associated with predicting long term remodelling [47]. Crucially, in 96.8% of patients, the optimal haemodynamic performance was associated with delivering pacing therapy at the site exhibiting the latest electrical activation. A similar figure (85%) was observed by van Gelder et al in their evaluation of the effects of LV endocardial pacing amongst a cohort of non-responders to epicardial CRT [197]. The small discrepancy may be attributed to the larger cohort of ischaemic patients in this study.

An advantage of the LVLED approach is that the degree of electrical latency at a particular location is qualified against the baseline state, creating a relative value which can be used to compare the degree of latency between patients who may have a differing baseline QRS duration. Q-LV can only ever be quantified as an absolute value and as such a higher value may not always correlate to late activation in situations where the baseline QRS duration is excessively delayed. Despite this benefit of LVLED, not all analyses using this metric have confirmed its utility. In recent work, the acute haemodynamic effect of delivering CRT pacing from each cathode on an quadripolar LV lead was correlated against each location's LVLED. While a good correlation was observed between progressive electrical delay and improvements in haemodynamics across the cohort, this was not consistently the case at an individual level. Whilst in some patients, LVLED

and stroke work displayed a linear relationship, in others an inverse relationship was observed, see Figure 12 [198].

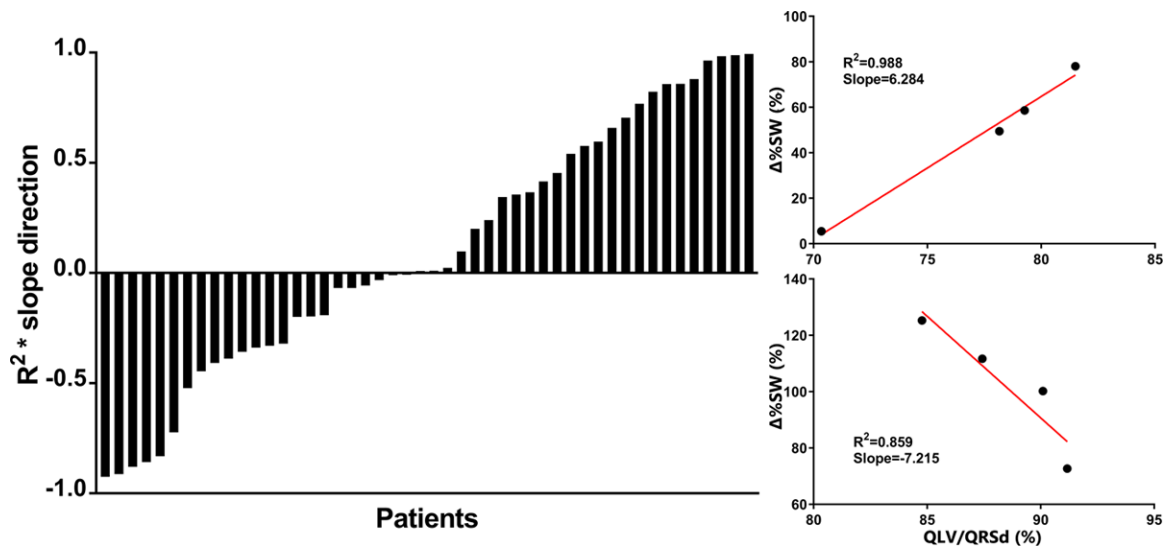


Figure 12. Distribution of the slope and coefficient of determination for percentage changes in SW ($\Delta\%SW$) and QLV/QRSD. The slope direction multiplied by the coefficient of determination (R^2) of the trend line fitted to QLV/QRSD and $\Delta\%SW$ for each patient. Values are arranged from the lowest to the highest value. There are 24 patients with a direct relation (positive slope) and 24 with an invert relation (negative slope). Examples of a direct relation (upper right) and an inverse relation (lower right) are shown [198].

Several hypotheses exist which may explain this finding. Firstly, LVLED was only tested along the course of the LV lead which was already positioned in an area of electrical latency with high LVLED values. Variation between the poles was thus relatively small. Animal models have shown that amongst patients with non-ischaemic cardiomyopathy the “sweet spot”, where LV stimulation will result in improvements in haemodynamics, is quite large. Thus, in contrast to the work of Zanon et al, where up to 11 sites were tested per patient, the analysis by van Everdingen et al evaluated just four sites in close proximity to one another. As such it is possible, markers of electrical latency may be able to identify a region where activation is likely to achieve improvements in haemodynamics but is a poor determinate of the optimal pacing site within that area, once a region has been identified.

3.5.2 Narrowing of the Paced QRS

Reductions in the paced QRSd during biventricular pacing may also aid identification of late activating tissue. Widening of the QRS after CRT implantation has been found to be an independent predictor of mortality or progression to heart transplantation [199] and achieving a reduction in the paced QRS has been shown to predict response in several studies [200] including via multi-variate logistic regression [201]. In other work, a reduction in paced QRS duration was found to be the only predictor of response [202]. However, this finding is disputed in other studies [203]. There is also no consensus as to whether delivering biventricular pacing at a site which achieves a narrowing of the paced QRS is associated with improvements in haemodynamics. Whilst some work has shown a correlation between narrowing of the QRS and improvements in AHR [196], this finding has not been consistently replicated [127].

3.5.3 Invasive Electro-Anatomical Mapping

Electroanatomical mapping has also been used to evaluate electrical activation and locate the site of LEA. Analysis of contact and non-contact mapping first data identified a “U shaped” pattern of activation during LBBB with depolarisation originating at a single septal breakthrough site [59]. Activation could not proceed directly from the anterior to the lateral wall, due to the presence of lines of block, forcing the depolarisation wave front to pass inferiorly around the apex. Crucially, even amongst patients who presented with LBBB on their surface ECG, the location of this line of block varied between patients, exposing the heterogeneity of this complex conduction disorder and the difficulty in establishing a universal site of LEA.

More detailed analysis of LV activation revealed heterogeneity in conduction velocities in both non-ischaemic and ischaemic patients at the site of LV stimulation in the lateral and posterolateral walls [149]. The location of these areas of slow conduction influenced the pattern and direction of wave front propagation. Whilst it was possible to mitigate the effects of positioning the lead in an area of slow conduction by altering the timing between LV and RV stimulation during CRT; locating and stimulating healthy, late activating tissue was consistently associated with superior haemodynamic improvements.

The anatomical constraints of transvenous, epicardial CRT mean that LV stimulation can only occur at a site accessible via a tributary of the coronary sinus. Coronary venous electroanatomical mapping allows the assessment of electrical latency exclusively within the coronary sinus [129]. A high degree of variability in the location of the site of LEA was observed between patients. Intra-

procedural assessment of latency utilising this technique is feasible and whilst of practical value to the implanting physician, is limited to only those sites accessible via the available coronary venous system.

3.5.4 Non-Invasive Electro-anatomical mapping of Electrical Activation

The heterogeneous nature of LV activation in patients with LBBB has also been described using ECGi. A key advantage of this technique is the ability to non-invasively identify the area of LEA and this approach has already been shown to allow peri-procedural guidance of the LV lead to the target site. ECGi can also compute an LV electrical dyssynchrony index and this metric appears may predict patients likely to respond to CRT and aid in identifying the optimal site during LV lead deployment [204,205].

3.5.5 Correlation between the site of LMA and LEA

One hypothesis advanced to explain the persistent issue of non-response to CRT is the existence of uncoupling of mechanical and electrical synchronicity. Whilst these two substrates can be assessed individually, performing an assessment of both may be preferable. Early work appeared to suggest that the site of LEA was synonymous with the area of LMA, when evaluated using non-contact EAM and TTE TDI [206]. Similar findings were observed when the LMA was assessed using CMR [207]. One explanation for this uniformity may be the crucial role played by aetiology and the disruptive effects of tissue heterogeneity. The impact of aetiology was better assessed by Fujiwara et al who included patients with both ischaemic and non-ischaemic cardiomyopathy in their study and identified a clear discrepancy between the site of LMA and LEA [208], see Figure 13. Unanimity between the LMA and the LEA site was only observed in 19% of patients.

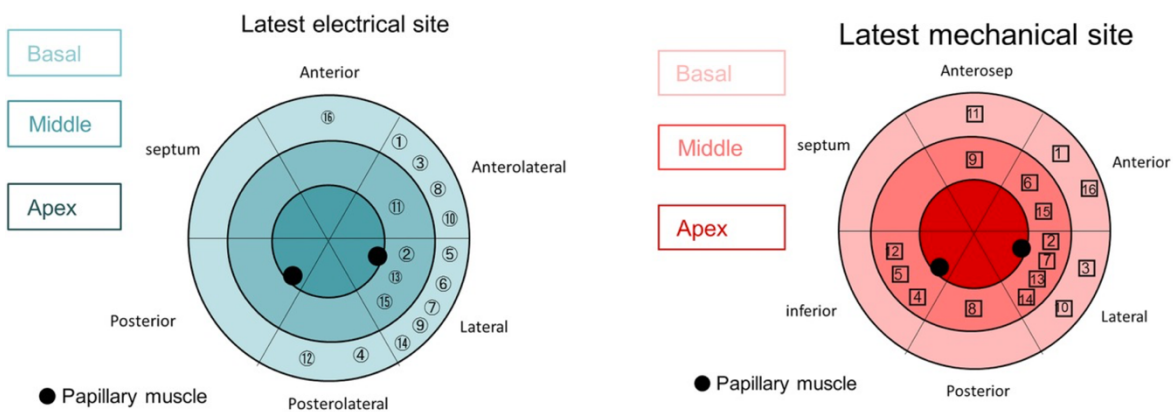


Figure 13. Comparison of sites of LEA (A) and LMA (B). The circled numbers refer to the patient numbers. Reproduced with permission from Pacing and Clinical Electrophysiology

3.5.6 Electrical Activation During RV Pacing & LBBB

Current class 1 indications for CRT include evidence of dyssynchronous electrical activation, manifest on the surface ECG by LBBB. Whilst there has been a great deal of focus on characterising the precise nature of LV depolarization which occurs during LBBB, activation during CRT occurs as a result of paced stimulation at the LV and typically, the RV apex. Whilst an RV paced event appears morphologically similar on the surface ECG to conduction resulting from LBBB, Eschali er et al set out to perform a more detailed examination. Non-invasive body surface mapping demonstrated clear differences in the depolarisation pattern of both the RV and LV during RV pacing and LBBB activation. Apical pacing resulted in slower RV conduction with lines of conduction detected around the pacing site [209]. LV depolarisation was also observed to be prolonged by RV pacing although lines of slow conduction were fewer and shorter in size in comparison to those observed during LBBB activation. The LV site of LEA was similar during both RV apical pacing and LBBB activation and was consistently located at the LV base.

3.5.7 Electrical Activation & RV Pacing Site Selection

RV pacing appears to result in delayed LV depolarisation and the deleterious effects of RV apical pacing have been widely acknowledged [210,211]. Positioning the RV lead in a septal position has been associated with beneficial haemodynamic effects [212]. Early work evaluating non-apical RV pacing conducted by Khan et al [213] showed that LV remodelling rates were unaffected by RV lead position while Kutuyifa et al [214] also highlighted a higher risk of ventricular arrhythmias. The SEPTAL CRT study randomly assigned patients to receive either an septal or apical RV lead and demonstrated no significant difference in clinical outcome [215].

It is worth noting that there is little consensus on a universal optimal site of LV lead deployment and instead an individualised approach which takes into account aetiology, tissue characterisation and the underlying electrical substrate appears to yield the greatest benefit [42]. Similarly, patient specific RV lead placement may represent a superior strategy, particularly when faced with limited viable LV pacing sites due to the anatomical constraints associated with transvenous, epicardial CRT. In a pilot study of seven patients, Kumar et al observed that patient specific RV

lead placement guided by real time assessment of the cardiac output resulted in significant acute haemodynamic improvements [216].

Electrical latency appears a useful marker when looking to identify the optimal LV pacing site [125,126] and a similar approach can also be used when looking to optimise RV lead position. In the INTER-V study, the measurement of paced RV-LV interlead electrical delay predicted mid-term CRT response [217]. In a blinded, randomised controlled trial which prospectively allocated patients to receive CRT with either RV apical pacing or RV pacing at a site guided by maximal electrical separation (MES), individualised RV lead placement was associated with increased rates of echocardiographic response [218].

3.6 SITE SELECTION DURING LV ONLY PACING

LV only pacing has also been proposed to avoid the negative sequelae associated with RV pacing by preserving intrinsic conduction via the right bundle branch. Different approaches to LV only pacing have been assessed for both epicardial and endocardial CRT.

3.6.1 LV Only Epicardial Pacing

Several comparative studies assessing LV only epicardial (LV_{EPI}) pacing timed to coincide with intrinsic RV activation have been performed. LV_{EPI} pacing has been shown to be associated with non-inferior outcomes [219–221], with some studies showing trends towards superior LV remodelling [222] and improvements in LVEF [223]. In all these studies, the LV lead was empirically placed in a lateral or posterolateral target vein and as such it is impossible to predict the implications of delivering LV_{EPI} pacing at an alternative site.

3.6.2 LV Only Endocardial Pacing

LV only endocardial (LV_{ENDO}) pacing has also been investigated. Activation of the LV endocardium during CRT is associated with a reduction in both LV and biventricular (BiV) activation time [224]. This is in part explained by the shorter activation path length but also earlier activation of fast-conducting endocardial tissue, which possess a higher conduction velocity. LV_{ENDO} pacing was

associated with greater improvements in AHR than could be achieved using conventional, transvenous CRT (BiV_{EPI}) [225]. Only biventricular endocardial CRT (BiV_{ENDO}) proved capable of yielding a similar haemodynamic improvement.

Much attention has been traditionally focussed on correcting the underlying electromechanical delay associated with LBBB by delivering LV stimulation at the site of latest activation, typically identified in the postero-lateral wall. An alternative approach is to try and replicate the activation sequence observed during normal sinus rhythm, where activation occurs initially at the left mid-septal endocardium [226,227]. When assessed, activation at this site results in an almost identical temporospatial activation envelope to that observed during normal sinus rhythm, especially when compared to BiV_{EPI}, LV_{EPI} and RV_{ENDO} pacing [228]. This can be achieved via a transvenous approach, using a bespoke delivery mechanism incorporating a custom pacing lead which is introduced transvenously into the RV and positioned against the RV septum, before being deployed through the interventricular septum until the left ventricular septum is reached but without perforating the LV septum [229]. One major benefit of this approach is it negates the need for long-term anti-coagulation, typically associated with lead based LV_{ENDO} pacing.

LV_{ENDO} septal pacing can achieve a haemodynamic performance similar to that observed during normal sinus rhythm in patients with preserved LV function [229]. The effects of LV_{ENDO} septal pacing have also been assessed in a small series of patients who fulfil current criteria for CRT implantation. A combination of RV_{ENDO} and LV_{ENDO} septal pacing achieved the greatest improvement in cardiac stroke work, suggesting that whilst the septum may represent a potential location to deliver stimulation in patients with impaired LV function, LV_{ENDO} septal pacing alone may not be sufficient to achieve optimal resynchronisation [230].

3.7 MULTI-MODALITY IMAGING & IMAGE FUSION TECHNOLOGY

3.7.1 Multi-Modality Imaging

A novel approach to site selection incorporates the fusion of two differing imaging modalities via multi-modality imaging in order to maximise the reliability of the acquisition. Bertini et al describe an excellent approach aimed at targeting late mechanically activating, viable tissue [231]. Patients first underwent a CMR scan where areas the myocardial wall displaying of > 75% LGE were excluded. The next stage of the “CRT Team” approach involved the use of 2D speckle tracking

Chapter 3

echocardiography which assessed global LV longitudinal strain in order to highlight the most delayed area between non-fibrotic segments. The highest frequency of reverse remodelling at six months (93.1%) was observed in the 58% of patients where the final lead position was concordant with the prespecified optimal site [231].

Another novel approach employs the fusion of pre-procedural CMR imaging with computer modelling to predict the optimal pacing site. In this series, a 3D navigation model was designed to rank the available sites for LV and RV lead deployment. Sites were graded to ensure the LV lead was directed into the segment with the lowest scar burden which exhibited the greatest mechanical delay whilst also maximising the geographic distance between the LV and RV pacing sites. The RV lead tip was directed to the area with lowest scar burden. The optimal location for the RV lead tip was assigned first followed by the preferential LV pacing site. At follow up, 74% of patients met the predefined echocardiographic criteria of a responder despite the fact that lead implantation was informed purely by fluoroscopy and visual assessment of the 3D models, and real time guidance was used [232].

3.7.2 Image Fusion and Guidance Technology

Optimal site selection can only be achieved when used in conjunction with a targeting system which can identify and inform pacing electrode deployment in real time during implantation. The use of fluoroscopy alone to facilitate targeted electrode deployment is challenging given the radiolucency of the cardiac silhouette and high variability in the rotation of the left and right sided chambers relative to one another. When previously evaluated, concordance between final fluoroscopic LV lead position & CT images was only observed in 35% of patients [233]. In over half of the cases studied, LV lead deployment had actually occurred in an adjacent segment, although this is hardly surprising given the relatively small size of an individual myocardial segment (order of magnitude, cms). As such, site selection and X-Ray co-registration are essential in order to ensure optimal electrode deployment.

3.7.3 Image Fusion with Fluoroscopic Coronary Sinus Balloon Venography

Both the TARGET and STARTER studies showed the benefits of targeting lead deployment at the site of latest mechanical activation, defined using TTE [119,122]. Unfortunately, in the STARTER study, it was only possible to deploy the lead at the target segment in 30% of patients due to issues with coronary venous anatomy and lead stability. Even in recent work where CMR was used to define the optimal pacing site, concordant LV lead positioning was only achieved in 52% of cases [190]. One approach to facilitate site selection at an achievable location subtended by a tributary of the coronary sinus is to evaluate both mechanical activation and coronary sinus anatomy. This can be achieved by fusing TTE derived 3D echo data with fluoroscopic coronary sinus balloon venography [120]. Use of this image guidance tool resulted in an LV reverse remodelling rate of 81% of patients, where concordance between final LV lead position and the site of LMA was confirmed. Whilst the use of coronary venous anatomy helps pre-procedural planning, this data was acquired via an additional invasive catheter study.

A more streamlined approach fusing peri-procedural fluoroscopic coronary sinus balloon venography with CMR imaging has also been developed [234], see Figure 14.

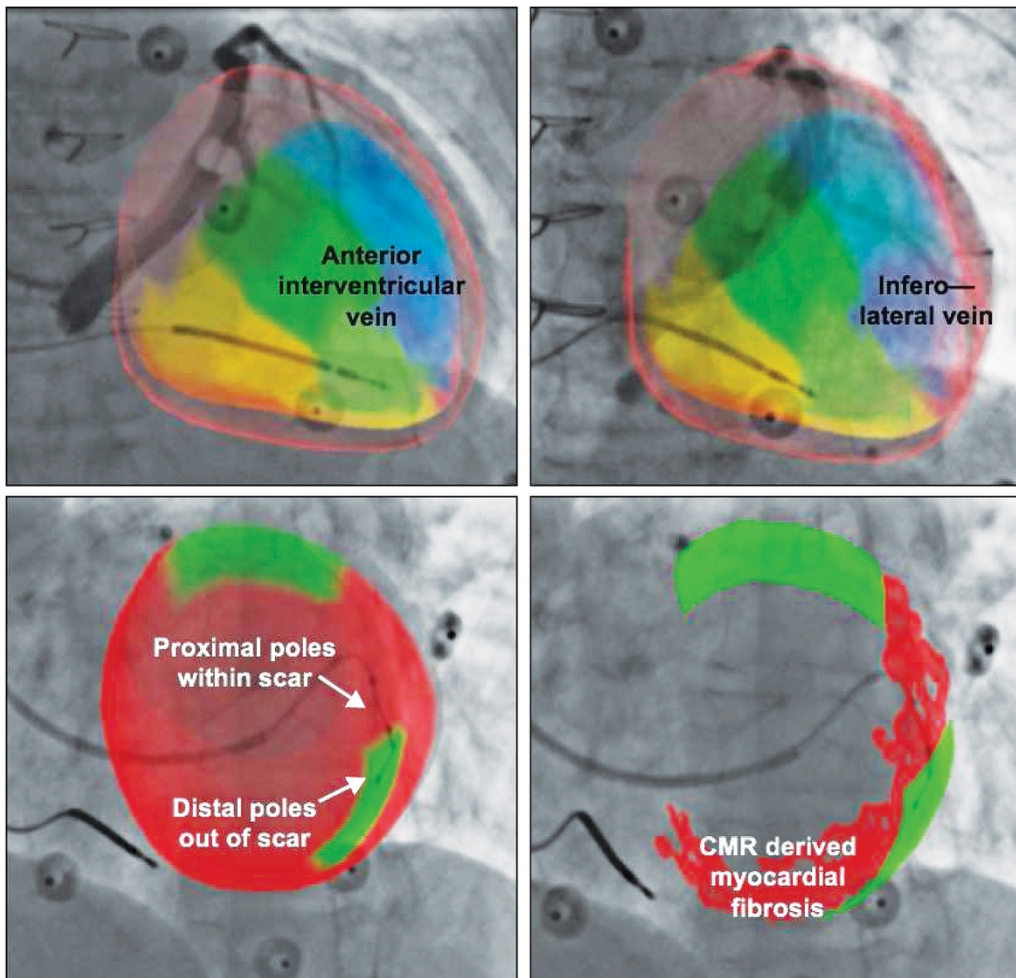


Figure 14. (Top left) Anteroposterior venogram with overlay of CMR-derived epicardial/endocardial shell with 16-segment American Heart Association model showing an anterior interventricular vein. The 3D CMR-derived shell has the same colours as displayed in the guidance platform as shown in Figures 2 and 3. Infero-septal, antero-septal, and anterior segments are coloured in yellow, green, and blue, respectively. (Top right) left anterior oblique (LAO) 20 venogram with automated rotation and alignment of the 16-segment model with the x-ray. Inferolateral veins are demonstrated. (Bottom left) LAO 40 projection. Positioning of a quadripolar left ventricular lead into a preselected target segment (green). (Bottom right) LAO 40 projection, alternate view with CMR-derived scar distribution (red). Attempted positioning and pacing using left ventricular poles out of regions of scar. [234] Reproduced with permission due to the creative commons license.

A major benefit of this system is the integrated nature of the GuideCRT platform (Siemens Healthineers, Erlangen, Germany). Image processing is automatic with manual verification. A quantitative analysis of late gadolinium enhancement is exported including information on scar location, burden and transmuralty. In addition, regional motion analysis of volume vs. time is

plotted via endocardial tracking for each of the 16 myocardial segments, allowing identification of the latest activating region, see Figure 15.

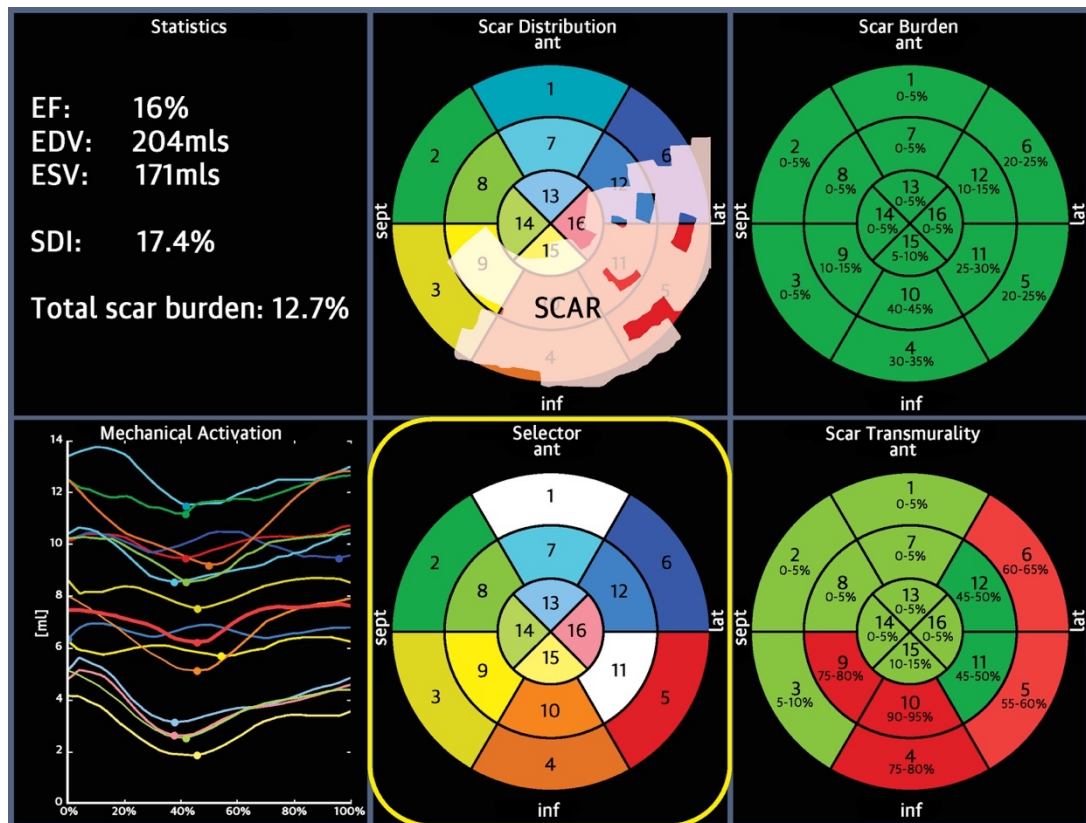


Figure 15. This display screen is seen following the processing of the CMR dataset and is mimicked on the large screen in the catheter laboratory. Total scar burden calculated as a mean of all myocardial segments. (Top middle) Scar distribution denoted in grey upon an American Heart Association 16-segment model. (Top right) Scar burden (% scar per myocardial segment volume), displayed in 5% ranges. (Bottom right) Scar transmurality demonstrating the mean transmurality from endocardium to epicardium. Those segments >50% transmural myocardial fibrosis are also denoted in red. (Bottom left) Mechanical activation curves for the 16 segments, corresponding to the colours shown in the middle panels. Endocardial tracking of the left ventricle provides absolute changes in the volume per segment (ml, y axis) over the cardiac cycle (0% end diastole, 30% to 50% end systole, 100% end diastole). Because these are absolute volume changes, the apical segments are always at the bottom because they have a smaller start and end volume. When the user hovers over a segment in the top middle panel, the associated volume time curve appears in bold; in this case, the target posterolateral segment is shown. (Bottom middle) Target selection panel. Upon reviewing the scar location, burden, transmurality, and mechanical activation curves, target segments are chosen (seen here in white; basal anterior, mid-posterolateral). EDV 1/4 end-diastolic volume; EF 1/4 ejection fraction; ESV 1/4 end-

systolic volume; SDI 1/4 systolic dyssynchrony using endocardial tracking of CMR cine images in short and long axis; Reproduced with permission due to the creative commons license. [234].

Image processing has now been accelerated to the stage (25 ± 8 mins) that the patient can undergo a CMR immediately prior to their CRT implant and by the time CS venography has been performed, image co-registration can be performed without delay.

Nuclear perfusion imaging can also usefully delineate areas of viable (non-scared) myocardium which display late activation [235]. Again as coronary venous anatomy is not delineated on SPECT imaging, geometric alignment, landmark-based registration and vessel-surface overlay were used to fuse the 3D venous anatomy with the epicardial mesh derived from the SPECT images [236], see Figure 16.

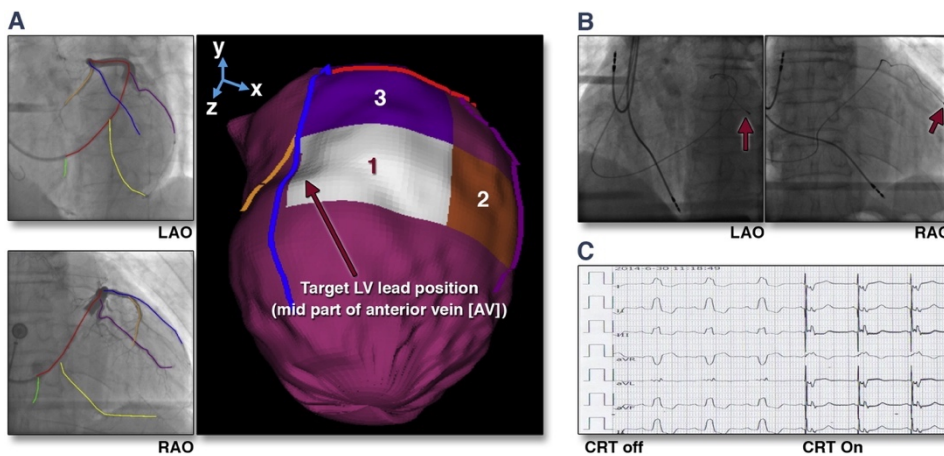


Figure 16. (A) Target venous site for LV lead placement. Major LV veins were drawn on fluoroscopic venograms, reconstructed to a 3D structure, and fused with SPECT LV epicardial surface. The mid part of AV (blue line) was aligned with the optimal segment (white segment) and so was targeted for lead placement. (B) Post-implant fluoroscopy. The LV lead was placed using the guidance in (A). The post-implant images show that the LV lead (red arrows) was on target. (C) Post-implant electrocardiogram. The QRS duration decreased from 168 to 140 ms immediately after the cardiac resynchronization therapy (CRT) device was turned on. RAO 1/4 right anterior oblique. Reproduced with permission from JACC: Cardiovascular Imaging [236]

3.7.4 Image Fusion and Guidance Technology Incorporating CT Derived Coronary Sinus Venography

Whilst it is possible to visualise the coronary sinus using CMR [237], direct imaging of the sub-branches can be difficult to consistently achieve. CT however is capable of accurately delineating the coronary venous tree with submillimetre spatial resolution via rapid acquisition, 3D, isotropic, whole heart data sets [238]. Co-registration between pre-procedural CT derived volumetric datasets and intra-operative 2D image acquisitions is more straight forward and can be performed using both a feature-based and an intensity-based methods [239]. Work evaluating the use of dual-source CT to both inform site selection and identify an overlying tributary of the contrary sinus subtending this area is currently ongoing [240], see Figure 5.

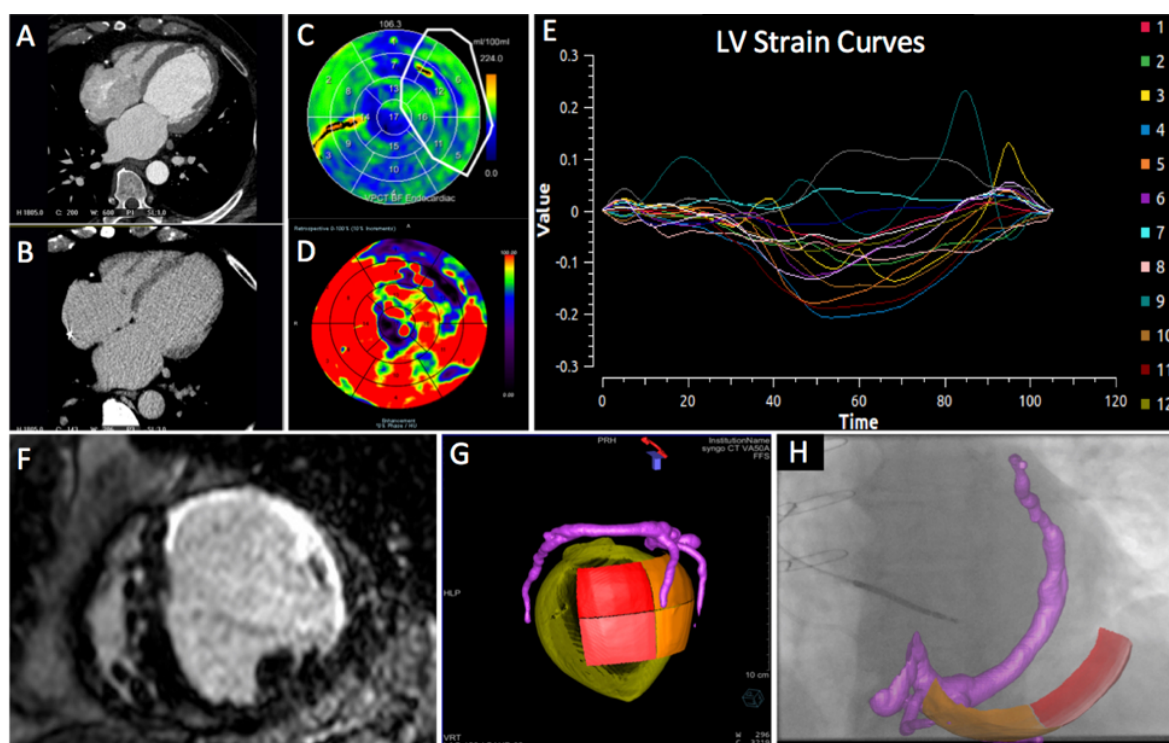


Figure 17. Series of DECT-derived scar and image overlay of the coronary sinus and optimal target segment derived from CT strain measurements from one patient: Retrospective CCT demonstrating calcification in a Left Anterior Descending (LAD) and circumflex territory infarct (A). Dual energy CCT demonstrating subtle ventricular scar in the LAD and circumflex territory (B). Late iodinated enhancement plotted on American Heart Association (AHA) 17 segment bull's-eye plot suggesting scar in the LAD and circumflex territory but also artefact from an existing RV pacing lead in the basal to mid antero-septum (C). First pass iodine uptake plotted on an AHA 17 segment bull's-eye plot showing what we believe to be residual iodine predominately in the LAD and circumflex territory (D). CCT-derived dyssynchrony curves calculated

by myocardial strain (E). Cardiac magnetic resonance short axis image of the mid LV showing late gadolinium enhancement of the same patient taken two years prior to any device implantation for comparison purposes (F). Pre-procedure DECCT-derived coronary sinus segmentation fused with latest mechanical activating segments determined from DECCT-derived strain (G) co-registered and overlaid onto live fluoroscopy using fusion software (H).[240]

Chapter 4 Strategies To Improve Response To CRT:

Biventricular Endocardial Cardiac Resynchronisation

Therapy

This section has been adapted from *Understanding non-response to cardiac resynchronisation therapy: common problems and potential solutions* (Sieniewicz, Gould, et al., 2018).

4.1 INTRODUCTION

The persistent rate of non-response to transvenous, epicardial CRT has led to the development of novel forms of undertaking CRT. Of these, biventricular endocardial pacing (BiV ENDO), where LV stimulation occurs from within the LV cavity, holds a great deal of promise. This technique is associated with several advantages over epicardial activation. BiV ENDO pacing can be achieved using several different approaches including the use of novel, leadless pacing.

4.2 BENEFITS OF BIVENTRICULAR ENDOCARDIAL PACING

A large body of evidence exists highlighting the potential benefits of BiV ENDO CRT.

4.2.1 Access to sites

Failure to implant an LV lead in a tributary of the coronary sinus during a transvenous, epicardial CRT procedure occurs in around 5-15% of cases [27,241,242]. Improvements in delivery kit [243] in conjunction with greater operator experience and the widespread adoption of quadripolar pacing leads [244] mean that in a more recent series, failure to implant an LV lead now occurs in under 5% of cases [245]. This can occur due to difficulty cannulating the coronary sinus ostium or passing the LV lead into a CS branch, unsatisfactory pacing parameters or phrenic nerve stimulation associated with LV pacing. Where LV lead implantation is feasible, it is confined to the available anatomy of the CS. Consequently, the final lead position is dependent on the presence of a suitable target vein and when none exists, it may be necessary to accept a sub-optimal position. In addition, around 26% of patients undergoing an upgrade procedure from a pre-existing bradycardia pacing system may have central venous stenoses preventing the implantation

of a transvenous LV lead [246]. In this population, it can prove impossible to implant an LV lead in 20-50% of patients [247,248].

BiV ENDO pacing is not reliant on the CS anatomy and instead, operators can choose to deliver stimulation at any site within the LV cavity. This allows for customisation of the stimulation site based on the patient's pathology and physiology. In addition, whilst lead based pacing systems may still encounter issues such as central venous stenosis and occlusion, particularly in the upgrade population, newer wireless pacing systems which can be delivered via a retrograde aortic approach eliminate the need for central venous access [249].

4.2.2 Phrenic Nerve Stimulation and Activation Threshold

Clinically relevant phrenic nerve stimulation can complicate LV lead deployment during transvenous, epicardial CRT implantation and this complication is encountered in over 20% of patients at implant or at follow up [250]. Unfortunately, the likelihood of encountering PNS increases when the lead is deployed at sites most associated LV reverse remodelling. Reducing the LV pacing output is a recognised technique for overcoming PNS and it's important to note that endocardial capture thresholds appear lower than equivalent parameters observed during BiV EPI [251]. In addition, if PNS is encountered during implantation of a BiV ENDO pacing system, the operator has the freedom of the entire LV cavity to select an alternative pacing site.

4.2.3 Activation Velocity

Endocardial stimulation of the LV facilitates more rapid myocardial depolarisation as wave front propagation occurs along the shorter endocardial surface of the heart. Several studies have also demonstrated enhanced conduction velocities associated with stimulation of endocardial tissue [224,252,253]. One hypothesis for this more rapid activation is the earlier recruitment of fast conducting Purkinje fibres with the capability of quickly disseminating activation. However, Purkinje fibres are largely electrically isolated from the surrounding myocardial tissue and require direct fibre stimulation [254]. Additionally, given the Purkinje fibres form a loose network within the LV endocardium, other factors are thought to play a more central role.

Hyde et al set out to establish a greater understanding of Fast Endocardial Conduction (FEC). Non-Purkinje sub-endocardial tissue conducts impulses faster than either mid-myocardial or epicardial fibres [254]. Instead fibre orientation and anisotropy appear critical [253,255] in addition to higher gap junction [256] and sodium channel [257] density and increased cell area at the endocardium [258].

Despite biventricular endocardial stimulation being associated with more rapid conduction velocities, it was not associated with a reduction in LV endocardial activation time (LVAT) over biventricular epicardial pacing, see Figure 18 [87].

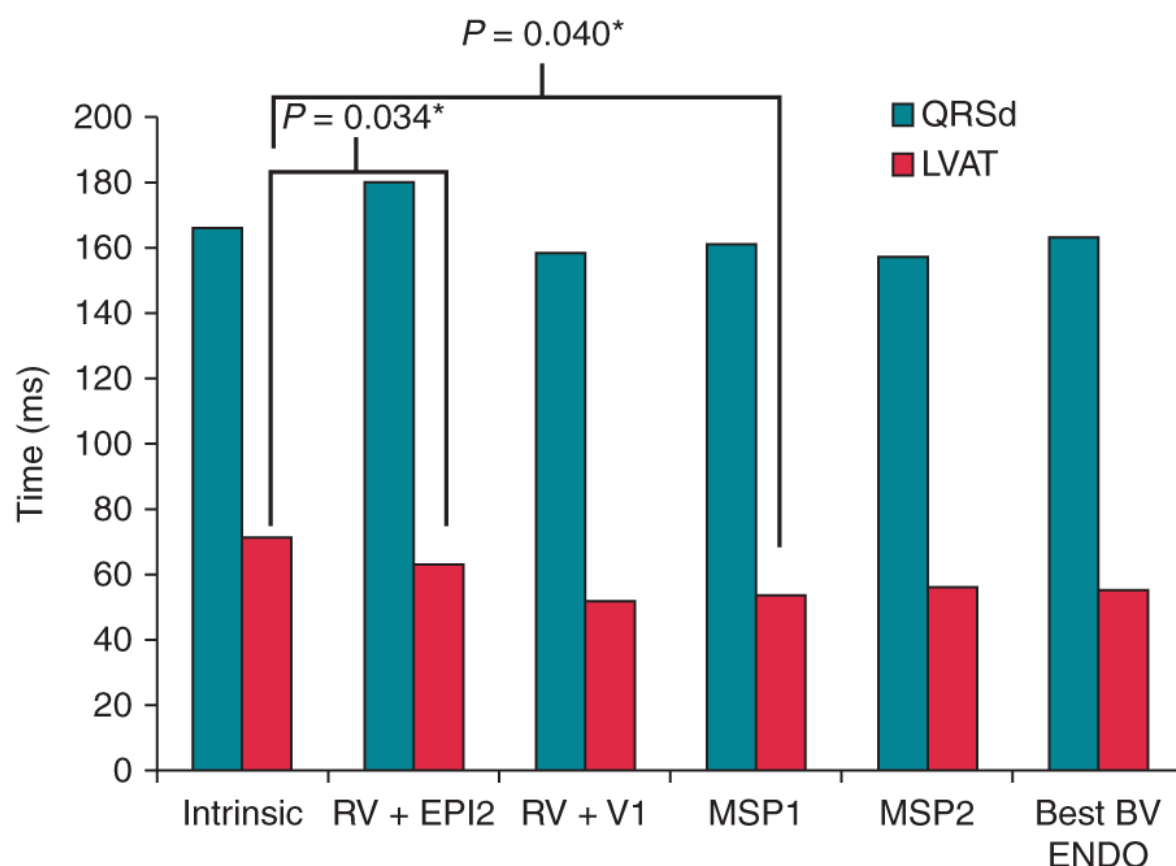


Figure 18. Left ventricular endocardial activation time and QRS duration for each pacing modality—mean times in ms for the 12 patients with full NCM data. *Statistically significant (no significant difference in QRSd or LVAT for all other pacing modalities shown compared with RV + V1) [87].

This replicates both animal work [259] and human data [225] which consistently show biventricular epicardial pacing achieves shorter LVAT than endocardial pacing. This phenomenon can be explained by evaluating the physiological differences associated with epicardial and endocardial LV activation in the context of electrical dyssynchrony. Firstly, during LV endocardial

stimulation, depolarisation is initiated at a single point whereas during LV epicardial pacing, by the time the stimulus has reached the endocardium, the wave front has become more dispersed, resulting in more widespread activation of the LV endocardium, and a paradoxically shorter LVAT.

4.2.4 Arrhythmogenesis

Traditional CRT delivers electrical stimulation to the epicardial surface of the LV wall. This pattern of activation is juxtaposed to the sequence exhibited during intrinsic myocardial activation which follows an endocardial to epicardial course. Reversing the normal depolarisation sequence is thought to promote repolarisation heterogeneity, which can prolong the QTc interval in susceptible patients and result in malignant arrhythmias [260–263]. In contrast, BiV ENDO pacing was associated with a reductions in both QT dispersion and T peak to end, two important markers of dispersion of repolarisation [264].

4.3 IMPROVING CRT RESPONSE THROUGH BIVENTRICULAR ENDOCARDIAL PACING

Increasing evidence supports the hypothesis that BiV ENDO pacing has the capability to achieve greater electrical resynchronisation and consequently, maximise response to CRT. Traditionally, BiV ENDO pacing has been performed in a relatively small number of patients, typically those with failure to achieve conventional CRT or those that have been non-responders. The recently published ALSYNC study was the first multi-centre study of LV endocardial pacing and demonstrated the feasibility and safety of LV endocardial CRT delivered through the atrial trans-septal approach [265]. In 138 patients with either prior suboptimal response to conventional CRT, failure of LV lead implantation or suboptimal coronary venous anatomy, the investigators achieved a high implant success rate (89.4%), with stable pacing parameters and an 82.2% freedom from complications at 6 months. Furthermore, clinical and echocardiographic improvement was 59% and 55% respectively in a group with prior non-response suggesting that LV endocardial pacing may overcome the issue of poor response to epicardial CRT. These figures are reinforced by a large meta-analysis of BiV ENDO which confirmed a meta-analytical echocardiographic response rate of 63.3% [266].

4.4 BIVENTRICULAR ENDOCARDIAL PACING SYSTEMS

4.4.1 Lead Based Pacing Systems

Chronic BiV ENDO CRT has traditionally been delivered via a pacing lead delivered via either a trans ventricular-septal or atrial-septal puncture. Due to the risk of thrombus formation resulting in systemic embolization, lead based LV endocardial pacing requires lifelong anti-coagulation. In a recent meta-analysis, the stroke rate was found to be 2.5 per 100 patient years [266]. Often, these events were attributed to periods of reduced anticoagulation given the difficulty associated with maintaining a therapeutic INR.

Following a trans-septal implant, the potential also exists for an adverse interaction between the mitral valve and an LV lead which passes through it. The presence of a pacing lead can worsen valvular regurgitation and this phenomenon has been acknowledged with right sided leads. Reassuringly in the largest series of trans-septal LV endocardial pacing to date, no system related valvular complications were recorded. Instead, echocardiography showed reductions in mitral regurgitation as a result of improved LV function [265]. The other major concern is the increased risk of mitral valve endocarditis should the system become infected. Secondary infectious foci including both cerebral and renal abscess formation are associated with the systemic embolization of vegetations.

4.4.1.1 Atrial Trans-septal

Lead based BiV ENDO is predominantly delivered via the atrial trans-septal approach [267]. Superior and inferior access is frequently required in order to puncture the atrial septum and successfully position the lead in the LV although several refinements of this procedure have been described.

4.4.1.2 Ventricular Trans-septal

Ventricular trans-septal techniques allow the deployment of the lead using only superior access, eliminating the need for femoral punctures [268]. This approach may be associated with both a lower risk of stroke and disruption to mitral valve function by eliminating the presence of pacing

leads in the left atrium crossing the mitral valve, although a target INR of 2.5-3 is still recommended [268].

4.4.1.3 Apical Trans-Septal

A hybrid surgical/percutaneous approach has also been described where the LV apex is accessed via a mini-thoracotomy facilitating the deployment of a lead at the LV apex, which is then tunneled up to a generator, implanted in the conventional sub-clavicular position [269]. Whilst the results from this series of 20 patients appear promising, this is a more invasive option and a higher target INR of 3-3.5 is recommended.

4.4.2 Leadless Pacing Systems

Whilst chronic BiV ENDO delivered via a pacing lead currently requires ongoing anti-coagulants due to the risk of thrombus formation, newer wireless technology almost entirely eliminated this risk. Formal anti-coagulation is not required and this development increases the likelihood of endocardial pacing becoming more widespread.

4.4.2.1 Trans-Arterial Leadless LV Endocardial Pacing

A leadless BiV ENDO CRT pacing system has been developed, which eliminates the need for any form of pacing lead to be present within the left ventricle. Instead stimulation is delivered to the endocardial surface of the heart acoustically from an ultrasound (USS) pulse generator, implanted subcutaneously in an intercostal space, .

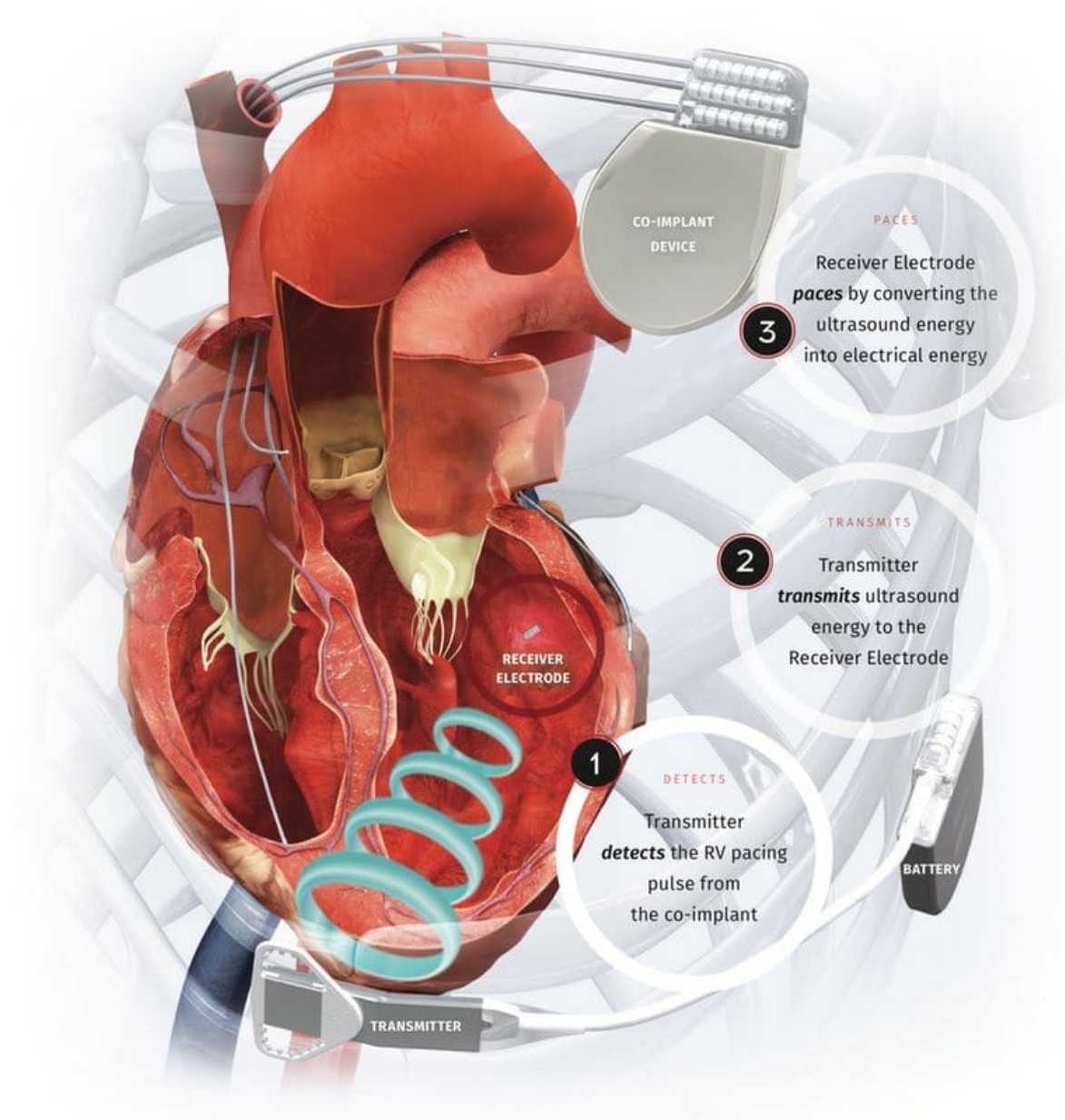


Figure 19. The WiSE CRT wireless biventricular endocardial pacing system. Reproduced with permission from EBR systems, Sunnyvale, California, USA.

The USS waves stimulate a small receiver-electrode which is deployed percutaneously via the femoral artery, into the LV cavity. Acoustic USS energy is converted to an electronic pacing pulse by the receiver electrode. The pulse generator is triggered by RV pacing, resulting in near simultaneous (within 3ms) LV & RV endocardial activation.

Whilst co-axial alignment of the USS pulse generator and pacing electrode is desirable, the USS transmitter uses beam-forming to direct the energy towards the pacing electrode, minimising the amount of energy required. Refinements of this generator mean it can now be implanted via a small horizontal incision and is attached to a dedicated battery, typically placed in the mid-axillary

line via traditional lead tunnelling techniques. Battery life of the current system is typically quoted at three years, but newer battery technology currently nearing release is expected to double this longevity to over six years.

Early clinical studies evaluating this system confirmed implantation was safe and capable of achieving consistent biventricular capture [249] whilst more recent work has shown the system to be highly efficacious and associated with a clinical response rate of 84.8% [270].

4.4.2.2 Trans-Venous Leadless LV Endocardial Pacing

The most commonly encountered complication associated with the use of the WiSE CRT system is femoral arterial access complications. In addition, not every patient has suitable anatomy to allow sufficient arterial access to allow the insertion of the electrode delivery catheter. Ischaemic heart disease is common in this population and as such, concurrent peripheral vascular disease is frequently encountered.

A method of trans-venously accessing the LV cavity via an atrial trans-septal puncture has been described to facilitate deployment of the pacing electrode [271]. The patient is first anaesthetised and trans-oesophageal echocardiography (TOE) is used to confirm the absence of left atrial appendage thrombus. Right femoral venous access is used to perform a trans-septal puncture with an 8Fr SL1 sheath using a Baylis NRG radiofrequency trans-septal needle under TOE guidance, see Figure 20. After full heparinization the sheath can be upsized (75cm-12 Fr Mullins sheath) and positioned across the mitral valve facilitating access to the lateral LV endocardial wall, see Figure 21. The WiCS[®]-LV delivery catheter can then be used to deploy the leadless pacing electrode in a favourable position.

WiSE CRT implantation is commonly performed by electrophysiologists who are typically more comfortable obtaining trans-septal access than managing wide bore arterial access and as such, this route holds a great deal of promise. Early series evaluating its use have confirmed the safety of this approach [272].

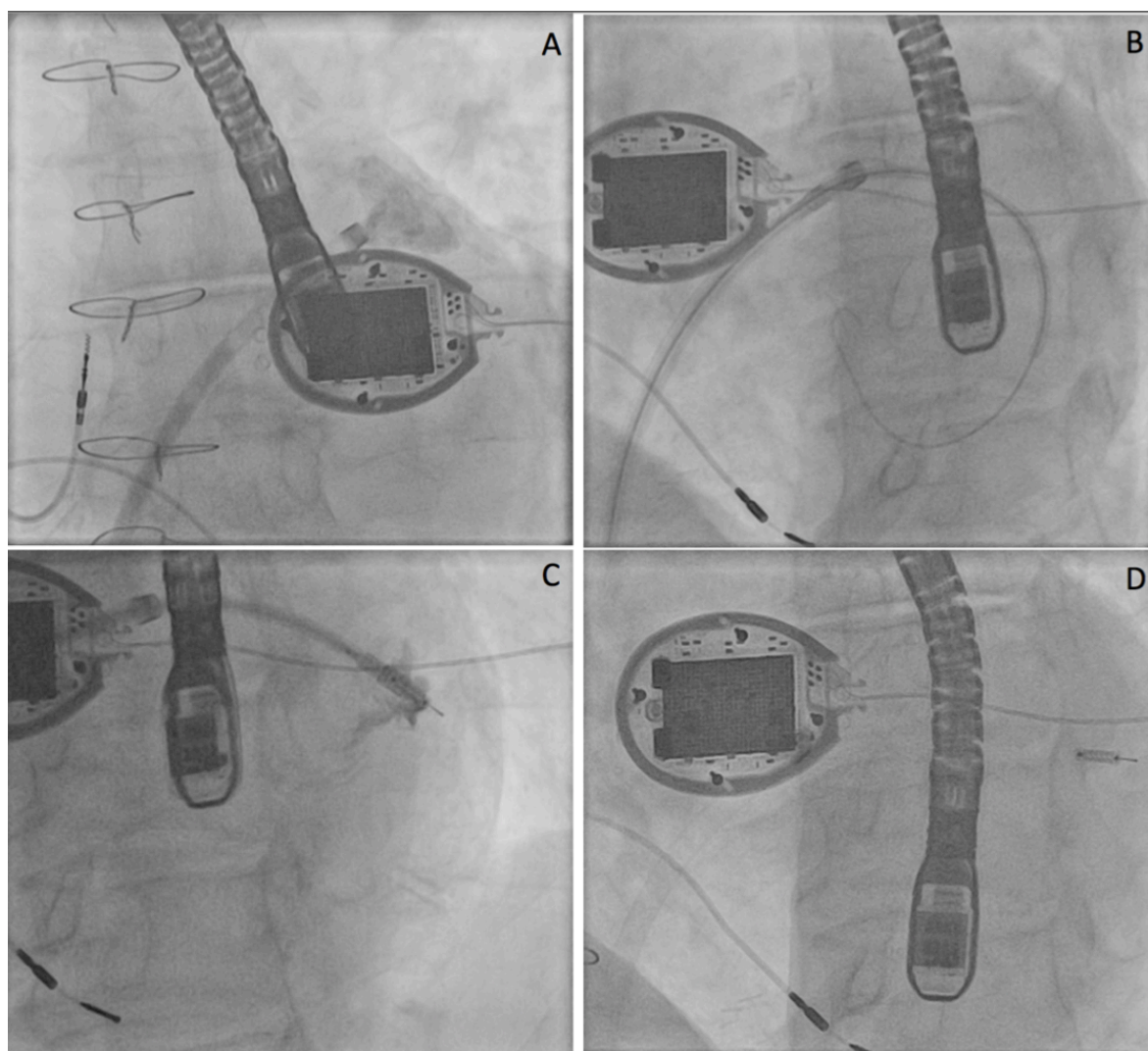


Figure 20. Multi-panel plot showing the transeptal deployment of a WiCS®-LV pacing electrode.

The atrial septum is identified (A) before a puncture is made and crossed with a guide wire (B). The WiCS®-LV delivery catheter can then be passed across the septum allowing the leadless pacing electrode to be deployed in the lateral wall (C). The device is detached from the delivery mechanism and the catheter is withdrawn (D)

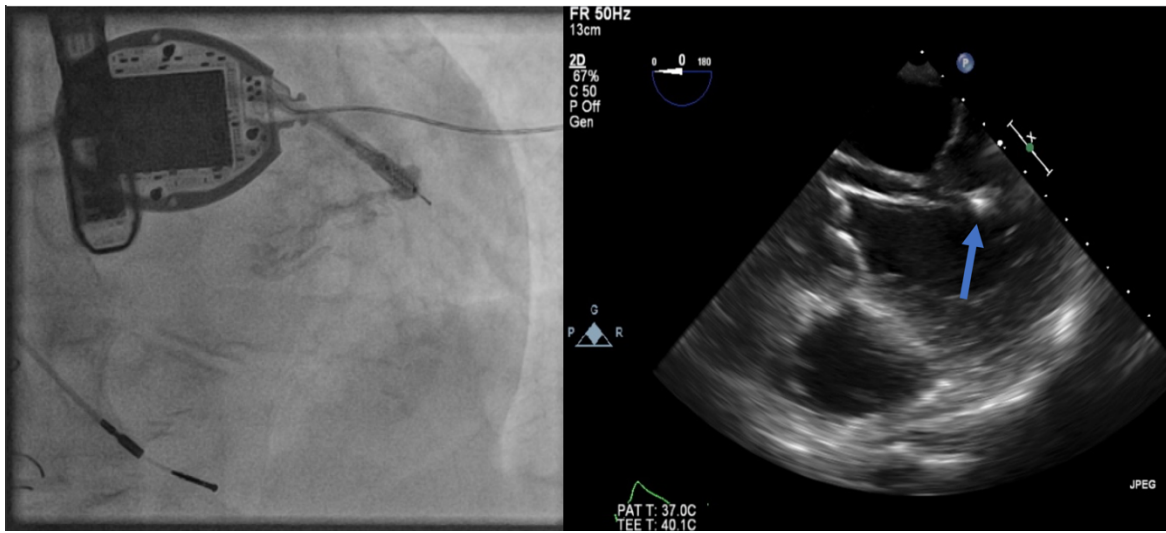


Figure 21. The WiCS®-LV delivery catheter (blue arrow) is advanced across the septum and through the mitral valve

Chapter 5 The Superiority of Biventricular Endocardial Pacing Over Biventricular Epicardial Pacing

5.1 INTRODUCTION

BiV ENDO stimulation has several advantages over conventional transvenous, epicardial CRT. Unconstrained by the anatomical limitations of the coronary sinus, LV stimulation can occur from any location. This also helps reduce phrenic nerve stimulation as areas which result in diaphragmatic pacing can be avoided. In addition capture thresholds with BiV ENDO pacing are typically lower than those required to perform BiV EPI [251]. LV activation occurs more rapidly [224,252,253] in part due to the shorter conduction path length associated with endocardial stimulation but also, depolarisation occurs more rapidly due to the intrinsic properties of endocardial tissue [224,253,255–258].

These benefits have led to the hypothesis that BiV ENDO CRT has the capability to achieve a greater degree of electrical resynchronisation than BiV EPI CRT and consequently, may result in more widespread response to treatment. This notion is reinforced by a large meta-analysis of BiV ENDO which revealed an echocardiographic response rate of 63.3% [266]. Previous work has confirmed BiV ENDO CRT is associated with significant improvements in both acute haemodynamic response [41,42,196,197] and longer term outcome [197,265], even amongst patients who have previously failed to respond to BiV EPI CRT. However, despite animal data revealing the superiority of BiV ENDO stimulation over BiV EPI pacing when delivered on opposing sides of the myocardium [259], most subsequent work has failed to replicate these benefits in human subjects [41,42,197].

We set out to investigate the hypothesis that BiV ENDO CRT would prove superior to BiV EPI pacing at the same stimulation site. Furthermore, given the widely acknowledged benefits associated with BiV ENDO stimulation, we sought to discover whether any BiV ENDO pacing location could yield an inferior haemodynamic response to that achievable using BiV EPI pacing.

5.2 METHODS:

5.2.1 Inclusion Criteria

Patients on optimal medical therapy (OMT) meeting European Society of Cardiology (ESC)[34] and/or Heart Rhythm Society (HRS)[273] criteria for CRT or those who had failed to respond to conventional CRT underwent an acute hemodynamic study. In all centres the procedures were undertaken following ethical approval from the local institution and all patients gave informed consent. The centres included in the analysis were Johns Hopkins University (Maryland, USA)[41]; University of Bordeaux (Bordeaux, France)[42]; Catharina Hospital (Eindhoven, the Netherlands)[197]; University of Oxford (Oxford University Hospitals NHS Foundation Trust) & Guy's and St Thomas' NHS Foundation Trust (London, United Kingdom)[196,225].

5.2.2 Data Collection

Data was only collected where an assessment of both BiV EPI CRT and BiV ENDO CRT had been undertaken. Acute haemodynamic response (AHR), a reproducible marker of acute LV contractility, was used to assess the efficacy of each pacing strategy. BiV EPI CRT pacing was delivered through the patients' own chronically implanted CRT system via an LV lead placed within the coronary sinus. BiV ENDO CRT pacing was delivered via an RV and LV endocardial catheter with simultaneous left ventricular & right ventricular (VV) timings. In all cases AHR (LV-dP/dt_{max}) was measured via a pressure wire placed directly into the LV cavity as previously described [196] and expressed as the change in the maximum rate of left ventricular pressure, from a baseline control state [41,42]. Where multiple measurements were taken in a particular location, an average value was used.

The optimal endocardial pacing location was defined as the pacing site where delivering temporary biventricular pacing resulted in the greatest change in AHR from baseline AAI pacing- or DDDR pacing for those with no underlying rhythm (% change in LVdP/dt_{max}). The sub-optimal biventricular endocardial pacing site was defined as the pacing site where delivering temporary biventricular pacing resulted in the least change in AHR from baseline pacing. BiV EPI pacing was performed at a single site only, due to immovable nature of the chronically implanted LV lead. Patient data was pooled from all the contributing centres. Individual data from these centres has previously been published [41,42,196,197].

5.2.3 Statistics

Continuous variables with a Gaussian distribution were described using mean values \pm standard deviation. Significance testing was performed using paired t tests where possible. AHR and electrical data passed the Shapiro-Wilk test for normality. Results were considered significant at $p < 0.05$. Analysis was performed on PASW Statistics 23 (SPSS Inc., Chicago, Illinois).

5.3 RESULTS:

5.3.1 Patient Characteristics

A total of 81 patients across the five centres underwent a study assessing both endocardial and epicardial biventricular pacing. Patient characteristics for the entire cohort are shown in Table 2.

Table 2. Patient demographics

	Mean \pmSD or Numbers (%)
Patients	81
Age (years)	66.8 \pm 10.6
Male (%)	74 (91.4%)
Female (%)	7 (8.6%)
LVEF (%)	25.1% \pm 7.4
NYHA	2.9 \pm 0.5
QRS duration (MS)	163.4 \pm 29.9
Aetiology	
Ischaemic (%)	39 (48.2%)
Dilated (%)	42 (51.9%)
Rhythm	
Sinus (%)	67 (82.7%)
AF (%)	8 (9.9%)
Paced (%)	6 (7.4%)
Morphology	
LBBB	63 (77.8%)
IVCD	6 (7.4%)
RBBB	3 (3.7%)
RV Paced	7 (8.6%)
BiV Paced	2 (2.5%)

5.3.2 Optimal Endocardial Biventricular Pacing vs Optimal Epicardial Biventricular Pacing

81 patients underwent an assessment of LV pacing comparing optimally delivered BiV ENDO pacing against BiV EPI CRT. BiV EPI CRT was performed via the chronically implanted LV lead. The site of stimulation varied due to the CS anatomy, however, a postero-lateral location is typically targeted at implantation. The optimal improvement in AHR was recorded for each pacing modality, see Figure 22. Optimally delivered BiV ENDO proved a superior pacing strategy 80% of the time and yielded a mean increase in AHR of $24.4\% \pm 18.4\%$. BiV EPI CRT meanwhile as associated with a mean improvement of $12.7\% \pm 16.6\%$ ($p < 0.01$).

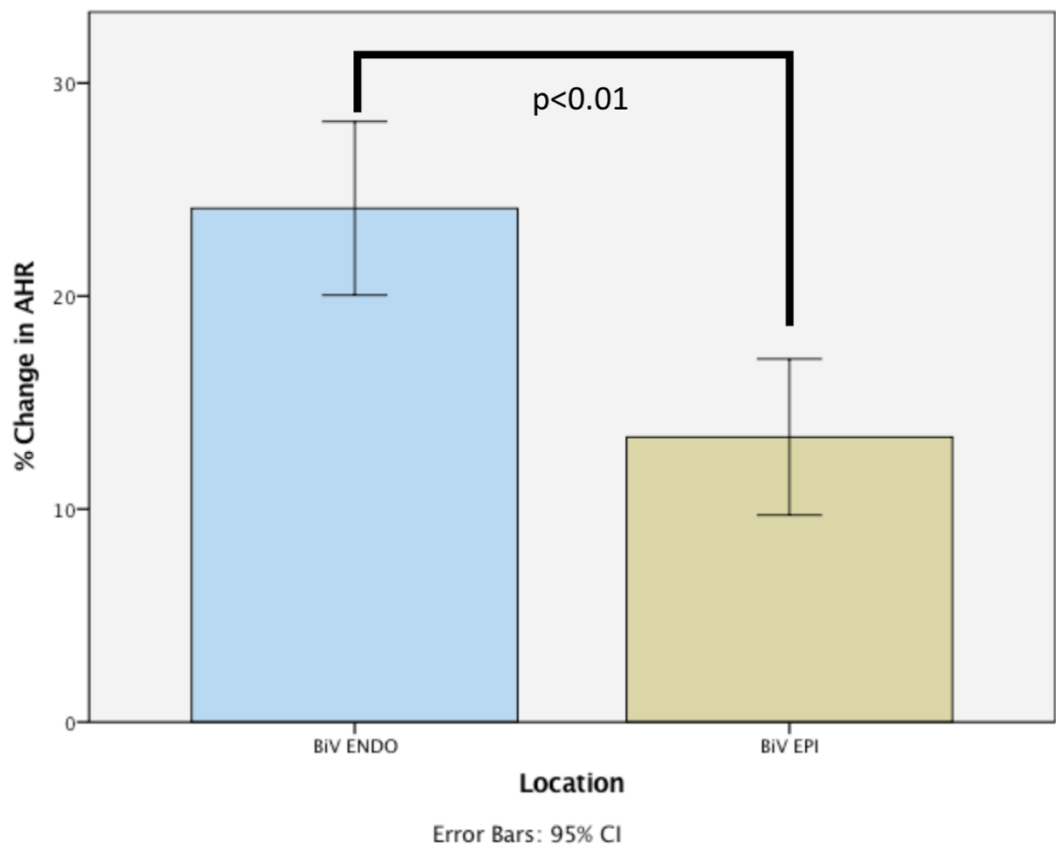


Figure 22. Change in AHR During Optimal BiV ENDO vs BiV EPI CRT

5.3.3 Endocardial Biventricular Pacing vs Epicardial Biventricular Pacing at the Same Site

In 77 patients, pacing was performed on opposing sides of the myocardium, directly comparing BiV ENDO CRT with BiV EPI CRT at the same site. In this context, BiV ENDO pacing yielded superior haemodynamics on 56% of occasions. The mean improvement in AHR did not significantly differ between the pacing strategies ($15.9\% \pm 18.21\%$ vs $12.7\% \pm 16.6\%$; $p=0.07$) although a definite trend was observed favouring BiV ENDO pacing, see Figure 23.

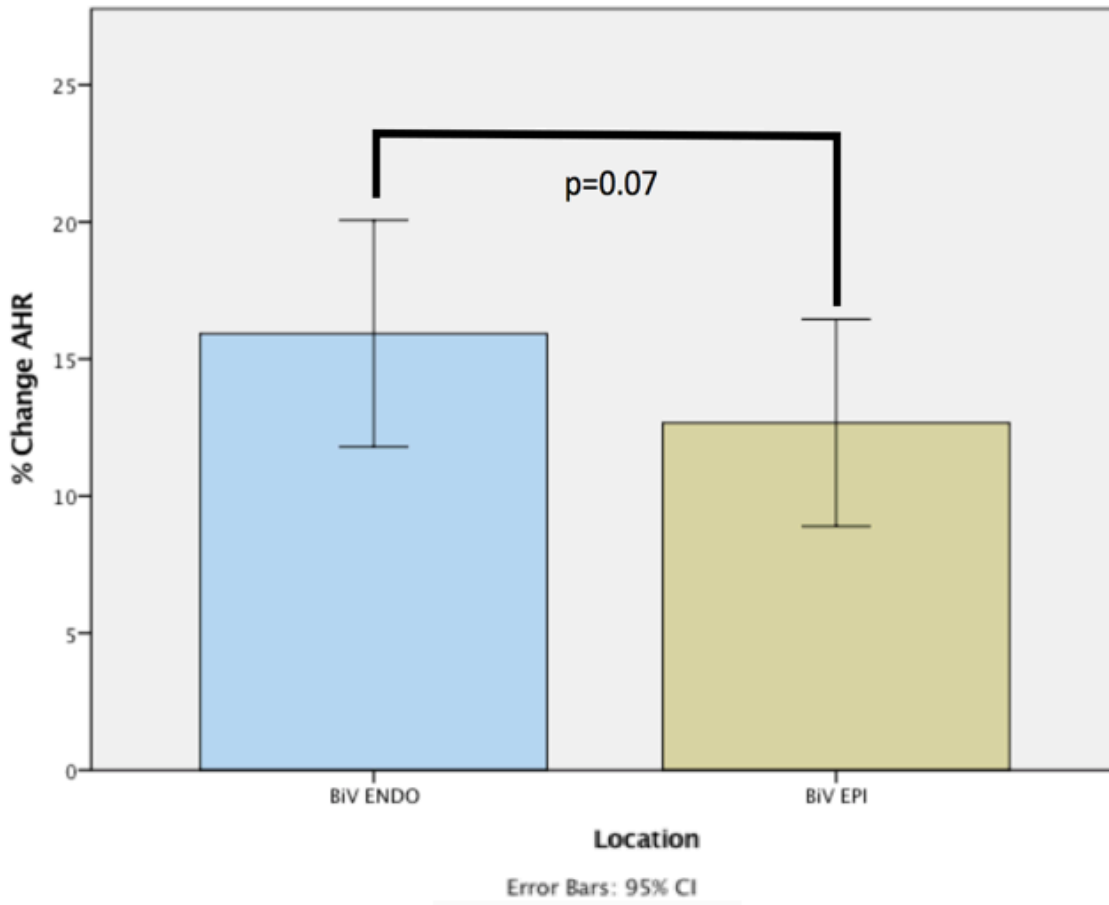


Figure 23. Change in AHR During BiV ENDO vs BiV EPI CRT at the Same Site

5.3.4 Suboptimal Endocardial Biventricular Pacing vs Epicardial Biventricular Pacing

An assessment comparing suboptimal BiV ENDO CRT with conventional BiV EPI was also performed in 70 patients. In this construct, BiV EPI consistently outperformed BiV ENDO and proved the superior pacing modality in 78% of patients. It also yielded a significantly greater mean improvement in AHR ($3.2\% \pm 11.9\%$ vs $11.9\% \pm 16.6\%$; $p<0.01$), see Figure 24.

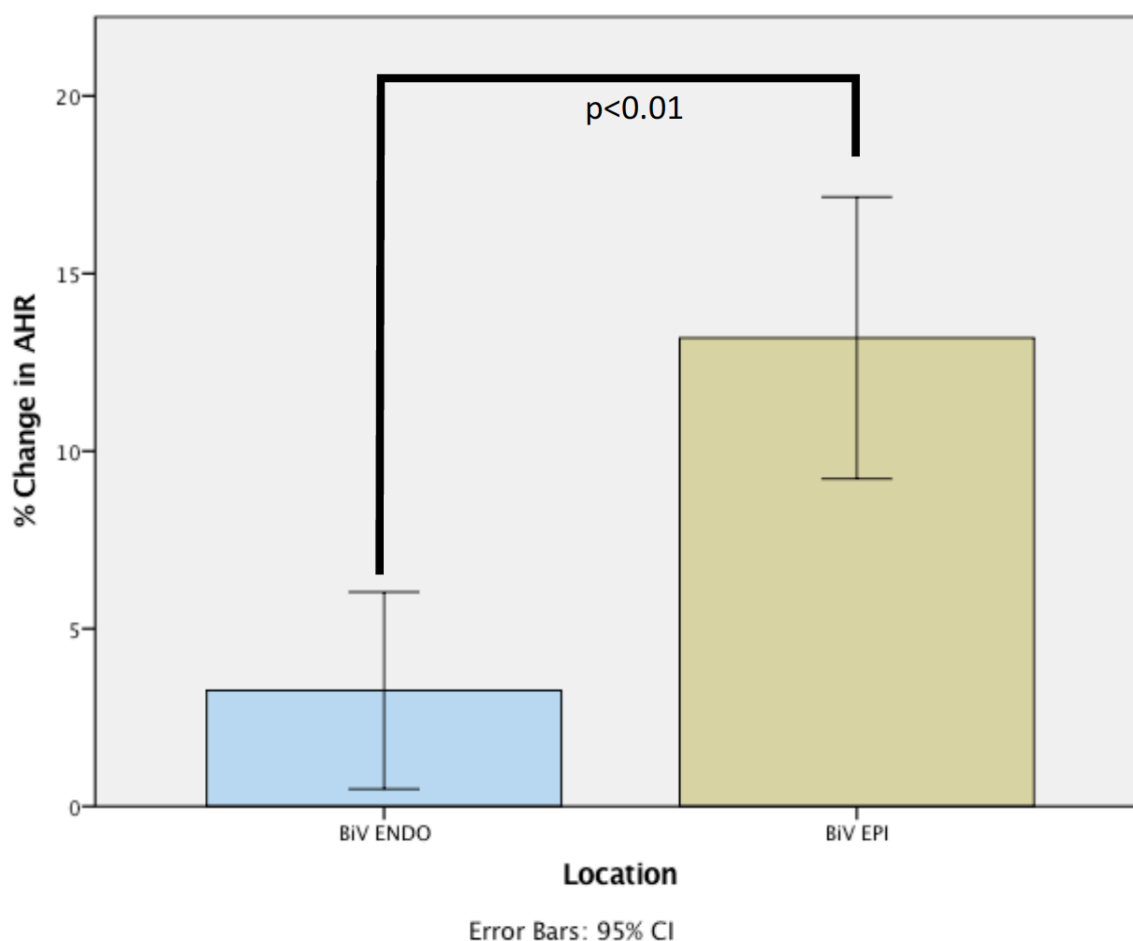


Figure 24. Sub-optimal BiV ENDO vs Optimised BiV EPI

5.4 DISCUSSION:

We sought to assess the changes in AHR observed in a cohort of patients undergoing both BiV ENDO CRT and BiV EPI pacing. A specific focus of our analysis was whether it was possible to achieve an inferior change in AHR during BiV ENDO pacing at any location, in comparison to that achievable using traditional, transvenous BiV EPI. Our principal findings were:

1. When delivered at the optimal location for that patient. BiV ENDO CRT consistently yielded greater improvements in AHR than was achieved via their chronically implanted transvenous, epicardial CRT system.
2. When pacing was delivered on opposing sides of the myocardium, a trend was observed favouring BiV ENDO pacing, although this failed to achieve statistical significance.
3. Sub-optimal BiV ENDO pacing proved inferior to traditional, transvenous epicardial CRT.

5.4.1 Comparison with previous studies

Our work confirms several important findings regarding the superiority of BiV ENDO pacing over traditional BiV EPI stimulation. Whilst previous work has highlighted the acute haemodynamic benefits associated with BiV ENDO pacing, this has typically occurred in cohorts of either ischaemic [41] or non-ischaemic [42] patients. In both of these studies, whilst trends were overserved suggesting that BiV ENDO pacing may prove superior to BiV EPI pacing at the same site, these failed to achieve statistical significance. Our analysis shows that when all these results are combined, in addition to data incorporating patients with a mix of aetiologies, BiV ENDO pacing again appears to yield superior haemodynamics over BiV EPI stimulation, but narrowly fails to achieve statistical significance.

Only one study has shown the superiority of BiV ENDO pacing at the same stimulation site as BiV EPI activation. Significantly in this analysis by Behar et al [196], BiV EPI pacing was rigorously optimised by delivering pacing from a multitude of epicardial sites both between and along the course of various veins to ensure that the chosen BiV EPI site truly represented the best possible pacing location. In previous work, a BiV ENDO position approximating the location of the chronically implanted LV lead had instead been chosen for comparison. It's possible, the incremental gain in haemodynamics associated with delivering optimised BiV ENDO pacing is so vast, that even when the AHR during BiV EPI improves, the gains associated with optimised BiV ENDO improve to a greater extent.

The results from our analysis confirm earlier findings that optimally delivered BiV ENDO pacing has the potential to yield consistently higher changes in AHR than can be achieved using BiV EPI. It is important to recognise however, that endocardial pacing is not a panacea. BiV ENDO pacing delivered at a sub-optimal location yielded inferior haemodynamics to conventional BiV EPI suggesting that in order to harness the potential benefits of this pacing strategy, it is necessary to identify and accurately target a specific location, which appears to show heterogeneity between patients.

5.4.2 Limitations

The findings of this study should to be interpreted within the context of how data was originally collected at the various centres. It was not possible to assess all the available endocardial sites during BiV ENDO pacing in all patients. Equally, in some patients, the epicardial site referenced represents the optimal site achieved during LV lead implantation and further optimisation was not

attempted. In addition, BiV EPI site selection is undoubtedly limited by the anatomical constraints of the coronary sinus however, this is an acknowledged limitation of the pacing modality.

Caution should also be taken when undertaking multiple measurements due to the risk of introducing statistical bias as a result of biological variability and the non-zero analytical nature of haemodynamic assessments of contractility using $LVdP/dt_{max}$. Mathematical modelling proves that a relatively small measurement error can project into a variety of extreme results when multiple measurement are tested against a single value [274]. Every attempt was made to preserve the reliability of the data during collection. AHR was calculated as a percentage change from baseline pacing, rather than described as a continuous scalar variable. After each target location had been assessed during pacing, a repeat baseline measurement was undertaken to account for any drift or physiological variation in haemodynamics.

5.5 CONCLUSION

Delivering pacing stimulation to the endocardial surface of the LV is associated with several advantages over traditional, transvenous epicardial CRT. The ability to access the entire ventricle predisposes this method of pacing to optimising the site of activation. When delivered at the same site, on opposing sides of the myocardium, BiV ENDO appears favourable although narrowly fails to prove conclusively superior. However, when the site of BiV EPI activation is robustly examined, the haemodynamics of BiV ENDO achieve statistical superiority. Whilst optimal BiV ENDO pacing is also frequently superior to BiV EPI, it is important to note that sub-optimal BiV ENDO can be associated with inferior changes in haemodynamics. It is widely acknowledged that the optimal BiV ENDO pacing site displays marked inter and intra-patient variability and as such, tailoring the site of LV stimulation to the individual patient's own unique anatomy, physiology and pathology will likely be required in order to maximise response.

Chapter 6 The Safety & Efficacy Of Leadless LV

Endocardial CRT Using The WiSE CRT Pacing System

This section has been adapted from *Real World Experience of Leadless Left Centric Endocardial CRT; A Multicentre International Registry of the WiSE-CRT Pacing System* (Sieniewicz, et al., 2018).

6.1 INTRODUCTION:

Heart failure remains a significant cause of morbidity and mortality [6] with disease progression resulting in adverse left ventricular (LV) remodelling and dyssynchronous electrical and mechanical activation [16]. Cardiac resynchronisation therapy (CRT) restores regional activation synchrony and enhances cardiac contractility [275]. However, 30-50% of patients fail to show improvement with conventional CRT delivered from an epicardial LV lead within a tributary of the coronary sinus (CS) [1,30,34]. In addition, technical and anatomical limitations mean it is not always possible to implant an epicardial LV lead [245], particularly in patients undergoing an upgrade from a pre-existing cardiac implantable electronic device (CIED) due to central venous stenosis/occlusion. [246].

LV endocardial pacing represents a potential therapy for patients who either cannot receive transvenous epicardial CRT or who have failed to adequately respond [265]. LV endocardial stimulation has traditionally been delivered via pacing leads placed trans-septally, mandating lifelong anti-coagulation due to the risk of thromboembolic complications. A novel wireless LV endocardial pacing system (WiSE-CRT System, EBR Systems, Sunnyvale, California) [249] delivers stimulation to the LV endocardial surface of the heart acoustically from an ultrasound (USS) pulse generator, implanted subcutaneously in an intercostal space, see Figure 25.

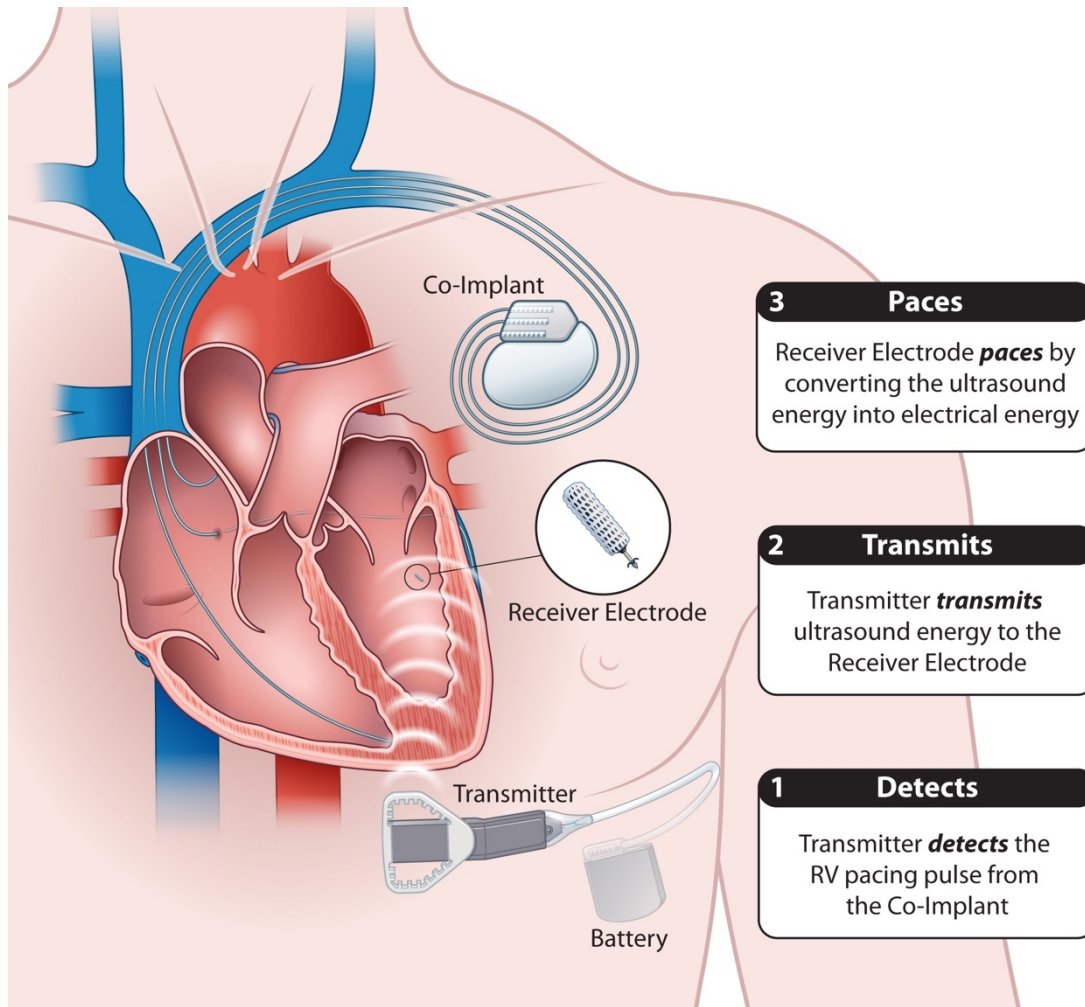


Figure 25. The WiSE CRT leadless LV pacing system

The USS waves stimulate a small receiver-electrode deployed percutaneously via the femoral artery, into the LV cavity avoiding the need for long-term anticoagulation. Acoustic USS energy is converted to an electronic pacing pulse by the receiver electrode triggered by RV pacing, resulting in near simultaneous (<3ms) LV & RV endocardial activation. The system has undergone single centre validation [276] and more recently the non-randomized SELECT LV study [270] implanted 35 patients across six centre achieving promising results in terms of clinical response and volumetric remodelling. Previous work has also evaluated the possibility of identifying and targeting the optimal pacing site [277].

The WICS Post Market Surveillance Registry (Clinical trial study number NCT02610673) was undertaken to investigate the safety and efficacy of the WiSE-CRT system in a real-world setting. The device is CE marked in Europe and is indicated in patients who are unable to receive CRT or who are non-responders. The Registry assessed the real-world implant success and safety as well as six month CRT response in 14 European centres.

6.2 METHODS:

6.2.1 Data Collection

The WICS Post Market Surveillance Registry prospectively collected data from all 14 European centres implanting the WiSE-CRT system. All patients studied gave full written consent to participate. The fourteen centres were; Guy's and St Thomas' NHS Foundation Trust (London, United Kingdom), the John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust (Oxford, United Kingdom), & The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust (Middlesbrough, UK), Immanuel Klinikum Bernau Herzzentrum Brandenburg (Bernau, Germany), St Antonius Ziekenhuis, Nieuwegein (Utrecht, Netherlands), Aalborg University Hospital (Aalborg, Denmark), Na Homolce Hospital (Prague, Czech Republic), Policlinico S'Orsola (Bologna, Italy), San Raffaele Hospital (Milan, Italy), University Hospital Erlangen, (Erlangen, Germany), St. Vincent's University Hospital (Dublin, Ireland), CHU Grenoble Alpes (Grenoble, France) & Hopital La Timone (Marseille, France), St Bartholomew's Hospital (London, UK).

6.2.2 Inclusion Criteria

The WiSE-CRT pacing system is CE marked for three licensed indications [270]; 1) patients where LV lead deployment was not possible or has previously failed due to anatomical constraints, high capture thresholds or phrenic nerve stimulation; 2) patients undergoing an upgrade to CRT where the implantation of an LV lead was impractical or complex due to issues with venous access or undesirable due to previous pocket infection; 3) patients who were previous non-responders to conventional transvenous, epicardial CRT. Non-responders were defined as patients in whom there was no change or worsening of symptoms or NYHA functional class after 6 months of treatment confirmed by the treating physician.

Patients were classified as having either ischemic cardiomyopathy (ICM) or non-ischemic cardiomyopathy (NICM) using a combination of cardiac MRI (CMR), electroanatomical mapping (EAM), coronary angiography and clinical history. The majority of patients were implanted via a retrograde trans-aortic approach as previously described (10). In a small minority of cases, where issues with arterial patency, tortuosity or aortic valve disease/replacement precluded a retrograde trans-aortic approach, a novel trans-septal approach was utilised (n=8) [271].

6.2.3 Endpoints

Three safety and efficacy assessments were performed:

1. Procedural success, requiring successful implantation of all WiSE-CRT components and confirmation of BiV pacing on a post-implant 12 lead ECG.
2. The safety of the system, evaluating both acute (<24hrs) and chronic (>24hrs-6 months) complications.
3. Clinical response to biventricular endocardial pacing from the WiSE-CRT System. Given no universally accepted definition of response to CRT exists, we analysed the proportion of patients who experienced an improvement in their clinical symptoms. We also assessed echocardiographic response to CRT.

6.2.3.1 CLINICAL RESPONSE

Clinical response was assessed in two ways. Firstly, an assessment of NYHA status was recorded at baseline and during follow up. In addition, a patient global assessment was recorded at follow up. This global assessment classified each patient into one of three categories; improved, worsened or unchanged. Patients were asked which of these three categories applied to their status.

6.2.3.2 ECHOCARDIOGRAPHIC RESPONSE

The most widely accepted definition of echocardiographic response involves an assessment of LV reverse remodeling six months after implantation. In accordance with previously published work [270], patients were considered echocardiographic responders to CRT if they exhibited a $\geq 15\%$ reduction in their end-systolic volume, measured using 2D trans-thoracic echocardiography.

6.2.4 Statistics

Continuous variables with a Gaussian distribution were described using mean values \pm standard deviation. AHR and EP data was tested for normality with the Shapiro-Wilk test. Significance testing on continuous, normally distributed paired data was performed using two tailed paired *t* tests. Significance testing on continuous, non-normally distributed paired data was performed using the Wilcoxon Signed Rank test. Significance testing on continuous, non-normally distributed un-paired data was performed using the Mann-Whitney U test. Where both independent and

dependant factors were categorical, significance testing was performed using the chi-squared test. Odds ratios were calculated using binary logistic regression. Where both independent and dependant factors were continuous, odds ratios and significance testing were performed using linear regression. Results were considered significant at $p < 0.05$. Analysis was performed on PASW Statistics 24 (SPSS Inc., Chicago, Illinois).

6.3 RESULTS:

6.3.1 Patient Characteristics

A total of 90 patients across the fourteen centres were implanted with the WiSE-CRT system, see Table 3.

Table 3. Patient demographics

	Mean \pm SD or Number (%)
Patients	90
Age (years)	68.2 \pm 10.5
Male	72 (80.0%)
ICM Aetiology	36 (40.0%)
NYHA	
1	1 (1.1%)
2	33 (36.7%)
3	56 (62.2%)
4	0 (0%)
Echocardiographic Data	
LVEF (%)	30.6 \pm 8.9
LVESV (ml)	130.4 \pm 78.5
LVEDV (ml)	185.7 \pm 93.0
ECG	
Atrial Arrhythmias	47 (52.2%)
QRS duration (ms)	180.7 \pm 27.0
RV Paced Morphology	81 (90.0%)
LBBB Morphology	6 (6.7%)
BiV Paced Morphology	3 (3.3%)
Indication	
Failed LV lead implant	44 (48.9%)
Complex upgrades	34 (37.8%)
Failure to respond to BiV EPI	12 (13.3%)

Patients were predominantly male (80.0%) with a mean age of 68.2 \pm 10.5 years and mean LVEF 30.6% \pm 8.9%. The mean QRS duration was 180.7 \pm 27.0ms and 40.0% of patients had an ischemic etiology. 48.9% of the patients had experienced a failed conventional transvenous CRT implant,

whilst 37.8% of patients were deemed complex upgrades. 13.3% of patients were prior non-responders to epicardial CRT.

6.3.2 Procedural Details & Safety Issues

Biventricular pacing was confirmed in 86 patients (95.6%). In four cases, it was not possible to achieve consistent capture of the LV endocardial pacing electrode. In two cases, failure of the screening process to exclude an un-suitable patient was later confirmed. The first of these patients had co-morbid COPD with significant lung encroachment affecting the USS signal between the sub-cutaneous transmitter array and LV endocardial pacing electrode. In the second patient, the distance between the position of the LV pacing electrode and the USS array was too great (> 13cm) to achieve consistent capture. One patient never received an LV pacing electrode due to peri-procedural tamponade which led to the implant procedure being aborted. In the final case, the electrode was implanted in non-viable tissue and subsequent attempts at delivering LV stimulation were associated with only intermittent capture.

6.3.3 Complications

Acute complications (<24 hrs) occurred in three (3.3%) patients, see Table 4.

Table 4. Acute and chronic complications

<24 hours	3 (3.3%)
Cardiac tamponade	1
Pneumothorax/Pleural Effusion	2
>24 hours – 6 months	18 (20%)
Arterial Access Complication	4
Pocket haematoma (generator)	4
Post Procedure Chest Sepsis	3
Pocket infection (generator)	3
Acute Kidney Injury	2
Post Procedure CVE	1
Extrastimulation During TTE	1

One patient experienced cardiac tamponade following electrode placement requiring pericardiocentesis and emergency thoracotomy where the LV perforation was repaired. The patient was initially transferred to ITU and eventually made a full recovery at which point a further attempt at electrode deployment was declined by the patient. While awaiting discharge, the patient was diagnosed with respiratory sepsis and ultimately died 39 days after the attempted implant. Although this death was not due to tamponade itself, the protected in-patient stay was a sequelae of a procedural complication.

Two patients suffered complications relating to USS transmitter array/battery placement including pneumothorax and pleural effusion although neither the effusion nor the pneumothorax required intervention and both resolved with conservative management.

Complications arising between 24hrs and six months occurred in 18 patients (20%). The most commonly encountered adverse events were related to femoral arterial access. These included one femoral haematoma treated with conservative management and three pseudo-aneurysms, two of which required surgical intervention. Other events included transmitter or battery pocket haematomas (4) and infections (3) as well as post procedure lower respiratory tract infections (3). One patient with known atrial fibrillation was admitted to their local hospital with dizzy spells, five months after implantation with the system. Subsequently they were found to have sustained a cerebellar infarct which was assessed not to be procedure or device related.

Stimulation of the WiSE-CRT system during echocardiography was observed in one patient during their six month follow up visit. The receiver electrode had been positioned in an apical position of the left ventricle. The sonographer observed a self-terminating run of ectopic ventricular extrasystoles whilst obtaining an apical four chamber view. The run of ectopic beats stopped immediately after the probe was withdrawn and the patient reported no symptoms.

6.3.4 Battery Longevity

Battery longevity was assessed at the time of implant and during each follow up attendance and an estimated battery longevity calculated for each patient. Longevity could be influenced by a variety of factors including the LV capture threshold, the distance and angle between LV pacing electrode and the USS transmitter and the type of USS transmitter implanted. Implants were initially performed using the first-generation USS pulse generator which had a larger surface area. A new transmitter received a CE mark mid-way through the Registry and was implanted in 33/90

patients. The ICTX 4100 second generation transmitter was engineered to deliver a more effective USS signal with its smaller size facilitating single stage implantation by a lone operator, see Figure 26.

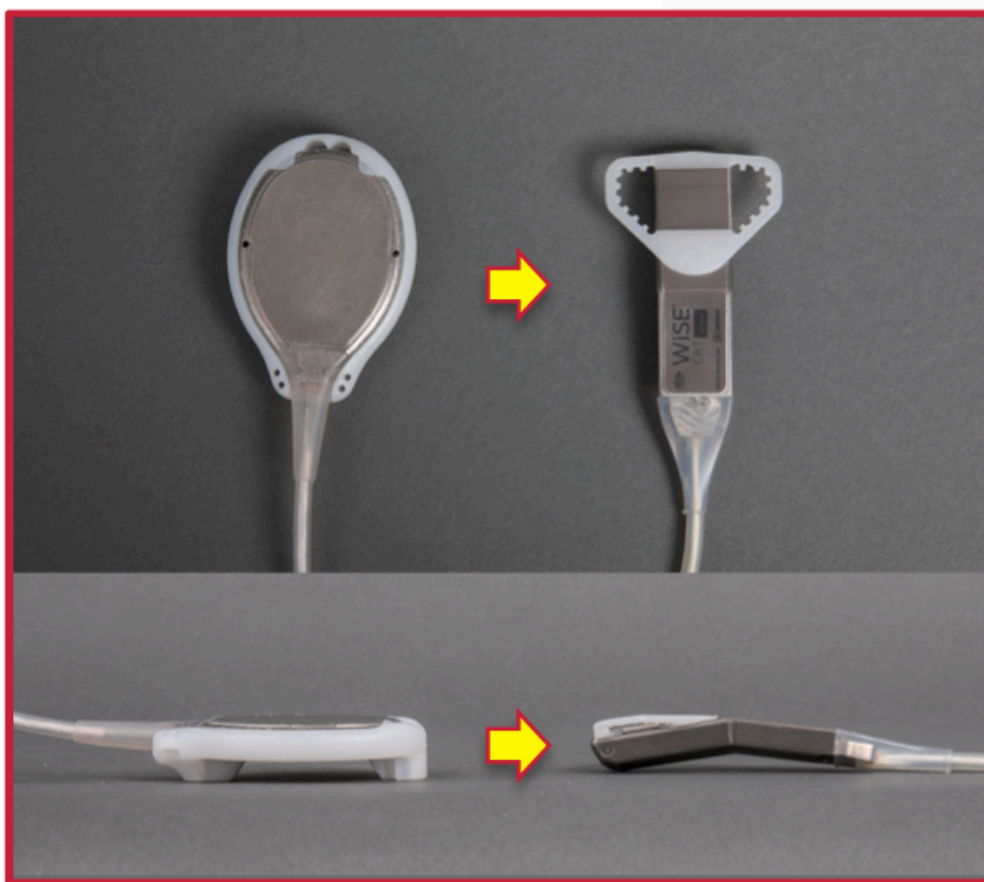


Figure 26. The first and second generation WiSE CRT USS transmitter

The first-generation USS transmitter was associated with a mean battery longevity of $1.98\text{yrs} \pm 0.8\text{yrs}$. The second-generation system was associated with longer mean battery longevity of $3.2\text{yrs} \pm 1.3\text{yrs}$ ($P < 0.005$). The minimum battery longevity prediction observed after implantation was 0.8yrs, whilst the longest was 6.1yrs.

6.3.5 Chronic Response

Three patients withdrew from the Registry after undergoing implantation with the system meaning no follow up data was recorded. In four patients, WiSE CRT pacing proved ineffective/inconsistent as outlined above, and as such- follow up data was not recorded. Seven patients died prior to undergoing a repeat assessment six-months after implantation. No patient deaths were related to complications resulting from implantation of the WiSE CRT System. Three

deaths were attributed to worsening chronic heart failure whilst the other four patient deaths were due to either worsening comorbid conditions or intercurrent illnesses. One patient died due to worsening comorbid dementia. One patient died after contracting pneumonia. One death occurred as a result of worsening acute onset chronic renal failure four months after implantation of the WiSE CRT System. The final patient death was due to general deterioration and occurred eight months after implantation of the system and meant no follow up data was recorded.

In the remaining 76 patients, all patients had data evaluating their clinical response whilst comprehensive follow up data including an echocardiographic assessment of ejection fraction and LV volumes was available in 66 patients. In total 60/76 (78.9%) experienced had an improvement in their clinical composite score, 12 patients (15.8%) reported no change in their symptoms while four (5.3%) had worsened. Significant improvements in echocardiographic endpoints were observed in 44/75 patients (58.7%). LV ejection fraction increased from 30.6% ± 8.9% at baseline to 37.0% ± 11.5% at six months, P<0.0001. LVEDV decreased from 185.6 ± 93mls to 161.0 ± 83.3 mls, P<0.0001 whilst LVESV decreased from 130.4 ± 78.5 to 107.0 ± 71.6mls, P<0.0001, see Table 5. Using the pre-specified endpoint of ≥15% reduction in their LVESV, 54.5% of patients were deemed echocardiographic responders. 55% of patients were deemed echocardiographic responders.

Parameter	Baseline ± SD	6 Months ± SD	P value	Response Definition	Response Rate at 6 Months
LVEF (%)	30.2 ± 8.8	37.2 ± 12.0	<0.0001		
LVEDV (ml)	186.9 ± 90.0	160.0 ± 83.4	<0.0001		
LVESV (ml)	132.3 ± 84.3	105.3 ± 73.1	0.0004	> 15% relative reduction	55.4%

Table 5. Chronic LV remodelling

6.4 DISCUSSION:

The WICS Post Market Surveillance Registry set out to investigate the safety and efficacy of leadless LV endocardial pacing in a real world setting.

The principal findings were:

1. The WiSE CRT system achieved procedural success with biventricular endocardial pacing confirmed in >95% of patients in the registry.

2. Device or procedural related adverse events encountered were similar to those seen in the SELECT-LV trial despite the multi-centre, real world nature of the registry.
3. At six months the system was associated with a clinical response rate of 79% and an echocardiographic remodelling response rate (>15% reduction in ESV) of 55%.

The most common complications related to femoral arterial access as the WiSE CRT system was designed to allow the deployment of the pacing electrode in the LV cavity via retrograde aortic access from the femoral artery. This required large bore femoral arterial access and closure- a skill not commonly required by practicing electrophysiology/complex device specialists who tend to implant this system. Three approaches have been devised to reduce the rate of femoral arterial access complications.

Firstly, vascular closure devices were employed at 12 centers to minimize bleeding and ensure effective arterial closure was achieved at the end of the case. At 11 centers the Perclose ProGlide (Abbott Medical, USA) vascular suture system was used. At one center the Prostar XL (Abbott Medical, USA) percutaneous vascular surgical system was used to assist vascular haemostasis. Vascular closure systems have been shown to reduce time to haemostasis [278].

Several operators also trialed the use of pre and peri-procedural imaging to guide arterial access. At five centers- this comprised real time USS guidance to identify the femoral artery and visualize guidewire deployment. In one center- access was initially gained in the contra-lateral femoral artery using a 5f sheath. A 5f pigtail catheter was then inserted and an aortogram performed which could then be used to inform the femoral puncture whilst also ensuring the site was at a location suitable to undergo closure with a Perclose ProGlide suture (Abbott). In addition, one center also routinely performed pre-procedural CT scanning on all patients to assess femoral arterial patency and the presence of vascular tortuosity.

Finally, the use of a trans-septal approach permitting electrode deployment in the LV endocardium following initial femoral venous access has also been shown to be possible [271]. This approach benefits from obviating the requirement for femoral arterial access in a series of 10 cases, successfully permitted electrode deployment without a single groin or thromboembolic complication [279]. This approach may be preferable amongst electrophysiologists who are familiar with performing trans-septal punctures.

The WiSE-CRT receiver electrode is typically not sensitive to routine ultrasound imaging however, in rare instances extra-stimulation of the device is possible. In our series, this event was observed in just one case. However, this is an important finding given the widespread use of ultrasonic imaging in medicine and specifically within the field of cardiology. Apical placement of the LV

pacing electrode appears to increase the potential for extra-stimulation, in particular whilst an apical four chamber view is being obtained using transthoracic echocardiography as this significantly reduces the distance between the receiver electrode and the alternate ultrasound source. Other risk factors for extra-stimulation include the use of high power settings, low frequency ultrasound (typically employed during harmonic imaging) and thin body habitus.

In order to avoid inadvertent extra-stimulation of the pacing electrode, all patients are issued with a medical device identification card, outlining that they have an ultrasound sensitive pacemaker. In cases where apical deployment of the pacing electrode has been confirmed an alternative echocardiography protocol has been developed and shown to successfully prevent further extra-stimulation.

The WiSE-CRT System remains uniquely adaptable to each individual patient, allowing variance in the access route (arterial or venous), USS transmitter array position and most importantly, stimulation site within the LV [280]. We have previously demonstrated that once a specific endocardial segment has been selected as the optimal site for electrode deployment, it is technically feasible to deploy the LV pacing electrode in this area in 92% of patients [277]. No intercostal space is associated with superior battery longevity and instead, it appears the best option is to use whichever space offers the best window for each patient. Overall, 79% of patients reported a subjective improvement in their clinical condition following implantation with the WiSE system. This translated into an echocardiographic response rate of 54.5% after six months of follow up. Crucially, rates of echocardiographic response were comparable amongst both previous non-responders and those undergoing an upgrade to biventricular endocardial pacing (55.6% vs 54.2%; P:0.619). This finding is in keeping with the LV reverse remodelling response rate of 55% identified in the ALSYNC study (9) supporting the use of endocardial CRT amongst patients who have previously failed to respond to transvenous epicardial CRT.

6.4.1 Comparison With Previous Studies

The results of the current registry compare favourably with the previously published SELECT-LV study which included 35 patients at six centres (12). In that analysis, 97% of patients experienced consistent biventricular endocardial capture whilst a similar figure (95%) met this end point in the registry, see Figure 27. Both early (<24 hrs; 8.6% SELECT LV vs 3.3% WiSE CRT Registry) and late complications (24hrs to 6 months; 22.3% vs 20%) were similar across both analyses and replicated the findings of the REPLACE registry (18.7%) which evaluated complications in a similar cohort of patients undergoing transvenous CRT upgrades [281]. Rates of clinical response (85% vs 78%) and

echocardiographic remodelling (52% vs 55%) were also similar across the SELECT LV vs WiSE CRT Registry.

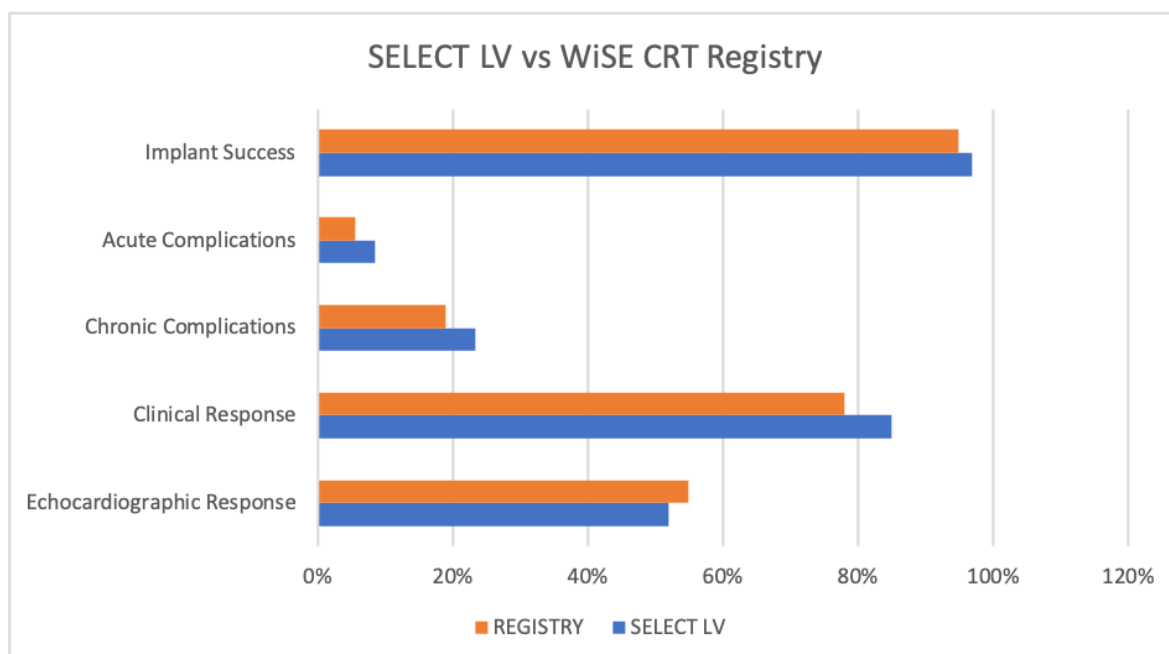


Figure 27. Comparison between SELECT LV Study & WiSE CRT Registry Results

72 patients (81%) recruited in the WiSE CRT Registry were male and in keeping with previous studies of CRT [64–67], less remodelling was observed amongst this group. The rates of LV remodelling were comparable amongst both previous non-responders and those undergoing an upgrade to biventricular endocardial pacing (55.6% vs 54.2%; $P:0.619$). This finding is in keeping with the remodelling response rate of 55% identified in the ALSYNC study (9) supporting the use of endocardial CRT in this population.

6.4.2 Limitations:

The main limitation of this current analysis is that it is a registry and therefore limited by the inherent constraints of a non-randomized study. Importantly neither patients nor investigators were blinded and all suitable patients enrolled in the WiSE CRT Registry were implanted with the system. Whilst LV remodelling was selected as an endpoint, other endpoints included subjective clinical response which may be more open to bias. A randomised, double-blinded evaluation of the WiSE CRT system is currently underway (Stimulation Of the Left Ventricular Endocardium for Cardiac Resynchronisation Therapy in Non-Responders and Previously Untreatable Patients (SOLVE CRT, ClinicalTrials.gov Identifier: NCT02922036). This study will hopefully provide an

unbiased assessment of symptomatic and echocardiographic response associated with endocardial pacing.

6.5 CONCLUSION:

This is the largest series of leadless endocardial pacing to date and importantly, demonstrates that the use of this novel pacing system appears effective during real world use with a similar response and complication rate compared to previous non-randomized studies. Response to this therapy is promising with nearly 80% of patients reporting an improvement in their clinical symptoms and 55% displaying evidence of volumetric remodelling at follow up. The registry results would suggest that endocardial CRT with this novel pacing system is an effective treatment for a high risk group of patients with heart failure who either cannot receive or who have not responded to conventional CRT.

Chapter 7 Metrics To Aid Identification Of The Optimal LV Endocardial Pacing Site

This section has been adapted from *Electrical latency predicts the optimal left ventricular endocardial pacing site: results from a multicentre international registry* (Sieniewicz, et al., 2018).

7.1 INTRODUCTION

Cardiac resynchronization therapy (CRT) is an effective treatment for selected patients with heart failure and electrical dyssynchrony[30,34] however 30% of patients fail to respond [1]. Attempts have been made to improve the response rate by defining the optimal LV lead implantation site. Targeting the epicardial LV lead position on the lateral wall via a lateral or posterolateral tributary of the coronary sinus is typically associated with superior improvements in LV contractility, as defined by the acute haemodynamic response (AHR) [88]. This reproducible marker of acute contractility is best expressed as the change in the maximum rate of left ventricular pressure (LV-dP/dt_{max}), from a baseline control state [41,42].

Until recently, attempts at lead targeting were confined to epicardial sites accessible from the coronary sinus (CS) venous system. Biventricular endocardial pacing (BiV ENDO) represents a new approach to deliver CRT and in contrast to conventional CRT (BiV EPI) is not constrained by the anatomical limitations of the CS. BiV ENDO pacing allows potential access to the entire surface of the LV endocardium and may facilitate the avoidance of scar and phrenic nerve stimulation whilst allowing the targeting of late activated sites, both critical determinants to achieving successful CRT [125,126,282]. In the recently published ALSYNC study, BiV ENDO was associated with a clinical and echocardiographic improvement of 59% and 55% respectively [265]. This was achieved in a cohort of previous non-responders to conventional CRT, suggesting that LV endocardial pacing may overcome the issue of poor response to CRT.

Previous work has highlighted the acute hemodynamic benefits of selecting the optimal LV pacing site [42] and whilst the LV_{ENDO} possess different material properties [224] rendering most sites superior to traditional BiV EPI, indiscriminate BiV ENDO can actually prove inferior to traditional CRT [42]. Given this variation in performance, identifying and implanting at the optimal location is essential. We sought to identify the optimal LV_{ENDO} pacing site from multiple studies of acute LV

Chapter 7

ENDO pacing in five international centres. The optimal site was that which yielded the optimal change in LV contractility, as measured by changes in acute hemodynamic response (AHR).

We hypothesized that the optimal BiV ENDO pacing site is patient specific but that amongst patients with a NICM, a lateral location would likely prove optimal. Furthermore, we sought to examine the relationship between AHR and features known to significantly impact AHR during BiV EPI pacing, including avoiding scarred tissue and pacing in areas of electrical latency. By evaluating the variation in AHR associated with delivering BiV ENDO pacing in and around areas of scar/fibrosis, we hoped to show the importance of targeting viable tissue. We also sought to evaluate the relationship between AHR and BiV ENDO pacing at locations which minimized activation time- as measured by paced QRS duration (QRSd) and Q-LV, defined by the time interval from the first deflection on a surface ECG to local intrinsic activation at the LV stimulation site. We also assessed LV Lead Electrical Delay (LVLED) where the Q-LV is divided by the QRS, accounting for inter-patient variability in the QRSd.

7.2 METHODS:

7.2.1 Data Collection

Data was collected from five international centres performing studies of BiV ENDO pacing where AHR was measured at different sites within the LV as part of an acute study. The centres were the Johns Hopkins University (Maryland, USA)[41]; University of Bordeaux (Bordeaux, France)[42]; Catharina Hospital (Eindhoven, the Netherlands)[197]; University of Oxford (Oxford University Hospitals NHS Foundation Trust) & Guy's and St Thomas' NHS Foundation Trust (London, United Kingdom)[196].

7.2.2 Inclusion Criteria

Patients on optimal medical therapy (OMT) meeting European Society of Cardiology (ESC)[34] and/or Heart Rhythm Society (HRS)[273] criteria for CRT or those who had failed to respond to conventional CRT underwent an acute hemodynamic study, see Table 6. Inclusion criteria.

Table 6. Inclusion criteria

Centre	Aetiology	NYHA	LVEF	ECG	Non-responders to CRT Included?
University of Bordeaux	NICM	III-IV	<35%	LBBB with QRS > 140ms	No
Johns Hopkins University	ICM	N/A	< 35%	Dyssynchronous ventricular activation	No
Guys and St Thomas' Hospital	Any	II-IV	< 35%	LBBB with QRS > 120ms	No
Catharina Hospital	Any	III-IV	< 35%	N/A	Exclusively
University of Oxford	Any	II-IV	< 35%	LBBB with QRS > 120ms	Yes

The underlying aetiology of heart failure was determined using angiography, clinical history, cardiac MRI (CMR) and invasive electro-anatomical mapping where available. In some centres, studies were performed in patients with specific aetiologies; ischaemic (Johns Hopkins) or non-ischaemic (Bordeaux). In the remaining centres (Oxford, Catharina and GSTT) a mixture of ischaemic (ICM) and non-ischaemic patients (NICM) were studied, see Table 7. In all centres the procedures were undertaken following ethical approval from the local institution and all patients gave informed consent.

Table 7. Patient aetiology

	ICM	NICM	HCM	TOTAL
University of Bordeaux	0	33	0	33
Johns Hopkins University	11	0	0	11
Guys & St Thomas'	16	5	0	21
Catharina Hospital	16	5	0	21
University of Oxford	9	8	1	18
TOTAL	52	51	1	104

In all centres BiV ENDO pacing was delivered via an RV and LV endocardial catheter with simultaneous left ventricular & right ventricular (VV) timings. In all cases AHR ($LV-dP/dt_{max}$) was measured via a pressure wire placed directly into the LV cavity as previously described [196]. Where multiple measurements were taken in a particular location, an average value was used. In order to make meaningful comparisons it was necessary to rank the performance of each location using the locally agreed method of obtaining acute hemodynamic data. Where possible, percentage change in AHR was used. Where this was not possible, maximal $LV-dP/dt_{max}$ values were compared. A BiV ENDO location approximating the position if the BiV EPI lead was used. Advanced localization techniques have confirmed the reliability of this method [283]. Locations were described using a nine segment circumferential polar plot, see Figure 28.

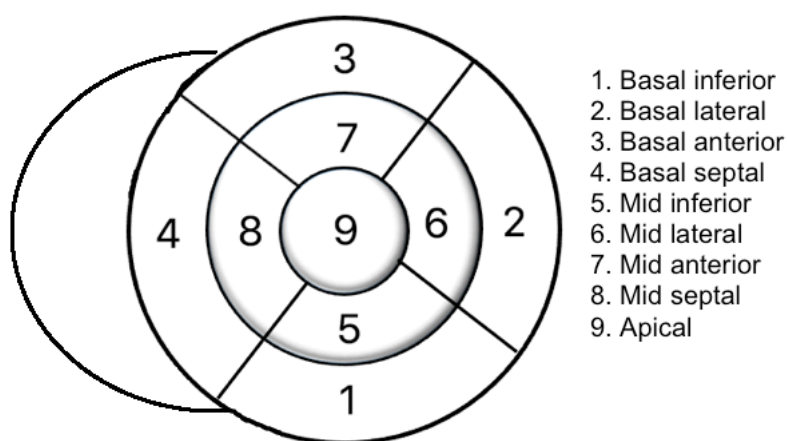


Figure 28. The 9 segment LV endocardial circumferential polar plot

The optimal location was defined as the pacing site where delivering temporary biventricular pacing resulted in the greatest change in AHR from baseline AAI pacing- or DDDR pacing for those with no underlying rhythm (% change in $\text{LVdP}/\text{dt}_{\text{max}}$). We assessed the optimal pacing location in terms of AHR and correlated this to Q-LV [125], LV Lead Electrical Delay (LVLED) [126], scar/fibrosis (if present) and paced QRSd. Patient data was pooled from all the contributing centres. Individual data from these centres has previously been published [41,42,196,197].

7.2.3 Statistics

Continuous variables with a Gaussian distribution were described using mean values \pm standard deviation. Categorical data were described by an absolute number of occurrences and associated frequency (%). Significance testing was performed using chi-squared and paired t tests. AHR and electrical data passed the Shapiro-Wilk test for normality. To account for the clustering of data and multiple measurements within each patient, a generalised linear mixed effect model was applied for all data points that achieved capture. Where multiple data points were recorded from an individual patient, this has been displayed on the scatterplot using a specific colour marker for each patient. Analysis of variance was performed to compare the means of several groups. Results were considered significant at $p < 0.05$. Analysis was performed on PASW Statistics 23 (SPSS Inc., Chicago, Illinois).

7.3 RESULTS:

7.3.1 Patient Characteristics

A total of 104 patients across the five centres were studied, incorporating 687 endocardial and 93 epicardial pacing locations. BiV ENDO pacing was performed in all cases with a mean of 6.5 LV endocardial sites per patient. Patient characteristics for the entire cohort are shown in

Table 8. Patients were predominantly male with a mean age of 66.4 ± 11.3 years, the mean LVEF was $24.6\% \pm 7.7\%$. The mean QRS duration was 163 ± 30 ms. There was a near equal distribution between ischaemic and non-ischaemic aetiology.

Table 8. Patient demographics

	Mean \pmSD or Numbers (%)
Patients	104
Age (years)	66.4 \pm 11.3
Male (%)	94 (90.4%)
Female (%)	10 (9.6%)
LVEF (%)	24.6% \pm 7.7
NYHA	2.9 \pm 0.5
QRS duration (MS)	163 \pm 30.0
Aetiology	
Ischaemic (%)	52 (50%)
Dilated (%)	51 (49.0%)

Other (%)	1 (1.0%)
Rhythm	
Sinus (%)	81 (77.9%)
AF (%)	16 (15.4%)
Paced (%)	7 (6.7%)
Morphology	
LBBB	78 (75.0%)
IVCD	7 (6.7%)
RBBB	5 (4.8%)
RV Paced	11 (10.6%)
BiV Paced	3 (2.9%)

7.3.2 Optimal Endocardial Pacing Site- Scar/Fibrotic Tissue

A total of 19 patients had MRI data allowing scar localization with late gadolinium enhancement allowing 158 LV endo positions to be analysed, 61 of which were identified as scarred. All patients were male and had ICM with a mean age 70.5 ± 6.4 years & the mean LVEF was $21.6 \pm 7.3\%$. Endocardial pacing in scarred segments was associated with a lower LV-dP/dt_{max} value compared to non-scar segments; 890 ± 316 mmHg/s vs 982 ± 274 (mmHg/s $p < 0.01$), see Figure 29.

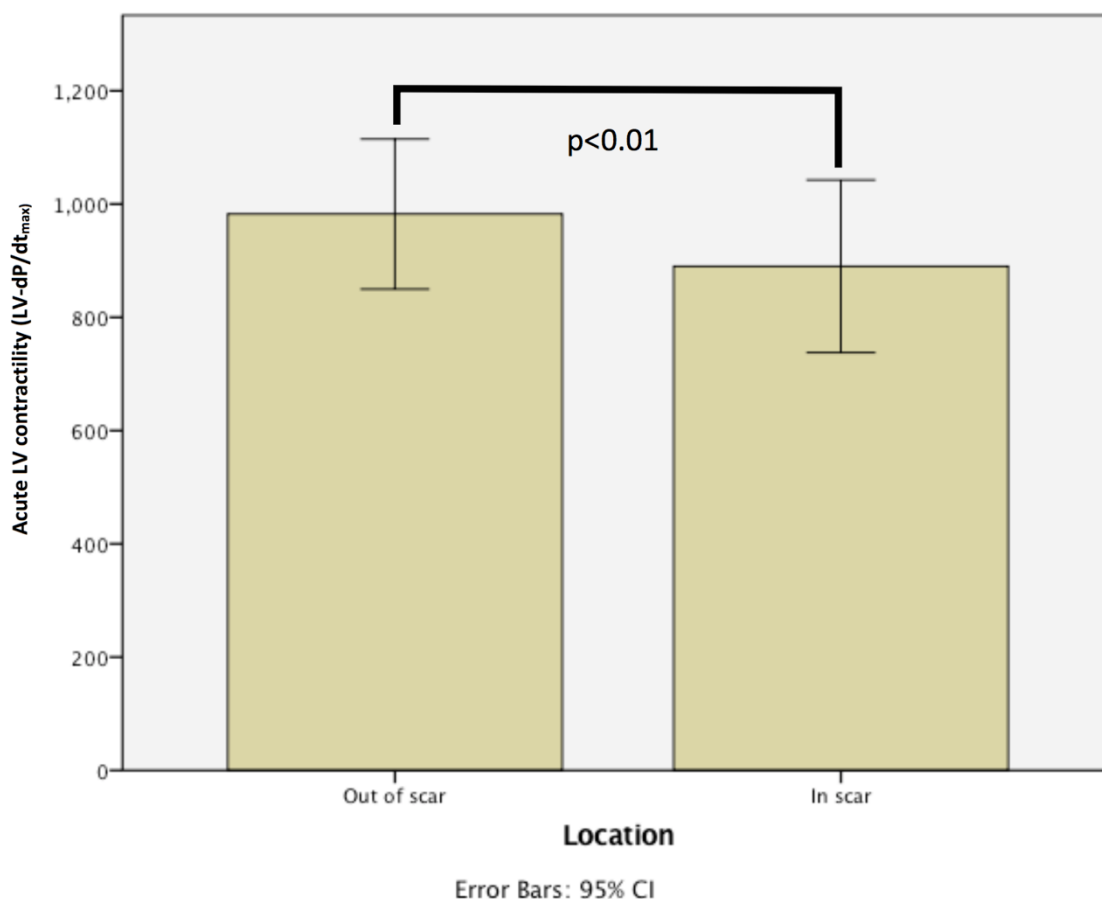


Figure 29. Graph comparing acute left ventricular contractility (LV dp/dtmax) and confidence interval during temporary biventricular endocardial pacing with the catheter placed in viable tissue (left) vs scar tissue (right).

7.3.3 Optimal Endocardial Pacing Site- Q-LV & LV Lead Electrical Delay (LVLED)

Q-LV was measured at the site of endocardial stimulation as previously described [42] and correlated against AHR. 37 patients had AHR and QLV measurements incorporating 191 endocardial pacing locations. Patients were predominantly male (92%) with a mean age of 68.8 ± 12.8 years, the mean LVEF was $25.9 \pm 7.6\%$. The mean QRS duration was 166 ± 28.0 ms. 68% (n=25) of patients had an ischaemic (ICM) aetiology.

Q-LV times were significantly longer at the optimal location than in the least favourable hemodynamic location (127ms vs 89ms, $p < 0.01$). Delivering BiV ENDO pacing in areas of electrical latency was strongly associated with greater improvements in AHR, see Figure 30.

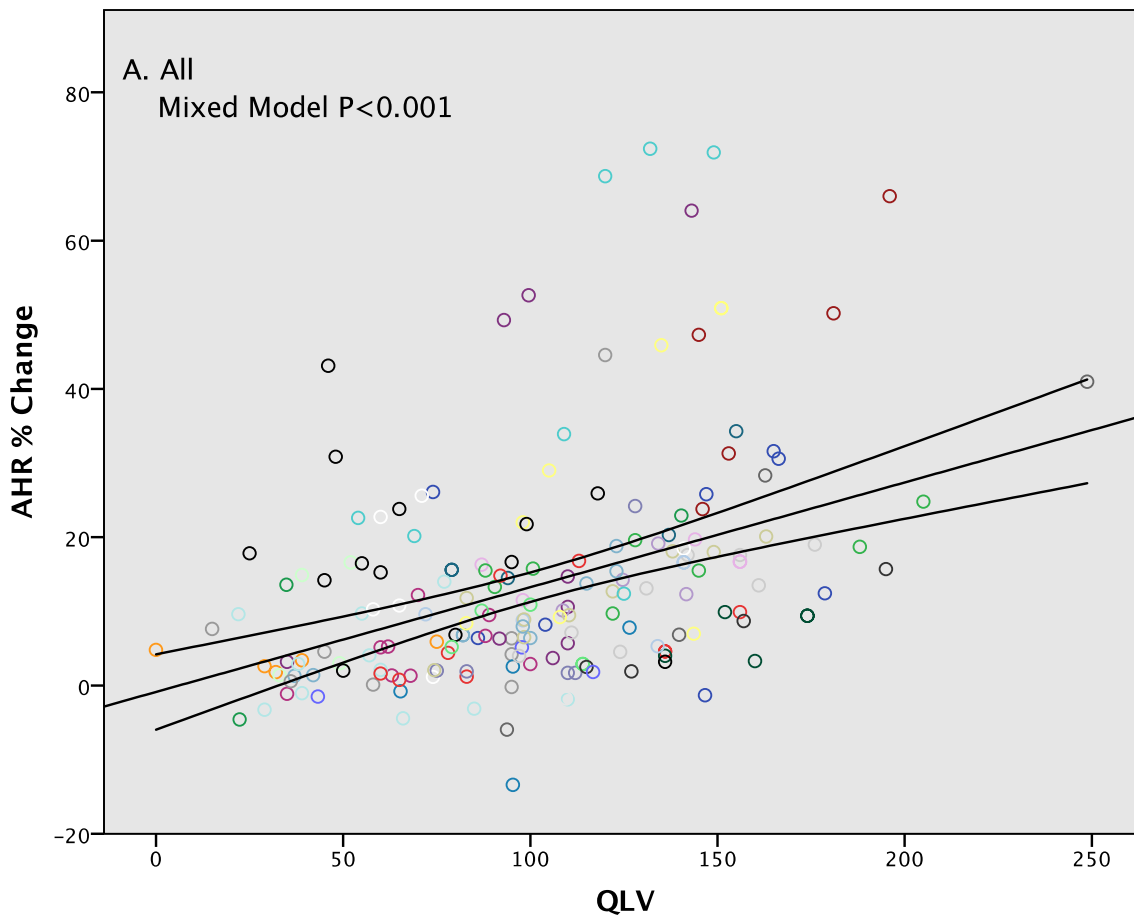


Figure 30. Scatter plot comparing electrical delay (Q-LV) vs change in acute left ventricular contractility (% change in LV dp/dtmax) during temporary biventricular endocardial pacing at various sites. Data from the same patient data has been uniquely colour coded. Error bars represent the 95% confidence interval. This graph shows data collected from all patients.

As multiple positions were analysed in each patient, a generalised linear mixed model analysis was used to control for non-independence among the repeated observations for each individual. Even when accounting for these repeated measures, the relationship between Q-LV and AHR retains statistical significance (mixed model: $p < 0.01$). This correlation was driven by the NICM cohort, where an even stronger correlation between AHR and Q-LV was identified (mixed model: $p=0.002$), see Figure 31.

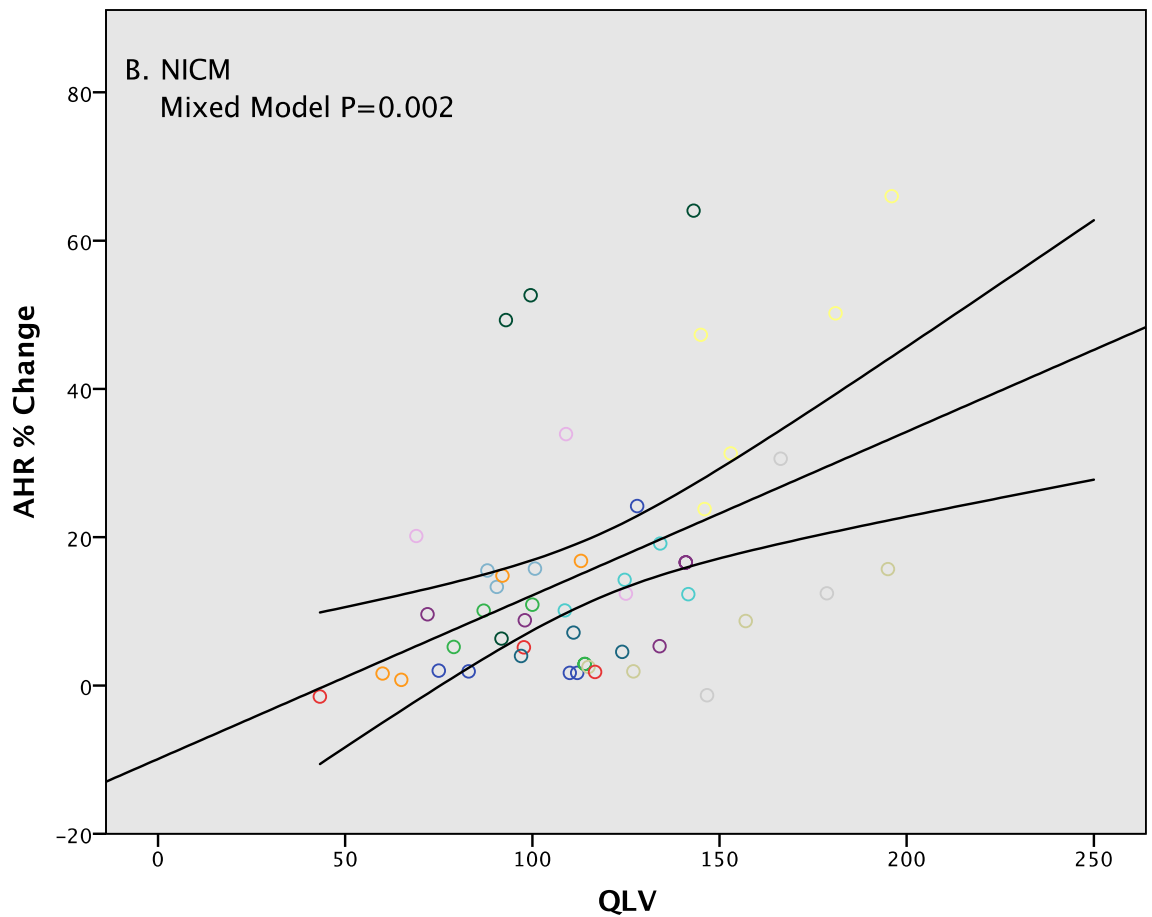


Figure 31. Scatter plot comparing electrical delay (Q-LV) vs change in acute left ventricular contractility (% change in LV dp/dtmax) during temporary biventricular endocardial pacing at various sites. Data from the same patient data has been uniquely colour code. Error bars represent the 95% confidence interval. This graph shows data collected from patients with non-ischaemic cardiomyopathy.

A greater degree of variance was noted amongst the ischaemic cohort where the magnitude of change was less than that seen in the NICM patients (mixed model: $p < 0.001$), see Figure 32.

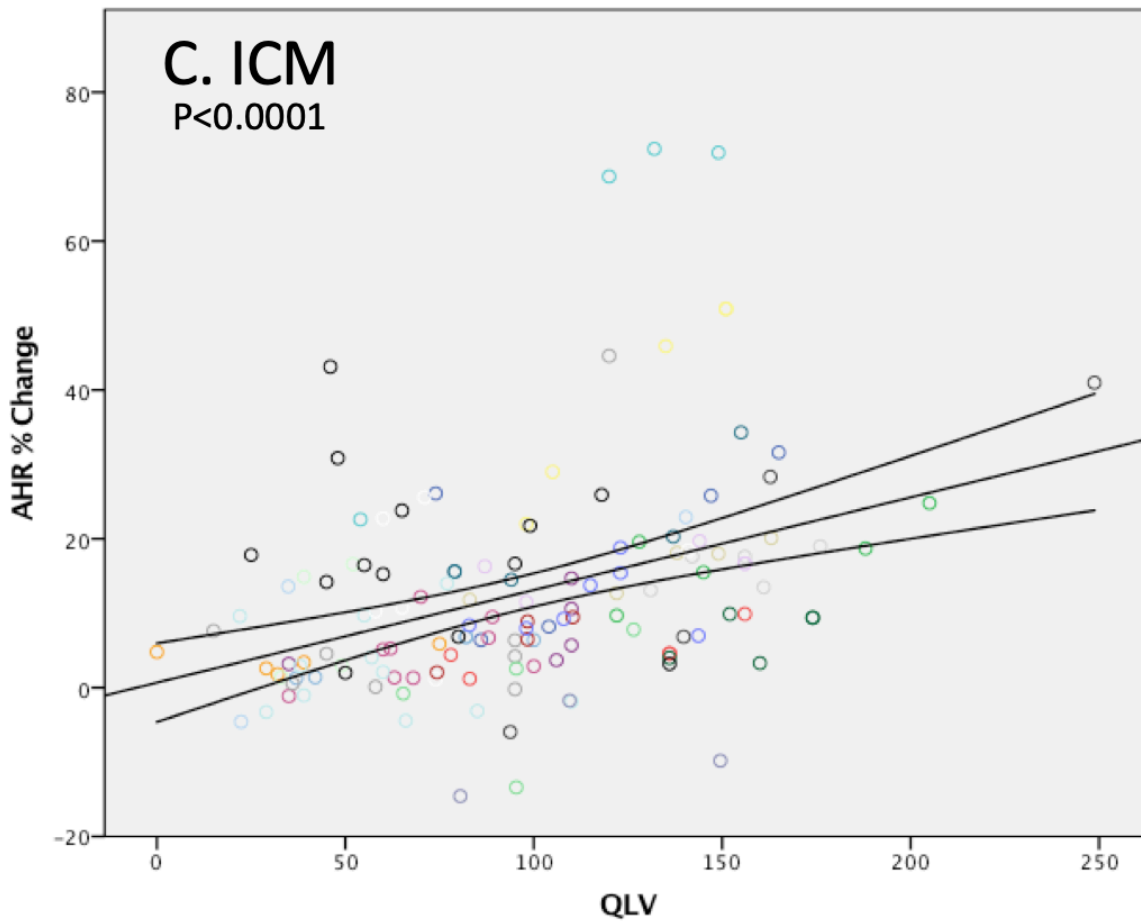
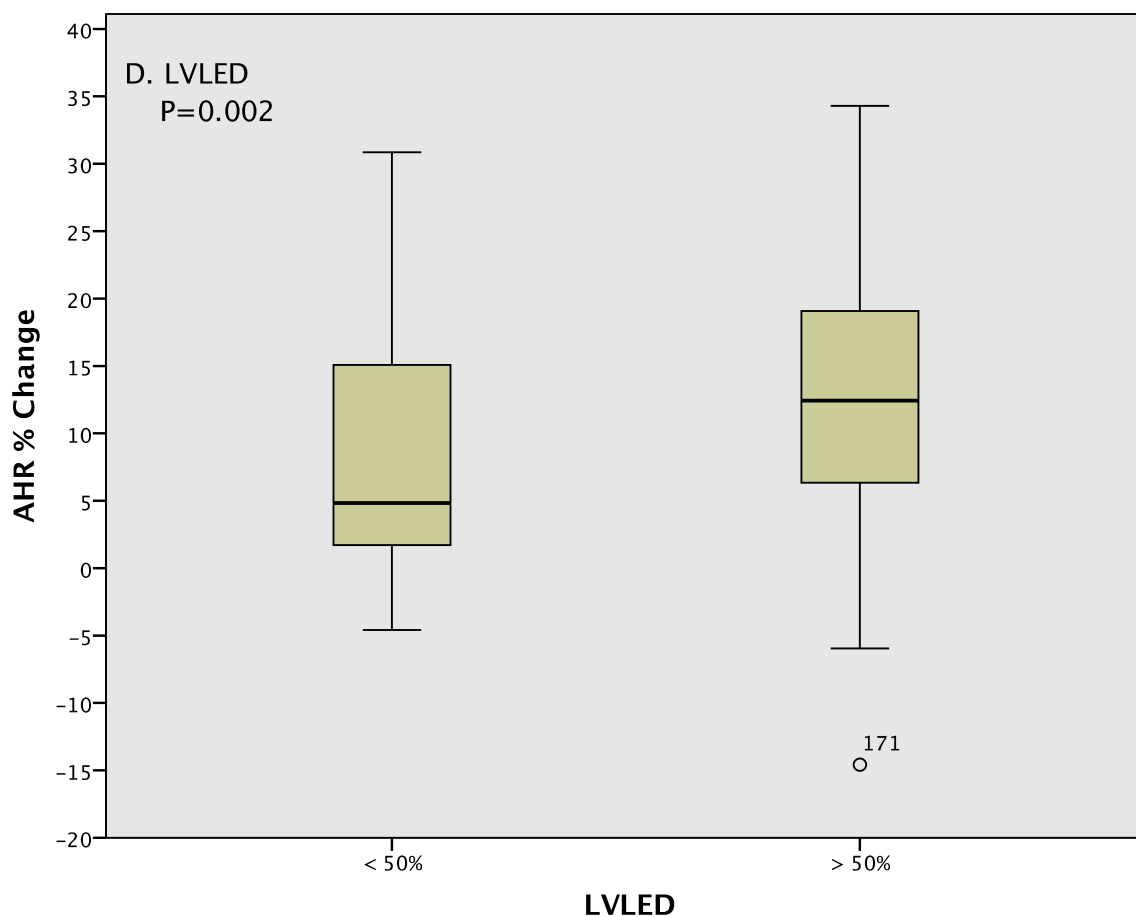


Figure 32. Scatter plot comparing electrical delay (Q-LV) vs change in acute left ventricular contractility (% change in LV dp/dtmax) during temporary biventricular endocardial pacing at various sites. Data from the same patient data has been uniquely colour code. Error bars represent the 95% confidence interval. This graph shows data collected from patients with non-ischaemic cardiomyopathy.



The LVLED was also calculated for each endocardial pacing site, by expressing the Q-LV at that site as a percentage of the baseline QRS [126]. This was then correlated against change in AHR. Delivering BiV EPI pacing in areas of electrical delay (defined as an LVLED > 50%) was associated with greater improvements in AHR and better long-term outcomes. When our cohort was dichotomised into endocardial locations with an LVLED > 50% and an LVLED < 50%, greater improvements in AHR were observed when endocardial pacing was delivered at areas exhibiting greater electrical latency ($8.6 \pm 9.6\%$ vs $16.1 \pm 16.2\%$, $P=0.002$), see Figure 33.

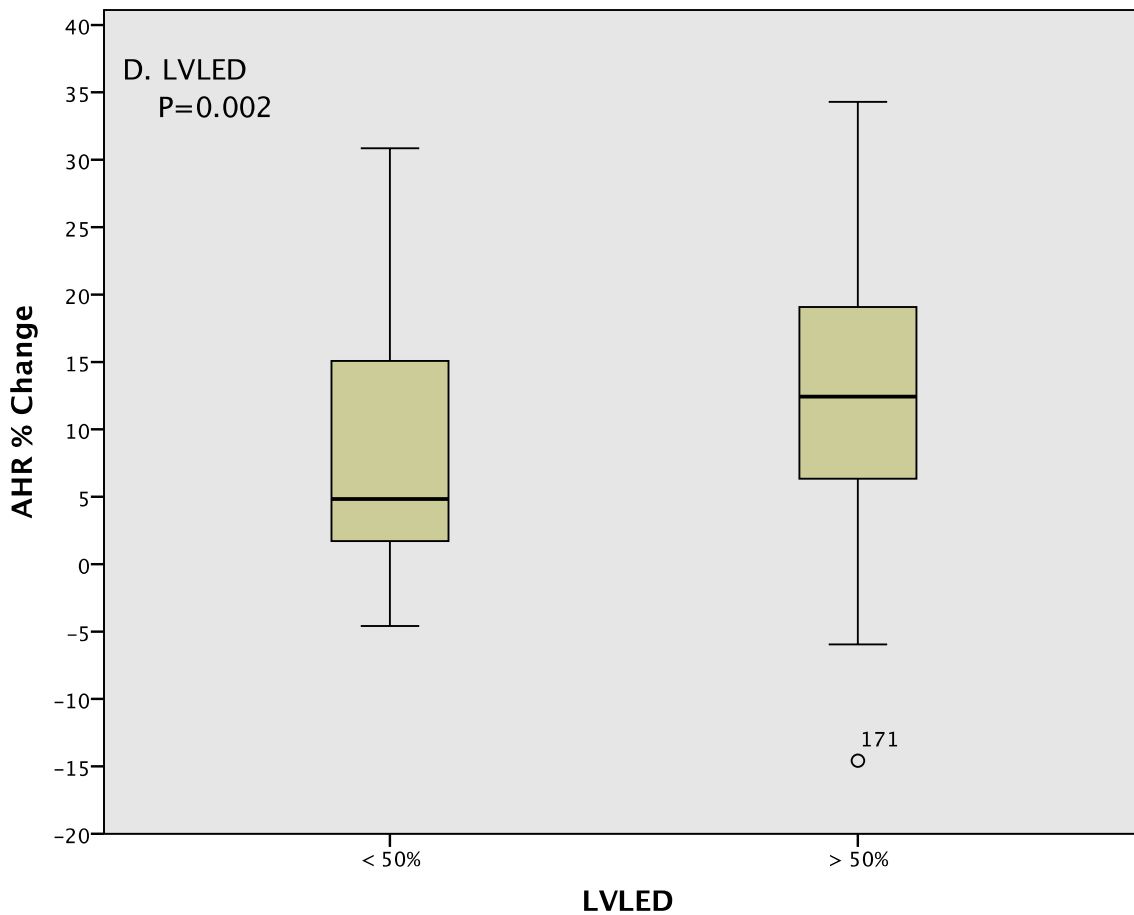


Figure 33. Boxplot & 95% confidence interval compare change in acute left ventricular contractility (% change in LV dp/dtmax) at locations with a Left Ventricular Electrical Lead Delay (LVLED) >50% & <50%.

7.3.4 Optimal Degree of Electrical Latency- Q-LV

Of the sites tested, the LV ENDO pacing location displaying the latest electrical activation (longest Q-LV time), was associated with the optimal AHR in just 62% of cases. Amongst patients with a DCM, the site displaying the latest activation proved optimal in 67% of patients for those with an ICM the latest activated site was associated with the optimal AHR in only 60% of patients.

7.3.5 Locating Late Activating Tissue- Q-LV

Across all patients, lateral LV ENDO locations tended to display the latest activation. For the entire cohort, LV ENDO location 2 (basal lateral) was associated with mean latest activation (135ms ± 8.2), see Figure 34. When only patients with a NICM were analysed, Q-LV predictably increased from septal to lateral segments and in these cases, targeting a lateral segment with late activation would seem to represent an optimal strategy, see Figure 35. LV ENDO location 6 (mid lateral) was associated with the latest activation (141.0 ms ± 29.3).

Amongst ICM patients, a greater variance in Q-LV was observed due to the impact of the underlying substrate and scar on electrical activation, see Figure 36. LV ENDO location 2 displayed the latest activation ($131.2 \text{ ms} \pm 41.0$) however, during univariate analysis, greater variance in the Q-LV was observed between each LV_{ENDO} location in patients with an ICM than was seen with a DCM ($p < 0.001$ vs $p = 0.17$).

All Patients

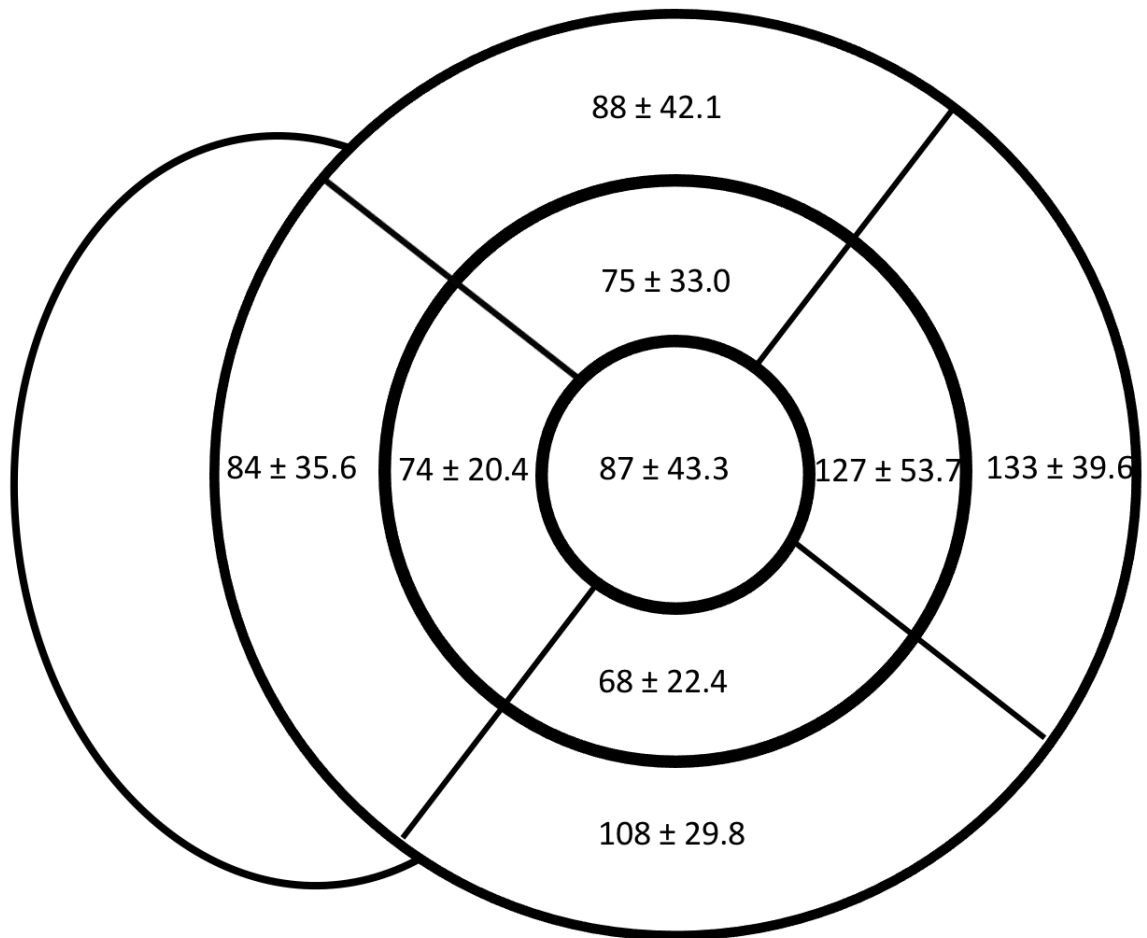


Figure 34. Circumferential polar plot demonstrating mean \pm standard deviation Q-LV times for each LV endocardial segment. This graphic shows data collected from all patients.

NICM

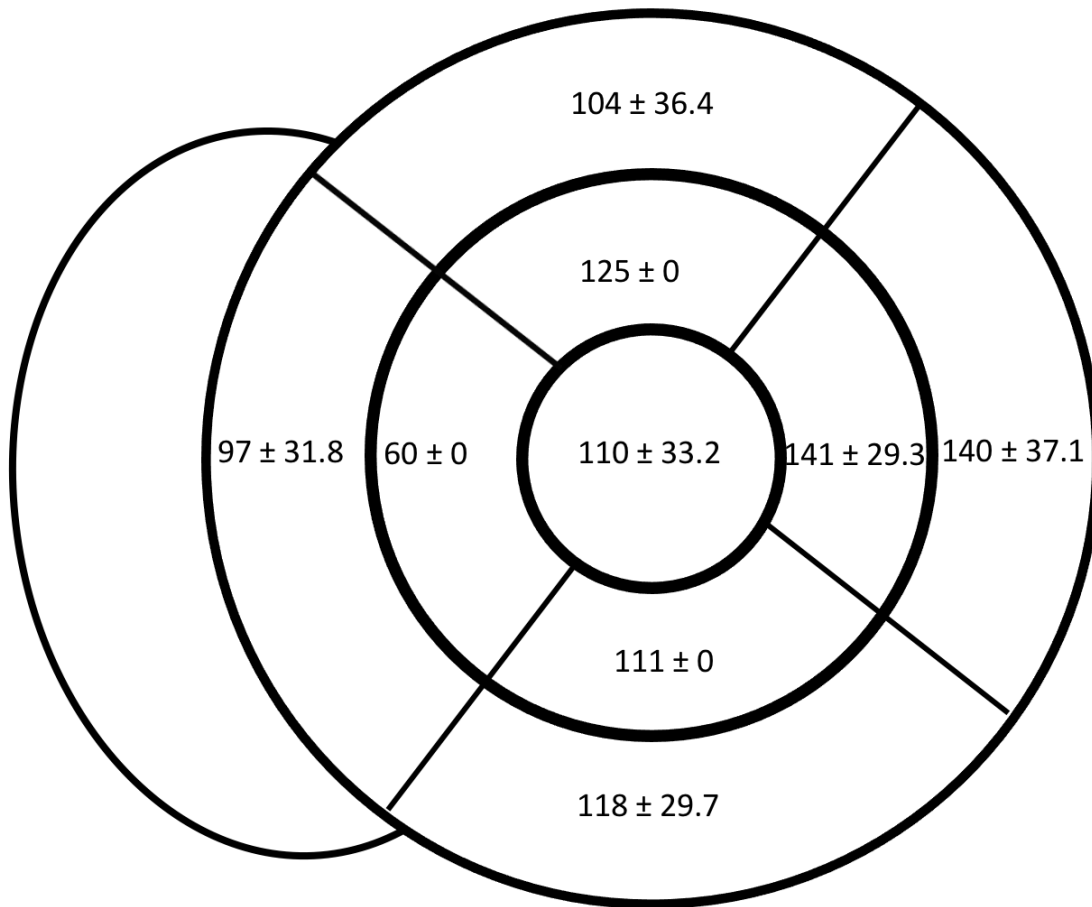


Figure 35. Circumferential polar plot demonstrating mean \pm standard deviation Q-LV times for each LV endocardial segment. This graphic shows data collected from patients with non-ischaemic cardiomyopathy.

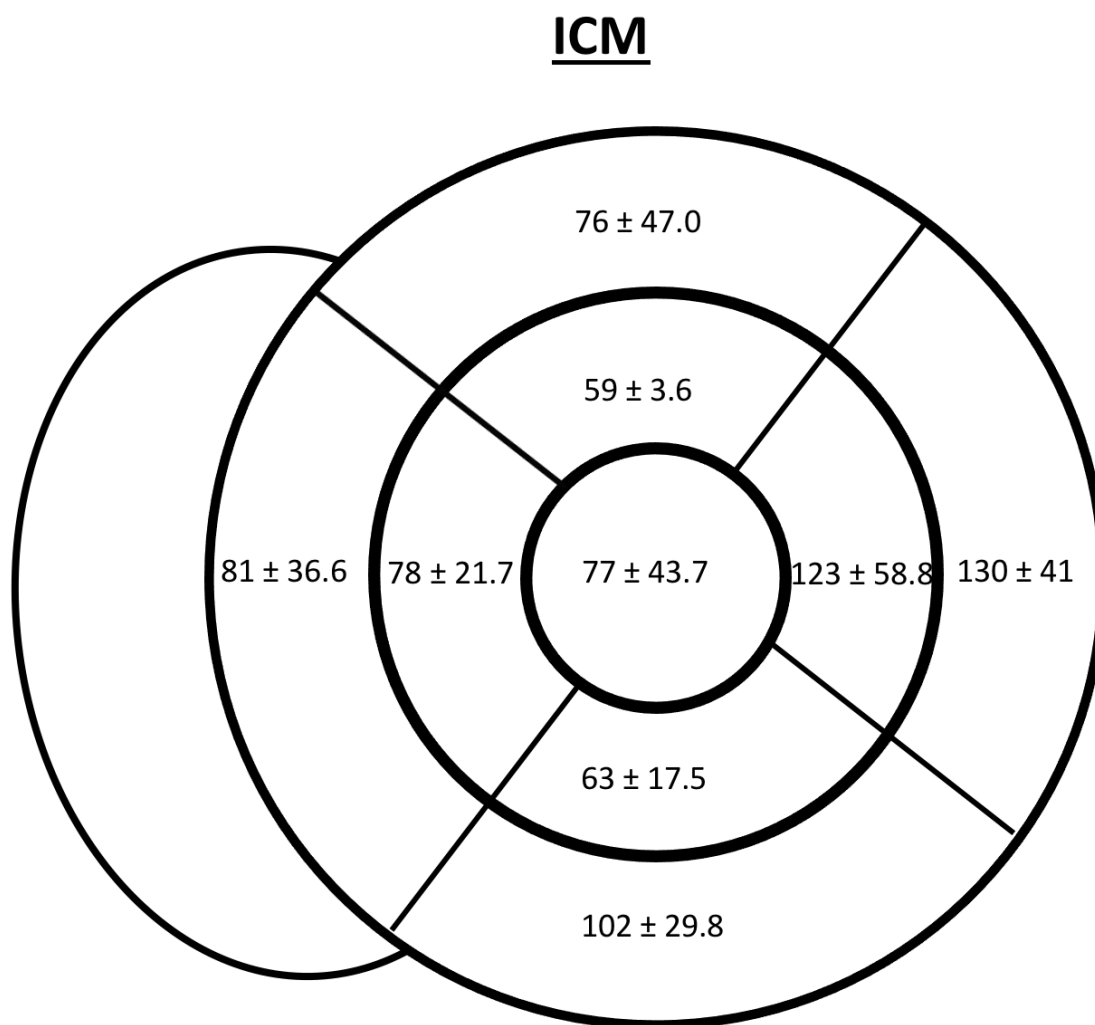


Figure 36. Circumferential polar plot demonstrating mean \pm standard deviation Q-LV times for each LV endocardial segment. This graphic shows data collected from patients with ischaemic cardiomyopathy.

7.3.6 Optimal Endocardial Pacing Site- QRS duration

75 patients had data correlating change in QRS duration to AHR at varying LV ENDO pacing locations, incorporating 574 LV ENDO positions. Patients were predominantly male (87%) with a mean age of 66.8 ± 12.5 years, the mean LVEF was $26.7 \pm 7.0\%$. The paced QRSd was significantly shorter at the optimal location than in the least favourable location (166.2ms vs 205.8ms, $p < 0.01$). Endocardial pacing in a position which resulted in a narrower paced QRSd showed a trend towards greater improvements in AHR however, when accounting for repeated measures in individual patients using mixed model analysis, this trend failed to achieve statistical significance (mixed model: $P=0.1$), see Figure 37. A similar non-significant trend was observed amongst the DCM patients (mixed model: $P=0.3$), Figure 38. Amongst the ICM patients no meaningful correlation could be identified (mixed model: $P=0.2$), see Figure 39.

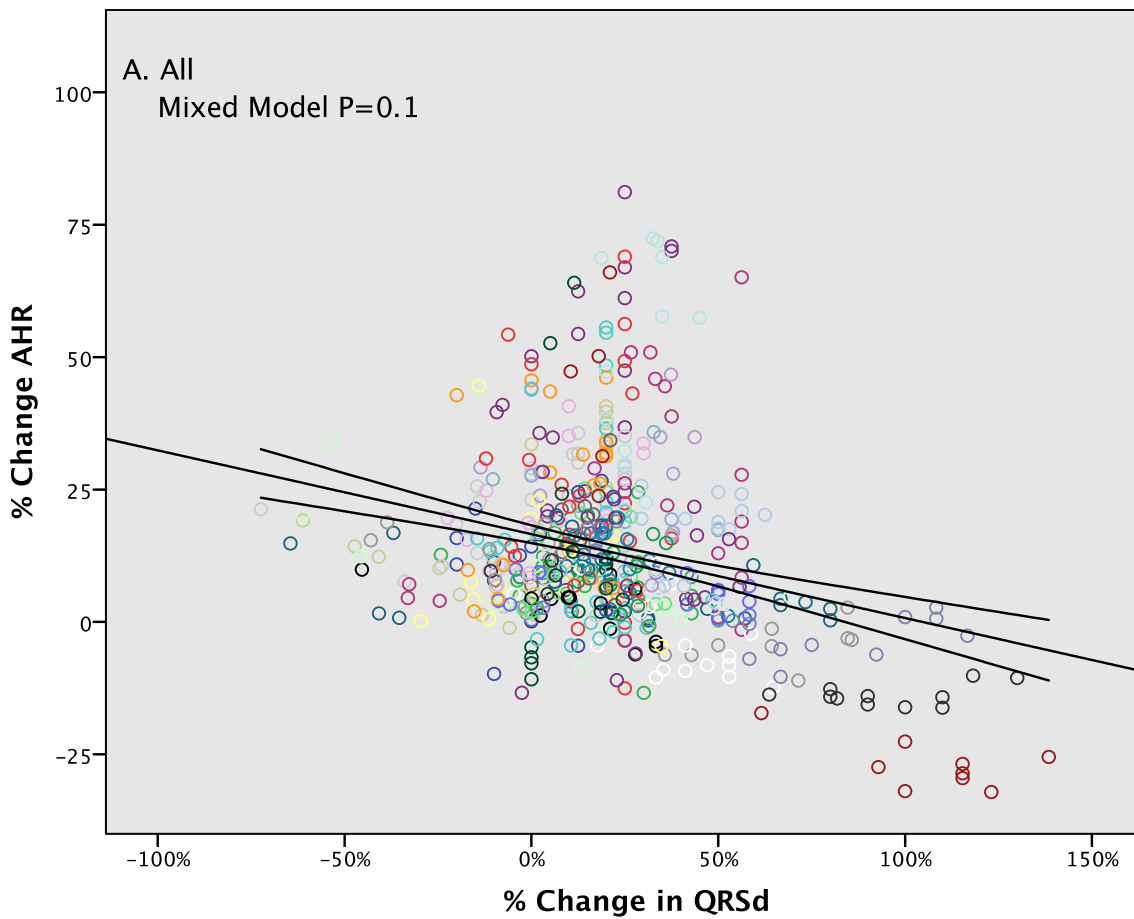


Figure 37. Scatter plot comparing electrical resynchronisation (% change in QRS duration from baseline) vs change in acute left ventricular contractility (% change in LV dp/dt_{max}) during temporary biventricular endocardial pacing at various sites. Percentage change in QRSd was calculated by comparing the baseline QRSd to the QRSd achieved during biventricular endocardial pacing at that site. Sites which achieved a narrowing of the QRS are represented by negative % change, whilst sites where biventricular endocardial pacing caused prolongation of the QRS are represented by positive % change values. Data from the same patient data has been uniquely colour coded. Error bars represent the 95% confidence interval. This graph shows data collected from all patients.

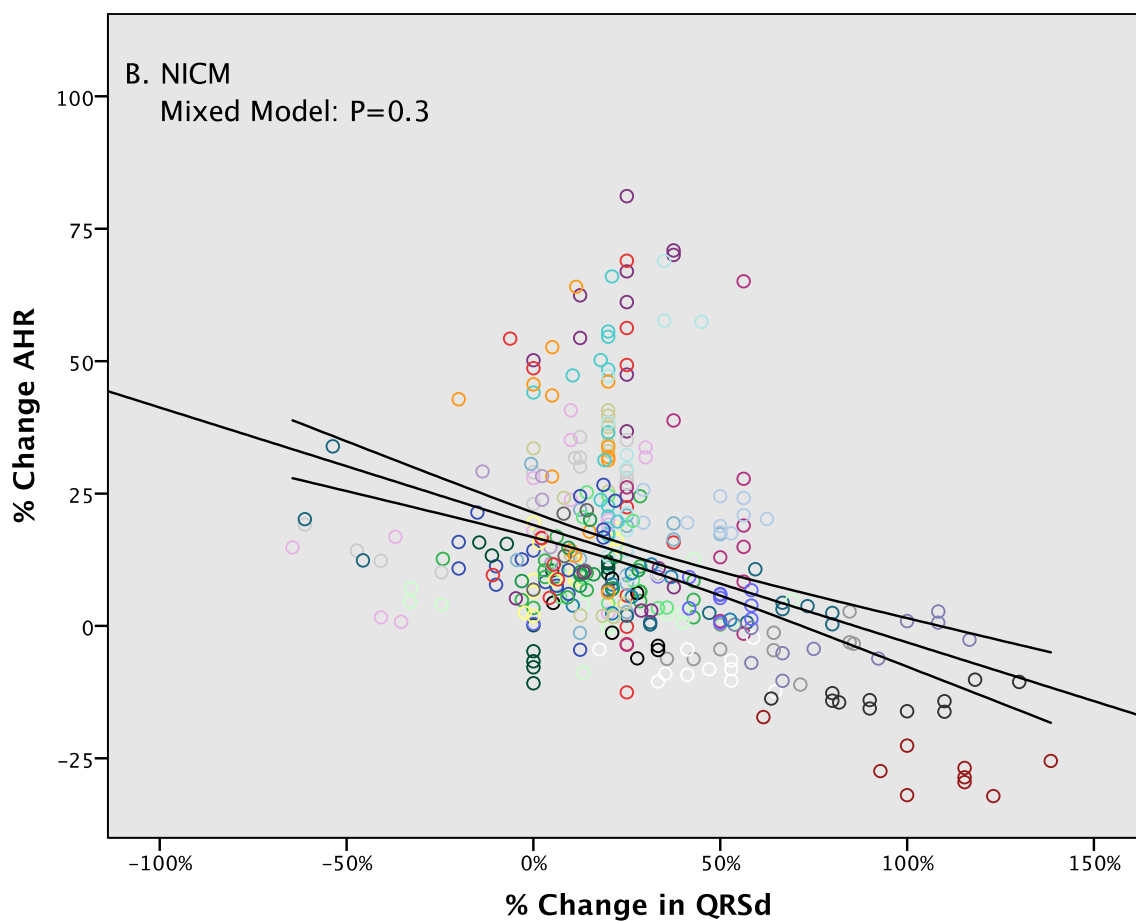


Figure 38. Scatter plot comparing electrical resynchronisation (% change in QRS duration from baseline) vs change in acute left ventricular contractility (% change in $LV dp/dt_{max}$) during temporary biventricular endocardial pacing at various sites. Percentage change in QRSd was calculated by comparing the baseline QRSd to the QRSd achieved during biventricular endocardial pacing at that site. Sites which achieved a narrowing of the QRS are represented by negative % change, whilst sites where biventricular endocardial pacing caused prolongation of the QRS are represented by positive % change values. Data from the same patient data has been uniquely colour coded. Error bars represent the 95% confidence interval. This graph shows data collected from patients with non-ischaemic cardiomyopathy.

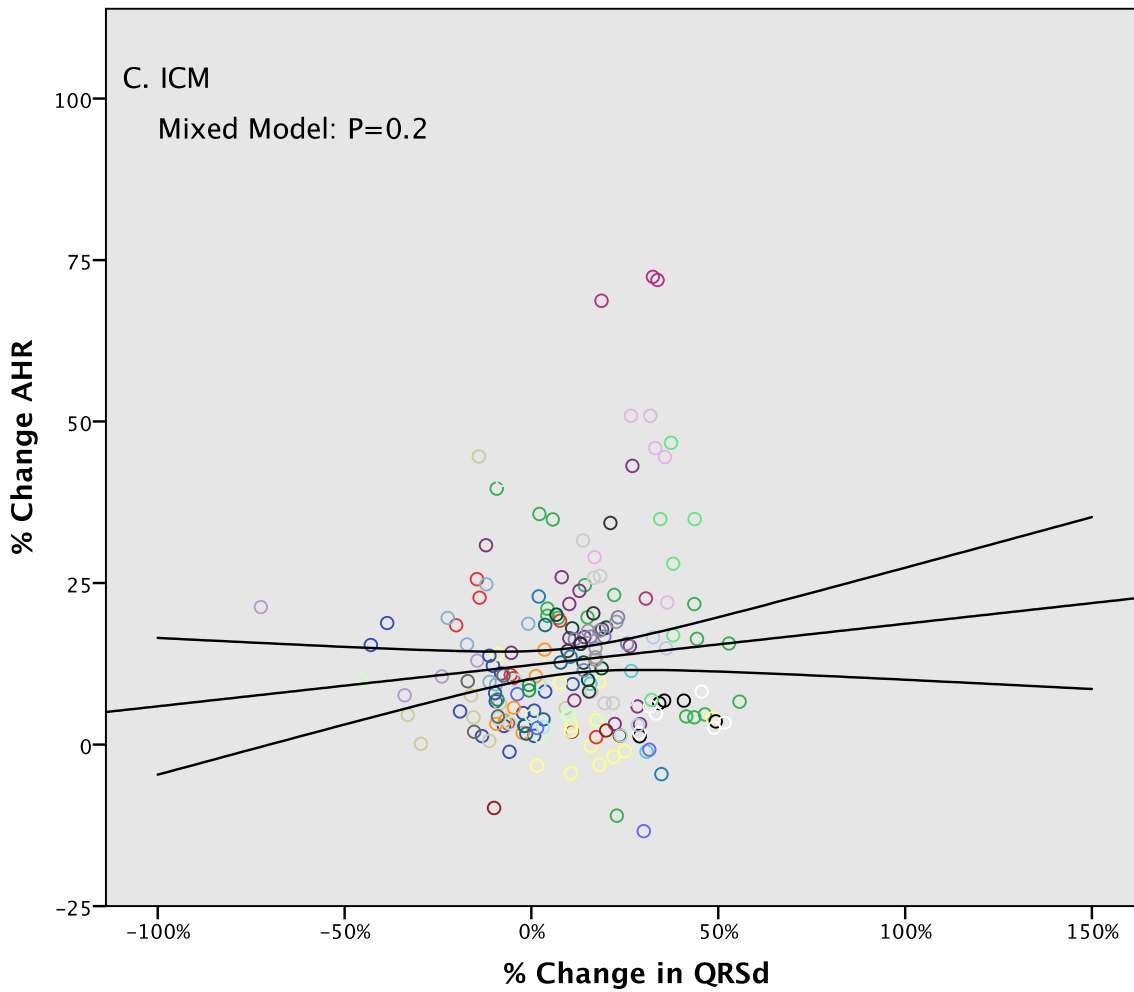


Figure 39. Scatter plot comparing electrical resynchronisation (% change in QRS duration from baseline) vs change in acute left ventricular contractility (% change in LV dp/dt_{max}) during temporary biventricular endocardial pacing at various sites. Percentage change in QRSd was calculated by comparing the baseline QRSd to the QRSd achieved during biventricular endocardial pacing at that site. Sites which achieved a narrowing of the QRS are represented by negative % change, whilst sites where biventricular endocardial pacing caused prolongation of the QRS are represented by positive % change values. Data from the same patient data has been uniquely colour coded. Error bars represent the 95% confidence interval. This graph shows data collected from patients with non-ischaemic cardiomyopathy.

7.4 DISCUSSION:

We sought to assess the characteristics of the optimal LV_{ENDO} pacing site in a registry of patients undergoing acute BiV ENDO pacing studies at five international centres. Previous single centre

observational studies have tended to focus on ischaemic or non-ischaemic cohorts. The principal findings were:

- 1) Pacing in areas of scarred or fibrotic myocardium was associated with lower AHR measurements.
- 2) Delivering BiV ENDO CRT LV ENDO sites with longer Q-LV times resulted in a superior AHR. This relationship was stronger in NICM patients.
- 3) LVLED was strongly correlated with AHR. Delivering BiV ENDO CRT at a location with an LVLED >50% was associated with a 16% improvement in AHR.
- 4) Maximal improvements in AHR were observed at sites displaying late electrical activation, but frequently this was not the site of latest activation, particularly amongst patients with an ICM.
- 5) Lateral LV ENDO pacing locations were associated with greater electrical delay in NICM patients but there was greater variation seen amongst ischaemic patients.
- 6) The paced QRSd was significantly shorter at the optimal location than in the least favourable location however, the correlation between paced QRS duration and AHR was not significant when repeated measurements in an individual patient were accounted for.

7.4.1 Comparison with previous studies

Our results confirm the finding that the optimal LV ENDO pacing location exhibits a marked degree of variability across both non-ischaemic and ischaemic patients. It would appear the BiV ENDO “sweet spot” is specific to each patient and individual tailoring of the endocardial position is likely to be required, in order to maximize response. Previous studies have focused predominantly on ischaemic or non-ischaemic cohorts. The current study allows comparison analysis in a larger number of both ischaemic and non-ischaemic patients.

The current analysis has highlighted several novel findings. Delivering BiV ENDO pacing in or near to sites of scar, is associated with a poor AHR. Previous studies have evaluated the role of some electrophysiological metrics of electrical latency (Q-LV timings) and found optimising these correlated with improved haemodynamics [197]. These findings appear significant amongst the larger patient population included in our registry. New analysis using LVLED further confirms the benefit of delivering BiV ENDO CRT in areas of greater electrical delay. Pacing in an area with an LVLED >50% was associated with a 16% improvement in AHR, whereas sites with an LVLED of <50% yielded a mean improvement of just 9%. Achieving a >10% improvement in AHR during acute BiV EPI CRT has been shown to be predictive of chronic reverse remodelling [47], suggesting patients will be more likely to remodel if a site with an LVLED of >50% is selected.

Chapter 7

Early work within the field, advanced the contention that the endocardial site observed to have the longest Q-LV interval was a reliable indicator for the optimal electrode position [197]. Our study refutes this, proving that the site of latest activation was associated with the optimal AHR in only around 60% of patients. Maximal improvements in AHR were observed at sites displaying late electrical activation, but frequently this was not the site of latest activation, particularly amongst patients with an ICM.

Amongst ischaemic patients, it is possible localised areas with late Q-LV could correspond to islands of viable tissue within areas of scar. Activation of such tissue would simply result in delayed impulse propagation during pacing. Under these constraints, selecting a site associated with a prolonged Q-LV may actually prove detrimental. Instead, Behar et al suggest the target for BiV ENDO should be a site which displays late activation but from which, conduction will not be delayed or blocked by regions of fibrosis or scar [196]. We found that the optimal degree of electrical latency appears to be around 90% of the maximal value, even amongst patients with a NICM who would not be expected to have marked myocardial fibrosis. It seems likely that even amongst this cohort, tissue characterisation is likely to be heterogeneous. When evaluated using non-contact mapping, patients with no evidence of late gadolinium enhancement on their MRI were observed to have evidence of conduction block [284]. It is possible that MRI is not capable of detecting the low degrees of diffuse fibrosis at the microscopic level, which correlate with slow conduction [285]. We would argue that fibrosis may not even be present but the disease process affects other myocardial properties, including gap junctions or ion channel remodelling, which could interfere with activation wave front propagation [284].

Similarly, the presence of a narrow paced QRSd appears to be more predictive amongst non-ischaemic patients. Selecting a site which results in a narrowing of the QRSd appears shows a clear trend with improvements in haemodynamics and yet pacing in the optimal haemodynamic location does not always achieve the narrowest paced QRS. Previous work has established that electrical and mechanical resynchronisation are not necessary synonymous. Lumens et al identified that reductions in LV endocardial activation time did not correlate with improvements in $LVDp/dt_{max}$ [286]. Similarly, Shetty et al observed that while BiV ENDO could be associated with significant haemodynamic improvements, these did not translate into reductions in LV activation time, which was frequently shorter during BiV EPI pacing [87]. Instead it has been postulated that improvements in AHR may correlate to more “effective” mechanical myocardial recruitment as opposed to simply shortening the LV activation time [284]. This disconnect between electrical and mechanical synchrony may explain why delivering LV_{ENDO} pacing to the intraventricular septum can result in very narrow QRS, while failing to achieve true mechanical synchrony. We would

therefore caution against using this metric alone when looking to identify the optimal endocardial pacing site.

Empirically, a lateral site is thought to represent the optimal location for LV stimulation as this represents the site of greatest electrical delay. CRT aims to restore regional activation synchrony and enhance cardiac contractility and the mechano-energetic efficiency of the heart [275]. Lateral LV ENDO pacing locations were typically associated with greater degrees of electrical delay. This was particularly true, amongst patients with a non-ischaemic aetiology, where the delay in activation progressively increased, in proportion to the distance from the septum. Amongst ischaemic patients however, this progressive delay in activation was not observed. The optimal site for the delivery of BiV ENDO pacing has been observed to vary significantly [41,196,197] particularly amongst ICM patients and our finding of heterogeneity in the LV ENDO site which displays the latest activation, would appear concordant with this finding.

7.4.2 Limitations

The main limitation of the current study is the differing protocols employed at each centre. Whilst inclusion and exclusion criteria, pacing protocol & AHR measurement technique were broadly similar at each site, they did differ subtly. The nomenclature used to describe the temporary pacing site differed with some centres using a 16 or 9 segment bulls eye plot whilst others merely described the anatomical location. It was necessary to describe the LV pacing location using a single standardized approach. We elected to use the 9-segment model both for simplicity, but more importantly, we feel this method yields an area it would be reasonable to accurately target, given the current technology available.

In addition, not all pacing protocols necessitated an AHR measurement be taken in every potential site and as such, not every patient had complete data set. It must be remembered, temporary endocardial pacing studies are invasive and time consuming and as such this data can be challenging to collect.

Despite the limitations acknowledged above, this study does give an insight of the performance of several different metrics at predicting the optimal site for BiV ENDO. Measurement of AHR was used as a surrogate for CRT response and there is conflicting evidence as to whether this translates into a chronic benefit. AHR however does lend itself to repeated measurements within the same patient. BiV ENDO pacing was delivered with differing AV intervals but simultaneous VV timings and it is possible that optimization of AV and/or VV timing may have resulted in significant differences in AHR. Such measurements however are time consuming and the fact that VV timings

were standardized across the groups is of benefit in making comparisons between different data-sets.

7.5 CONCLUSION

BiV ENDO pacing may offer a technique to improve CRT response especially in patients with ischaemic aetiology. Avoidance of scar and targeting late activated regions would appear important and may require individual assessment of tissue characterization and latency especially in ischemic patients. It is likely the ideal pacing location may be as unique as the patient's own pathology.

Chapter 8 A Pilot Assessment Of Guidance & Site

Selection Methods During Biventricular Endocardial

Pacing

This section has been adapted from Guidance for *Optimal Site Selection of a Leadless Left Ventricular Endocardial Electrode Improves Acute Hemodynamic Response and Chronic Remodeling* (Sieniewicz, Behar, et al., 2018).

8.1 INTRODUCTION:

A significant number of patients fail to respond to CRT when delivered through an epicardial LV lead placed via the coronary sinus (CS) [1,30,34]. Furthermore technical and anatomical limitations mean it is not always possible to implant an LV lead [92] and patients upgrading from a pre-existing pacing system may have central venous stenoses preventing transvenous LV lead implantation [246]. To overcome these challenges, novel methods of CRT delivery have been developed including LV endocardial stimulation [196,197]. Chronic LV endocardial pacing was initially delivered via trans-septal pacing leads, mandating lifelong anti-coagulation but the introduction of new wireless technology may increase the use of LV endocardial pacing and avoid anticoagulation [270,276].

The optimal LV endocardial pacing location exhibits marked variability in ischemic [42] and non-ischemic patients [41,86,87] with indiscriminate LV endocardial CRT being inferior to traditional transvenous epicardial CRT [196]. Avoiding scarred tissue whilst targeting viable, late activating sites may improve conventional CRT response [125,126,282]. Targeting the site of latest mechanical activation using speckle-tracking in the TARGET study improved the reverse remodelling rate to over 70% [119]. Alternative strategies include targeting the site of latest electrical activation, using Q-LV [125], or using cardiac magnetic resonance (CMR) to identify late activating, viable tissue [234].

We hypothesised that identification of the optimal LV endocardial location for a wireless LV pacing electrode would result in improved acute hemodynamic response and chronic remodelling. We performed LV endocardial pacing using the WiSE-CRT, wireless pacing system (WiSE-CRT System, EBR Systems, Sunnyvale, California) in conjunction with guidance to identify late

activating, viable LV endocardial segments and measured acute markers of contractility and chronic markers of CRT response (reverse remodelling).

8.2 METHODS:

Data was collected from three centres implanting the WiSE-CRT system. This co-implant system uses ultrasound energy to activate a small leadless pacing electrode which is deployed trans-arterially via a retrograde trans-aortic approach in the LV endocardial cavity. The ultrasound (USS) array implanted sub-cutaneously, is triggered by the implanted pacemaker or transvenous defibrillator. Patients studied were part of the WICS Post Market Surveillance Registry (Clinical trial study number NCT02610673) and all patients gave full written consent to participate in the study. The centres were the John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust (Oxford, United Kingdom), Guy's and St Thomas' NHS Foundation Trust (London, United Kingdom) & The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust (Middlesbrough, UK).

8.2.1 LV electrode guidance

At each centre, a combination of either pre-procedural imaging and/or electro-anatomical mapping was used to identify the optimal LV endocardial pacing site.

8.2.1.1 Echocardiographic guided approach. The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust (Middlesbrough, UK).

Echocardiography using speckle-tracking 2D radial strain analysis was used to identify and target the latest mechanically activated LV segment using multi-segment models as described previously [122]. Regions of scar were defined as segments <0.5mm thick and displaying abnormal increase in acoustic reflection. In addition, any myocardium which exhibited low amplitude strain curves and a peak radial strain <16.5% was defined as scar [157,287]. During LV electrode implantation, the LV free wall was visualised using fluoroscopy and sub-divided into four segments according to coronary venous anatomy; anterolateral, lateral, posterolateral & posterior, as previously described [122]. The electrode could then be implanted into the target segment.

8.2.1.2 Electrical latency (QL-V). John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust (Oxford, UK).

Electrical latency was assessed using the WiSE-CRT delivery catheter. A minimum of three sites were tested. Two indices of electrical latency were used to identify the optimal pacing site; the Q-

LV activation time [125] and the Q-LV/QRS ratio [126,197]. Sites with a Q-LV of less than 100ms were excluded. The optimal target was the site which displayed the latest Q-LV during RV pacing and a Q-LV/QRS ratio of >0.66 . Viability was assessed by excluding any sites with a pacing capture threshold of $>2V$.

8.2.1.3 Electro-anatomical mapping & cardiac magnetic resonance. Guy's and St Thomas' NHS Foundation Trust (London, United Kingdom).

Patients were implanted using a hybrid approach of electro-anatomical mapping (EAM) and where possible, CMR imaging which had been performed prior to implantation of the co-implant device. This technique allowed the identification of areas exhibiting late electrical activation (bipolar activation map) and areas of low voltage (bipolar scar map) using CARTO 3 (Biosense Webster, Diamond Bar, California), as previously described [288]. When available, prior CMR data was also analysed allowing the identification of both late mechanically activated tissue and via analysis of late gadolinium enhancement (LGE) imaging, areas of scarred or fibrotic myocardium (Siemens Magnetom Aera 1.5-T magnetic resonance imaging scanner, Siemens Healthcare, Erlangen, Germany).

8.2.2 Inclusion Criteria

The WiSE-CRT pacing system is CE marked for three indications [270]. Patients classified as non-responders to conventional CRT, those where LV lead deployment is not possible (due to anatomical constraints, high capture thresholds or phrenic nerve stimulation) and in patients undergoing CRT upgrade where implanting an LV lead was impractical due to venous access or previous pocket infection. Patients meeting any of the above criteria were included in this study. Patients were classified as having either ischemic cardiomyopathy (ICM) using a combination of cardiac MRI, coronary angiography and clinical history or non-ischemic cardiomyopathy (NICM). Patients were implanted via a retrograde trans-aortic approach as previously described (10).

8.2.3 Acute Hemodynamic Response

Acute hemodynamic response (AHR) was used to assess the immediate response to LV endocardial stimulation [88]. This reproducible marker of acute contractility is best expressed as the change in the maximum rate of left ventricular pressure ($LV-dP/dt_{max}$), from a baseline control state measured using a pressure wire positioned within in the LV cavity [47]. Temporary BiV ENDO pacing was performed using the patient's own co-implant device and either the WiSE-CRT delivery catheter or a mapping catheter placed within the LV cavity. During temporary BiV ENDO pacing,

the A-V interval was deliberately not optimised. The A-V interval of the co-implant device was employed with simultaneous V-V stimulation. We assessed how AHR varied according to measures of electrical latency including Q-LV [125], Q-LV/QRS ratio and paced QRSD. AHR values were obtained in multiple areas where BiV_{ENDO} capture was performed. Acute responders were defined as those which achieved a > 10% increase in their AHR during LV endocardial stimulation at the location chosen to deploy the WiSE-CRT LV electrode.

8.2.4 Chronic response to CRT (remodelling)

Patient were considered echocardiographic responders to CRT if they exhibited a $\geq 15\%$ reduction in end-systolic volume, measured using trans-thoracic echocardiography and/or a $\geq 5\%$ improvement in LVEF 6 months post implant [40].

8.2.5 Statistics

Continuous variables with a Gaussian distribution were described using mean values \pm standard deviation. AHR and EP data was tested for normality with the Shapiro-Wilk test. Significance testing on normally distributed paired data was performed using two tailed paired *t* tests. Significance testing on non-normally distributed paired data was performed using the Wilcoxon Signed Rank test. Significance testing on non-normally distributed un-paired data was performed using the Mann-Whitney U test. To account for the clustering of data and multiple measurements within each patient, a generalised linear mixed effect model was applied for all data points that achieved capture. Where multiple data points were recorded from an individual patient, this has been displayed on the scatterplot using a specific colour marker for each patient. Lines of best fit with 95% confidence interval were shown to aid understanding. Results were considered significant at $p < 0.05$. Analysis was performed on PASW Statistics 24 (SPSS Inc., Chicago, Illinois).

8.3 RESULTS:

8.3.1 Patient Characteristics

A total of 26 patients across the three centres were implanted with the WiSE-CRT system using a guided approach, see Table 9.

Table 9. Patient demographics

	Mean \pm SD or Numbers (%)
Patients	26
Age (years)	68.8 \pm 8.4
Male (%)	22 (84.6%)
LVEF (%)	34.2% \pm 7.8
NYHA	2.6 \pm 0.5
QRS duration (ms)	163.8 \pm 26.7
QRS Morphology	
RV Paced	24 (92%)
LBBB	2 (8%)
Aetiology	
ICM (%)	8 (30.8%)
Indication	
Difficult CS anatomy/access	14 (53.8%)
Complex Upgrade	10 (38.4%)
Failure to respond to BiV EPI	2 (8.0%)
Guidance Technique	
Echocardiographic	9 (34.6%)
Electrical Latency	10 (38.5%)
CMR and EAM	7 (26.9%)

Patients were predominantly male with a mean age of 68.8 \pm 8.4 years, mean LVEF 34.2% \pm 7.8 (Min: 19%, Max: 51%). The mean QRS duration was 163.8 \pm 26.7ms. In 92% of patients, the baseline QRS morphology was an RV paced rhythm due to the co-implant nature of the WiSE CRT pacing system. 31% of patients had experienced AV block requiring pacemaker insertion prior to

implantation with the WiSE CRT device. 30.8% of patients had an ischemic aetiology. 53% of the patients had experienced a failed conventional transvenous CRT implant, 8% of patients were prior non-responders. 38% of patients had a baseline LVEF >35%. Patients with a baseline LVEF of > 35% were recruited if they required an upgrade to a CRT system, but it proved impossible to site a transvenous, epicardial lead. Some patients had also previously received transvenous, epicardial CRT and had experienced a degree of LV remodelling but gone on to develop issues with their LV lead and required an alternative means of LV stimulation.

8.3.2 Procedural Details & Safety Issues

Procedure times were 126±65mins with a mean of 3.0 ± 2.6 LV endocardial sites tested per patient. A similar complication rate was observed to that recognised in the literature [270], see Table 10.

Table 10. Complications resulting from electrode deployment

<24 hours	1 (3.8%)
Cardiac tamponade	1
>24 hours – 1 month	7 (26.9%)
Pseudo-aneurysm	3
Unable to pace LV electrode (1m)	2
Pocket infection (generator)	1

Acute complications relating to electrode implantation (<24 hrs) occurred in one patient with cardiac tamponade requiring emergency thoracotomy. The most commonly encountered adverse events >24 hours to 1 month were complications arising from femoral arterial access. These included pseudo-aneurysm formation requiring surgical intervention. In two cases, it was not possible to achieve consistent capture of the LV endocardial pacing electrode. In both cases, failure of the screening procedure to exclude an un-suitable patient was later confirmed. One patient had co-morbid COPD with significant lung encroachment affecting the USS signal between the sub-cutaneous array and endocardial pacing electrode. In the other case, the eventual

distance between the LV pacing electrode and the USS array was too great to achieve consistent capture.

8.3.3 Acute Hemodynamic Response

In 16 of the patients undergoing guided electrode placement, AHR was measured intra-procedurally. A significant change in the mean LV-dP/dt_{max} was observed during BiV ENDO pacing at the target site (baseline 915.3 ± 211.4 mmHg/s vs BiV ENDO CRT 1107.4 ± 369.5 mmHg/s, $p = 0.0047$) yielding a mean improvement in AHR of 21.0%, see Figure 40.

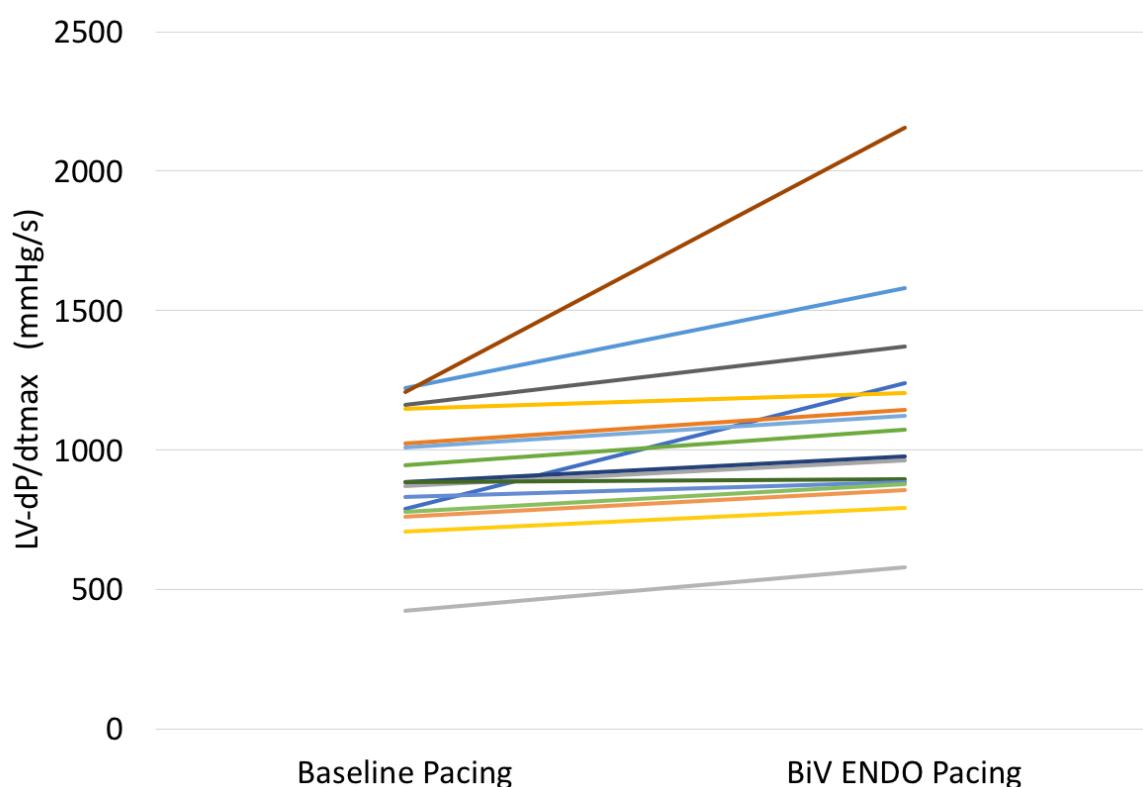


Figure 40. Change in AHR from baseline during biventricular endocardial pacing

Six-month follow-up data was available for comparison in 14 of the patients who had undergone electrode deployment validated by AHR. Of the 12 patients who experienced a >10% improvement in AHR at the target site and of these, 92% ($n=11$) met the definition of an echocardiographic responder while this was true for only 50% ($n=1$) of the patients who failed to achieve a 10% improvement in AHR at the target site. Q-LV was measured at the site of endocardial stimulation as described previously [42] and correlated against the observed AHR. Delivering BiV ENDO pacing in areas of delayed electrical activation was associated with greater improvements in AHR and remained significant, even when accounting for repeated measures in individual patients using generalised linear mixed model analysis (mixed model: $P=0.0007$), see Figure 41.

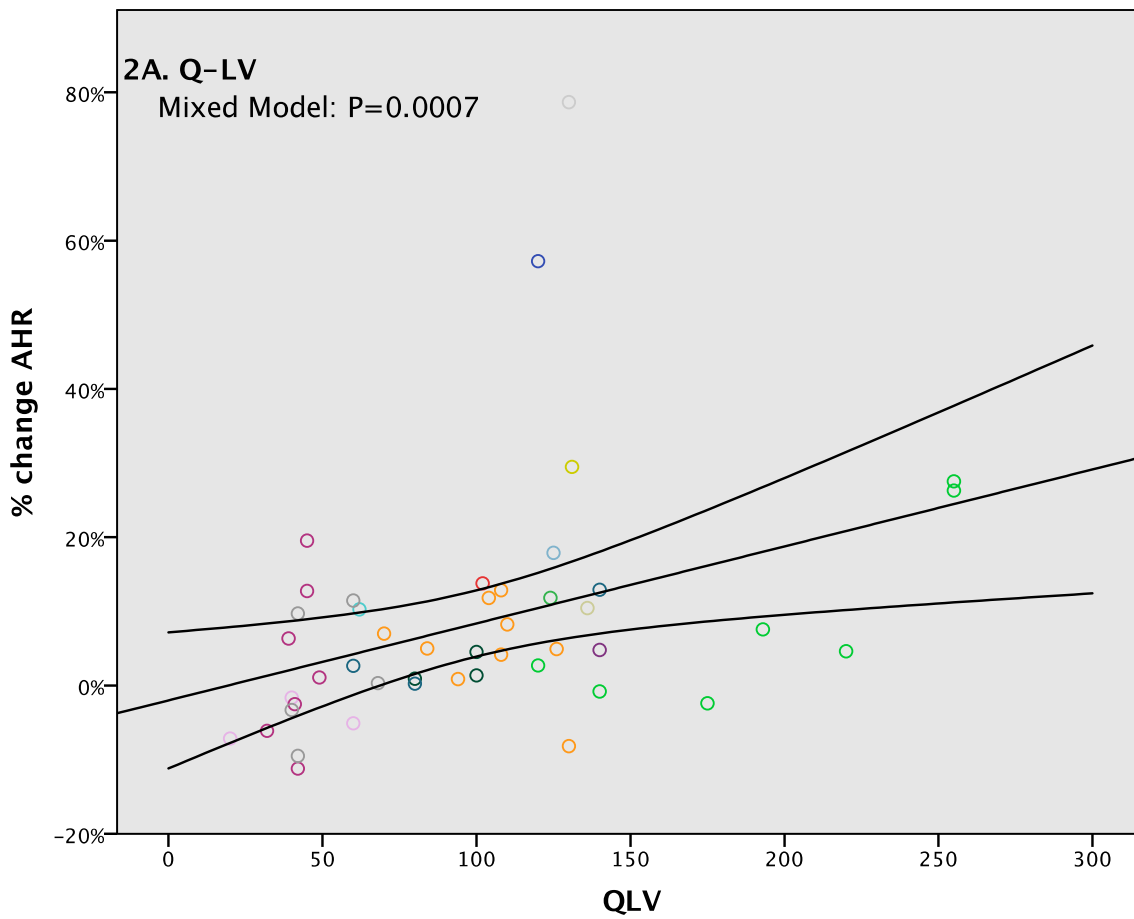


Figure 41. Change in AHR at various LV endocardial locations vs electrical delay measured using QLV.

An even stronger correlation was found between AHR and Q-LV/QRS ratio. Again, this correlation remained significant when repeated measures in individual patients were accounting for (mixed model: P=0.0009), see Figure 42.

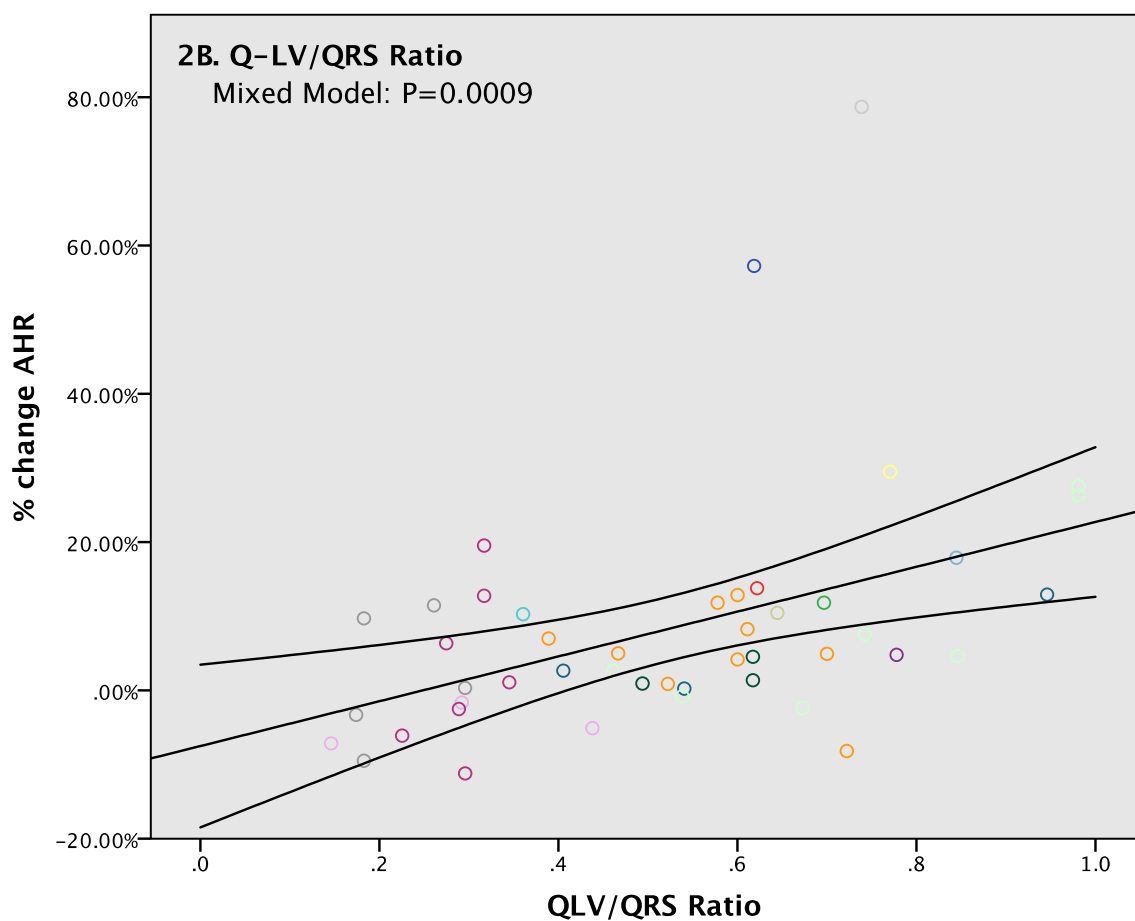


Figure 42. Change in AHR at various LV endocardial locations vs electrical delay measured using QLV/QRS Ratio.

When our cohort was dichotomised into endocardial locations with a Q-LV/QRS ratio > 0.5 and a Q-LV/QRS ratio < 0.5, greater improvements in AHR were observed when endocardial pacing was delivered at areas displaying greater electrical latency ($14.4 \pm 19.7\%$ vs $2.3 \pm 7.6\%$, $P=0.01$), see Figure 43.

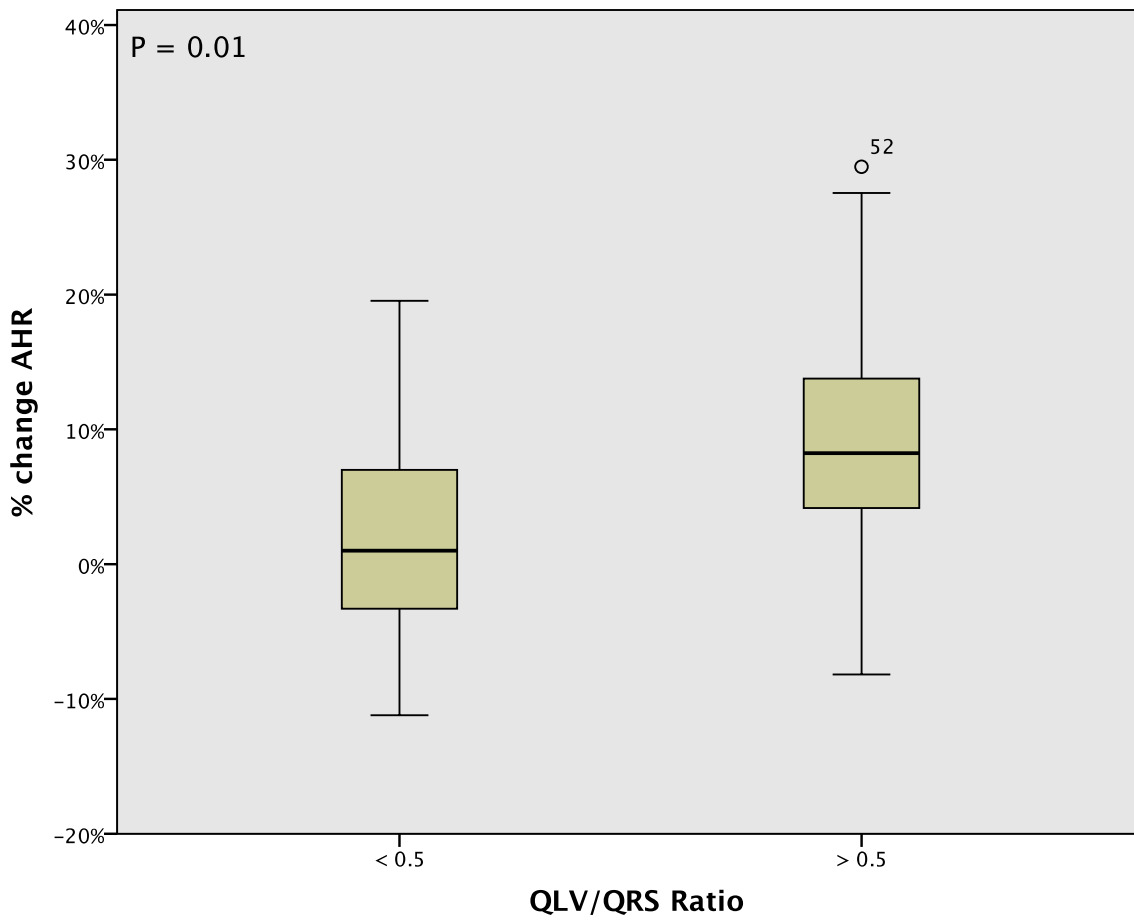


Figure 43. Change in AHR vs Q-LV/QRS Ratio of > 0.5.

Delivering endocardial pacing in a position which achieved a narrower paced QRSd showed a trend towards greater improvements in AHR but this relationship failed to achieve statistical significance when evaluated for repeated measures (mixed model: P=0.06), see Figure 44.

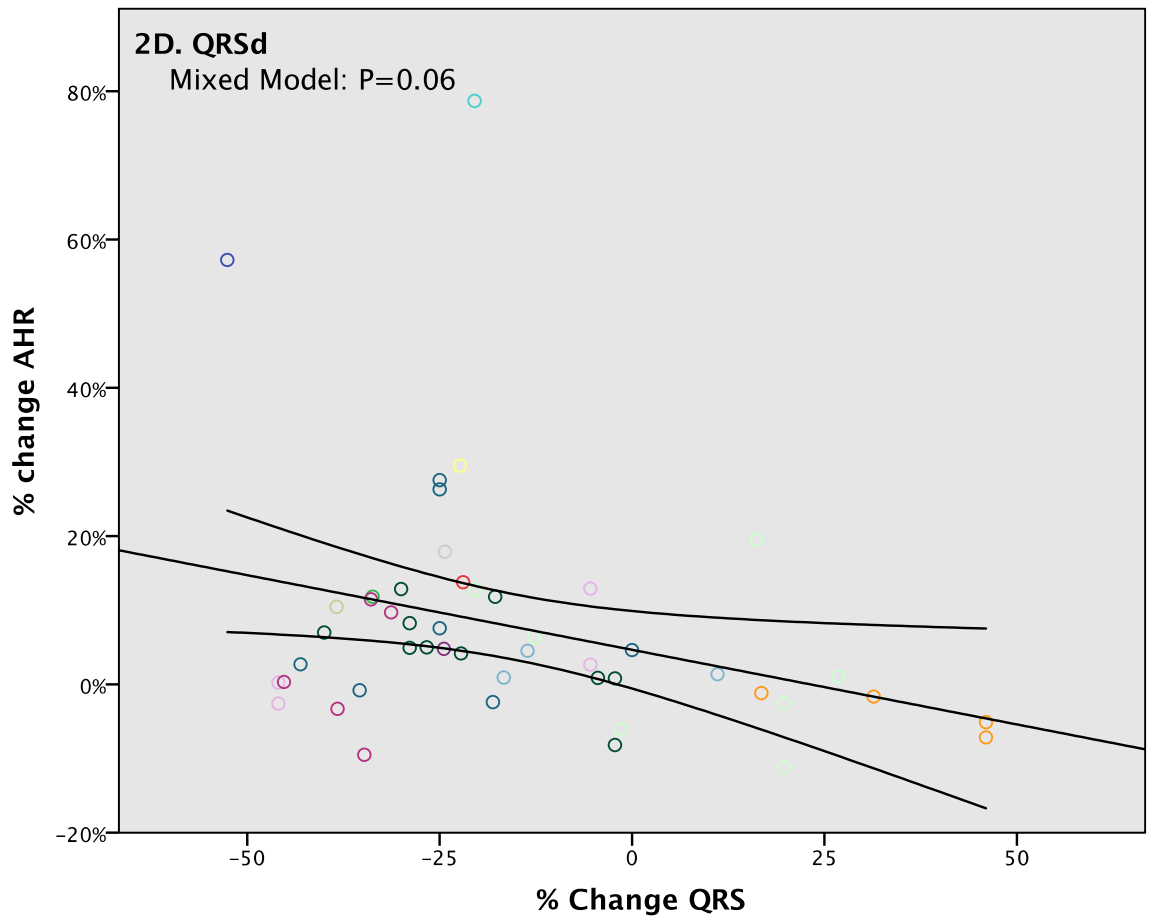


Figure 44. Change in AHR at various LV endocardial locations vs electrical delay measured using change in paced QRSd.

8.3.4 Tissue Viability

Scar was identified using pre-implant CMR and/or EAM. Seven patients had data comparing information on tissue viability and AHR, allowing the analysis of 38 positions. The mean change in AHR varied depending on whether stimulation was performed in an area of viable or scarred tissue, ($-3.9\% \pm 5.9$ vs $+4.6\% \pm 8.8$, $p=0.0456$), see Figure 45.

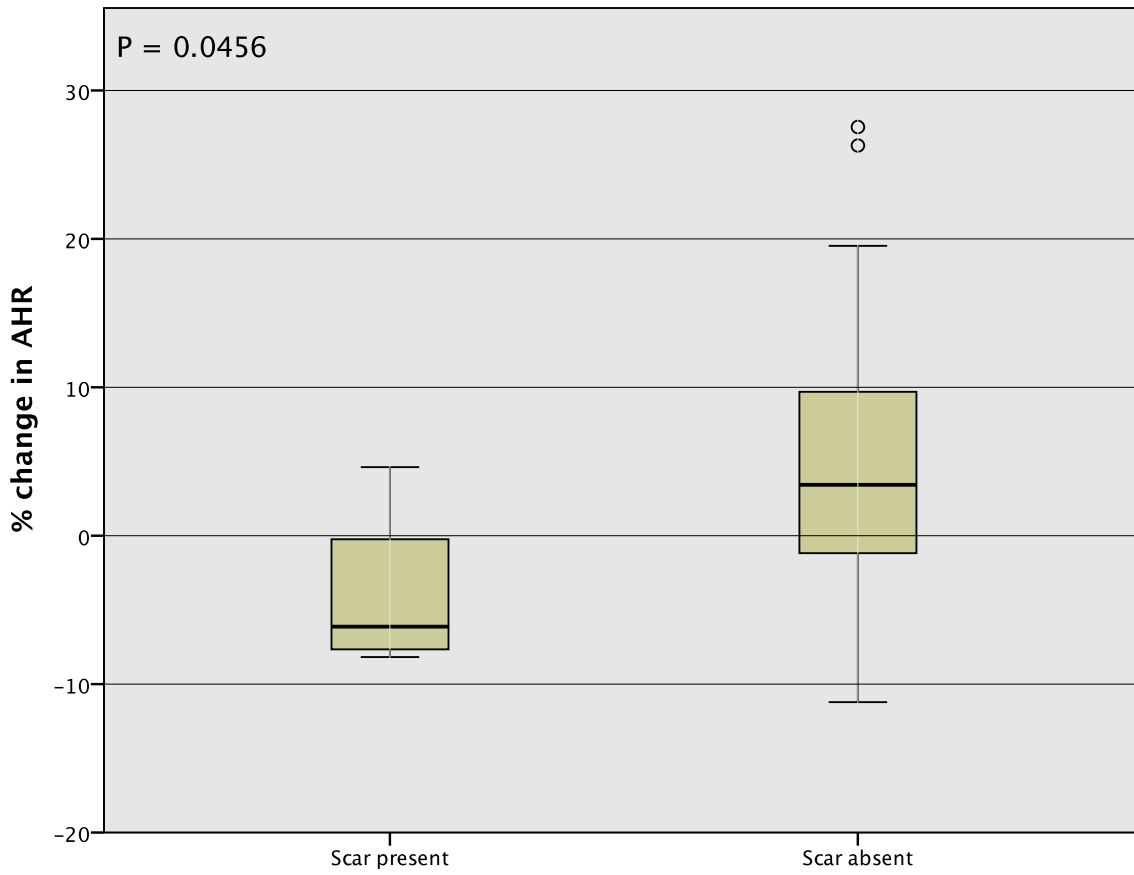


Figure 45. Tissue viability assessment comparing scarred tissue with non-scarred tissue

8.3.5 Optimal Endocardial Site Selection

AHR varied significantly depending on the location where LV_{ENDO} stimulation was performed. Inferior and lateral segments were frequently identified as the optimal targets using pre-procedural imaging, see Figure 46.

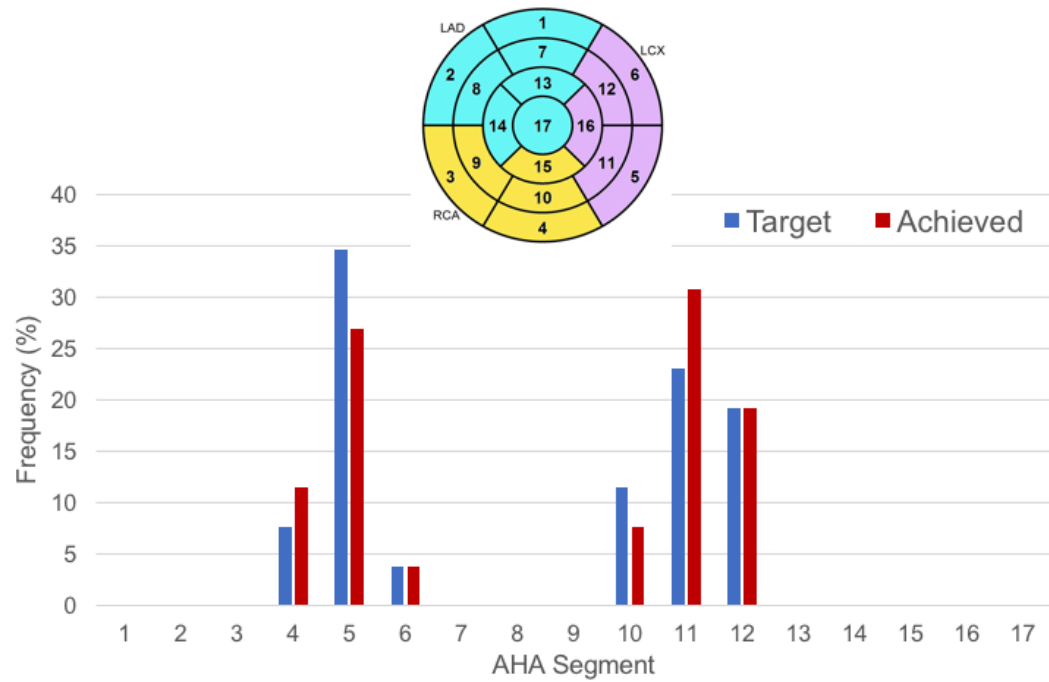


Figure 46. Target site selection vs actual site achieved

The basal infero-lateral segment (AHA segment 5) was most frequently identified as the optimal target, (n=8). Once a segment had been selected, it proved technically feasible to deploy the LV_{ENDO} electrode in this area in 92% of patients. In the remaining cases the electrode was successfully deployed in an adjacent AHA segment.

8.3.6 Chronic Response

6 month follow-up data was available in 21 of the 26 patients implanted with a guided approach. Chronic BiV_{ENDO} pacing could not be delivered effectively post implant in two patients. One patient exited the study prior to follow up due to worsening dementia. One patient had poor echocardiographic windows rendering assessment of LV performance post implant impossible and follow up data was not available in one patient. Follow-up data for our cohort is presented in Table 11.

Table 11. Chronic response to guided BiV ENDO implants

Parameter	Baseline ± SD	6 Months ± SD	P value
QRSd	167.0 ± 27.9	134.8 ± 25.6	0.002
LVESV	116.0 ± 69.3	85.9 ± 52.3	<0.0001
LVEF	35.0 ± 7.8	39 ± 9.8	0.008

There was a significant reduction in QRS duration with BiV ENDO pacing (baseline 163.8±26.7ms vs 6 months 134.8±25.6 ms, p=0.002). LVESV was significantly reduced at 6 months (112.7±64.4 at baseline vs 85±9±52.3 at 6 months, P<0.0001). LVEF increased from a baseline of 34.2±7.8% to 39±9.8%, p=0.008). Reverse remodelling (<15% reduction ESV) was observed in 71% patients (n=15). 90% (n=19) of patients met the definition of echocardiographic responder (LVESV >15% reduction and/or >5% EF increase).

8.4 DISCUSSION:

We hypothesised that guided placement of the WiSE-CRT LV endocardial pacing electrode would achieve greater improvements in acute markers of contractility and chronic markers of CRT response. The principal findings were that:

- 1) It proved technically feasible to selectively target and deploy the pacing electrode in a chosen endocardial segment in almost all cases with a similar complication rate to that observed in the published literature [270].
- 2) The use of a guided approach to facilitate optimal deployment of the WiSE-CRT LV endocardial pacing electrode was associated with a reverse remodelling rate of 71%, while 90% of patients met the definition of an echocardiographic responder.

8.4.1 Peri-Procedural Metrics For Optimal Endocardial Site Selection:

The optimal LV ENDO pacing site displays large inter and intra-patient variability. Previous work identified that a “lateral area strategy” of delivering BiV ENDO pacing at the lateral wall in a cohort

of NICM patients, yielded similar hemodynamic improvements to both conventional epicardial CRT and echocardiographically guided LV endocardial lead placement [42]. In our analysis, inferior and infero-lateral segments were most commonly identified as representing the optimal target for WiSE-CRT LV electrode delivery.

Our analysis provides several insights into how best to determine the optimal LV pacing site. Tissue characterisation is fundamental to achieving optimal CRT. Leyva et al [114] have previously shown the value of LGE CMR to optimise epicardial LV lead deployment. Our study confirms that delivering endocardial pacing in areas of scarred or fibrotic tissue, prospectively defined using either CMR or EAM, resulted in a reduction in acute haemodynamics. The mean AHR associated with delivering BiV_{ENDO} CRT in viable tissue showed statistical supremacy over stimulating fibrotic tissue and in no-patient was the optimal segment noted to be scarred/fibrotic. Narrowing of the paced QRSd during acute BiV_{ENDO} pacing showed a trend favouring greater improvements in AHR, although this failed to achieve statistical significance when repeated measures in some patients were accounted for. A strong linear relationship was however, identified between AHR and both Q-LV and Q-LV/QRSd ratio. As such, targeting locations which exhibit electrical latency would appear useful when looking to identify the optimal pacing site. Endocardial locations with a Q-LV/QRS ratio > 0.5 were associated with a 14.3±19.7% improvement in AHR. Achieving a >10% improvement in AHR during acute BiV_{EPI} CRT has been shown to be predictive of chronic reverse remodelling [47], suggesting patients will be more likely to remodel if a site with an LV/QRS ratio of 0.5 is selected.

8.4.2 Clinical importance:

In the current study the use of a guided approach to identify and target the optimal endocardial pacing location resulted in an impressive reverse remodelling rate of 71% and a composite echocardiographic response rate of 90%. These results compare favourably to the recently published SELECT LV study where indiscriminate deployment of the LV pacing electrode achieved a remodelling rate of only 52% [270]. This figure is consistent with the response rate of 40-50% reported in a large meta-analysis of endocardial CRT [266]. Our results would suggest that a guided approach may be able to improve remodelling response rates in patients receiving BiV_{ENDO} CRT. This is in keeping with previous studies of epicardial CRT where guidance increased LV reverse remodelling from 55% to 70% [119,125].

8.4.3 Limitations:

The majority of our cohort were patients receiving an upgrade from a pre-existing single or dual chamber pacing system or where an attempt at implanting an LV lead had previously failed. Echocardiographic response rates amongst those receiving an up-grade to epicardial CRT have been found to be comparable to those receiving a de-novo implant however the rate of reverse remodelling identified in our cohort (71%) exceeded the degree of remodelling expected [289,290]. This rate compares very favourably to that observed in the SELECT-LV study [270] although, the number of patients in our analysis whose indication for the WiSE-CRT LV pacing system was prior non-response to CRT was lower than in SELECT-LV (8% vs 29%). The use of LV reverse remodelling as a surrogate for longer term CRT response is also open to criticism, however it is an objective and reproducible metric of CRT response.

Whilst each centre used a combination of pre-procedural imaging and electro-anatomical mapping to identify the optimal pacing site, the precise guidance protocol varied between centres. However, all techniques targeted viable tissue which displayed late electrical and or mechanical activation. The utility of speckle tracking radial strain echocardiography to identify the optimal pacing site has been assessed in two large prospective studies [119,122]. Speckle tracking echocardiography does suffer from technical limitations, including the requirement for image quality to be sufficient to allow reliable offline analysis. Interobserver variability can also be an issue with ultrasound based imaging modalities. Finally, whilst speckle tracking echo can identify areas of the LV displaying late activation, the operator is required to use this information to target the optimal site using conventional fluoroscopy alone.

The role of intraprocedural assessments of electrical latency to identify the optimal pacing site has also been proven in large clinical trials [125,126] and this approach benefits from eradicating the need to collect/analyse pre-procedural data. Instead the operator can test a variety of locations until a desirable site is located. Site selection data does not need to be co-registered during the electrode implant, as all the data can be collected using the delivery catheter system. However, more recent data has highlighted the potential for this approach to identify a region of the LV where stimulation may result in favourable activation, but not the optimal location within that area [198].

CMR is the gold standard technique for the assessment of tissue characterisation and the avoidance of scar is critical determinant of CRT outcome [114]. CMR also benefits from greater reproducibility, less artefact secondary to patient habitus and greater spatial resolution. Data also exists confirming the feasibility of CMR derived circumferential strain to identify the latest mechanically activated viable segment [190]. However, in order for this analysis to accurately

inform site selection it needs to be co-registered with the real time fluoroscopic data visible to the operator. The integrated XMR guidance platform utilised in this study has undergone validation but limited data exists correlating the use of this system and improvements in CRT response [234].

8.5 CONCLUSION:

Guided endocardial implants were associated with a higher degree of chronic LV remodelling compared to historical non-guided approaches. WiSE-CRT offers a feasible alternative for patients who fail to derive benefit or who cannot be implanted with a conventional CRT system. The ability to target the LV endocardium irrespective of coronary venous anatomy, without any incidence of PNS is a unique advantage. Targeting late activating, non-scarred areas of the endocardium may further improve CRT outcome in this patient group.

Chapter 9 A Direct Comparison Of Empirical vs Guided LV Electrode Deployment Using The WiSE CRT Pacing System

9.1 INTRODUCTION:

Persistent non-response to traditional, transvenous epicardial CRT has driven the evolution of resynchronisation pacing. Attempts at optimising the LV pacing site in epicardial CRT have shown promise [119,122,234] but are consistently limited by the need to place the pacing lead in a tributary of the coronary sinus. LV endocardial stimulation confers several advantages over epicardial activation, including allowing unfettered access to the entire LV endocardial surface. LV endocardial pacing also has the potential to yield greater improvements in both LV activation [224,252,253] and LV contractility [41,291–293]. Delivering stimulation at a sub-optimal LV endocardial site meanwhile, can yield less effective resynchronisation pacing [196,291]. The optimal LV endocardial pacing site displays marked variability, with no one location proving consistently superior [291], implying a role for individualised optimisation.

The optimal LV pacing site can be defined electrically, mechanically or through an assessment of tissue characterisation [294] and several different methods of identifying this location have been proposed. These include the use of electrical activation metrics to target areas of late depolarisation, CMR and EAM to target viable late activating tissue, or speckle tracking radial strain to restore regional activation synchrony to the site of latest mechanical activation. All three methods were assessed in a pilot study, which examined both their safety and efficacy [277].

The WiSE CRT Post Market Surveillance Registry (Clinical trial study number NCT02610673) assessed the real world safety of delivering biventricular endocardial stimulation via a novel leadless LV endocardial stimulation system in 14 different European centres. Following implantation, this novel wireless pacing system was able to achieve consistent biventricular capture in 95.6% of patients, with 79% reporting a subjective improvement in their symptoms and 55% displaying evidence of LV remodelling.

It is well recognised that CRT non-response is more common amongst specific cohorts including: male gender [64–67], ischaemic aetiology [69,70] & concurrent atrial arrhythmias [75]. This

analysis aims to specifically evaluate whether biventricular endocardial pacing appears equally effective amongst all patient cohorts including amongst those where guidance was used to target the optimal pacing site.

9.2 METHODS:

9.2.1 Data Collection

The WICS Post Market Surveillance Registry (Clinical trial study number NCT02610673) prospectively collected data from all 14 European centres implanting the WiSE-CRT system. All patients studied gave full written consent to participate. The fourteen centres were; Guy's and St Thomas' NHS Foundation Trust (London, United Kingdom), the John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust (Oxford, United Kingdom), & The James Cook University Hospital, South Tees Hospitals NHS Foundation Trust (Middlesbrough, UK), Immanuel Klinikum Bernau Herzzentrum Brandenburg (Bernau, Germany), St Antonius Ziekenhuis, Nieuwegein (Utrecht, Netherlands), Aalborg University Hospital (Aalborg, Denmark), Na Homolce Hospital (Prague, Czech Republic), Policlinico S'Orsola (Bologna, Italy), San Raffaele Hospital (Milan, Italy), University Hospital Erlangen, (Erlangen, Germany), St. Vincent's University Hospital (Dublin, Ireland), CHU Grenoble Alpes (Grenoble, France) & Hopital La Timone (Marseille, France), St Bartholomew's Hospital (London, UK).

9.2.2 Inclusion Criteria

The WiSE-CRT system delivers LV endocardial stimulation through the acoustic activation of a piezoelectric crystal tipped receiver electrode, embedded in the LV wall. Currently the system has three licensed indications. Patients where LV lead deployment is not possible or has previously failed due to anatomical constraints, high capture thresholds or phrenic nerve stimulation. WiSE-CRT implantation can also be performed in patients undergoing an upgrade to CRT where the implantation of an LV lead was impractical due to issues with venous access or undesirable due to previous pocket infection. Finally, patients who were previous non-responders to conventional transvenous, epicardial CRT could also receive the WiSE CRT system. Non-responders were defined as patients in whom conventional CRT had been successfully delivered for at least six months but who had experienced no improvement in their clinical status or reverse remodelling.

A combination of cardiac MRI (CMR), electroanatomical mapping (EAM), coronary angiography and clinical history was used to classify patients as having either ischemic cardiomyopathy (ICM) or non-ischemic cardiomyopathy (NICM) using. Patients were routinely implanted using a retrograde trans-aortic approach as previously described (10). Where issues with arterial patency, tortuosity or aortic valve disease/replacement precluded a retrograde trans-aortic approach, a trans-septal approach was adopted to facilitate electrode deployment [271].

9.2.3 Endpoints

Two endpoints were assessed:

1. Adverse events including both acute (<24hrs) and chronic (>24hrs-6months) complications.
2. Clinical response to biventricular endocardial pacing from the WISE-CRT System.

CLINICAL RESPONSE

A patient global assessment was recorded at follow up. This global assessment classified each patient into one of three categories; improved, worsened or unchanged. Patients were asked which of these three categories applied to their status. Patients were considered a clinical responder if they felt there had been an improvement in their symptoms.

ECHOCARDIOGRAPHIC RESPONSE

In accordance with previously published work [270] patients were considered echocardiographic responders to CRT if they exhibited a $\geq 15\%$ reduction in their end-systolic volume, measured using 2D trans-thoracic echocardiography.

9.2.4 Statistics

Continuous variables with a Gaussian distribution were described using mean values \pm standard deviation. Significance testing on continuous, normally distributed paired data was performed using two tailed paired *t* tests. Significance testing on continuous, non-normally distributed paired data was performed using the Wilcoxon Signed Rank test. Significance testing on continuous, non-normally distributed un-paired data was performed using the Mann-Whitney U test. Where both independent and dependant factors were categorical, significance testing was performed using the fisher's exact test. Odds ratios were calculated using binary logistic regression. Where both independent and dependant factors were continuous, odds ratios and significance testing were

performed using linear regression. Results were considered significant at $p < 0.05$. Analysis was performed on PASW Statistics 24 (SPSS Inc., Chicago, Illinois).

9.3 RESULTS:

9.3.1 Empirical vs Guided LV Electrode Deployment

90 patients across 14 centres underwent implantation with the WiSE-CRT system. The entire cohort was predominantly male, aged 68.2 ± 10.5 yrs; LVEF $30.6\% \pm 8.9$; mean QRS duration 180.7 ± 27.0 ms. Ischaemic (ICM) aetiology was present in 40% of patients. Our cohort was dichotomised into patients who had received guidance during electrode implantation and those who had undergone empirical positioning of the pacing electrode, see Table 12 for patient demographics. 63 patients underwent empirical implantation of the pacing system, whilst 27 patients received an implant facilitated by guidance.

Table 12. Demographics of sub-analysis evaluating LV electrode guidance vs empirical site selection

	Empirical Placement	Guided Placement	P Value
Patients	63	27	
Age (years)	68.2 ± 11.2	68.3 ± 8.5	NS
Male	50 (79.4%)	22 (81.5%)	NS
ICM Aetiology	26 (41.3)	10 (37%)	NS
NYHA			
1	1 (1.6%)	0	NS
2	23 (36.5%)	10 (40%)	NS
3	39 (61.9%)	15 (60%)	NS
4	0	0	NS
Echocardiographic Data			
LVEF (%)	29.0 ± 8.6	33.1 ± 8.5	0.004
LVESV (ml)	135.5 ± 79.4	126.1 ± 94.6	NS
LVEDV (ml)	189.0 ± 92.9	182.6 ± 112.0	NS
ECG			
Atrial Arrhythmias	35 (55.6%)	12 (44.4%)	NS
QRS duration (ms)	185.8 ± 27.5	168.8 ± 22.0	0.006
Indication			
Failed LV lead implant	31 (49.2%)	13 (48.1%)	NS
Complex upgrades	24 (38.1%)	11 (40.7%)	NS
Failure to respond to BiV EPI	8 (12.7%)	4 (14.8%)	NS

A larger proportion of patients received empirical site selection however, our two sub-groups were well balanced. Significant differences were noted in baseline LVEF with those undergoing empirical placement of the electrode displaying a lower baseline ejection fraction ($29.0 \pm 8.6\%$ vs 33.1 ± 8.5 ; $P=0.004$) as well as a broader baseline QRS duration (185.8 ± 27.5 vs 168.8 ± 22.0 ; $P=0.006$).

9.3.2 Adverse Events

The use of pre and peri-procedural guidance to identify and selectively target the optimal LV endocardial pacing site was not associated with a higher overall rate of either acute (empirical 1.6% vs guided 7.4%; $P=NS$) or chronic (empirical 15.9% vs guided 29.6%; $P=NS$) complications, see Table 13.

Table 13. Adverse events

Complications	Empirical Placement (n=63)	Guided Placement (n=27)	P Value
<24 hours	1 (1.6%)	2 (7.4%)	NS
Cardiac tamponade	0	1 (3.7%)	NS
Pneumothorax/Pleural Effusion	1 (1.6%)	1 (3.7%)	NS
>24 hours – 6 months	10 (15.9%)	8 (29.6%)	NS
Arterial Access Complication	1 (1.6%)	3 (11.1%)	0.046
Pocket haematoma (generator)	3 (4.8%)	1 (3.7%)	NS
Post Procedure Chest Sepsis	1 (1.6%)	2 (7.4%)	NS
Pocket infection (generator)	2 (3.2%)	1 (3.7%)	NS
Acute Kidney Injury	1 (1.6%)	1 (3.7%)	NS
Post Procedure CVE	1 (1.6%)	0	NS
Extrastimulation During TTE	1 (1.5%)	0	NS

In both cohorts, biventricular pacing was ultimately confirmed via a 12 lead ECG (empirical 98% vs guided 89%; $P=NS$). Guided implantation was associated with a higher rate of arterial access complications (11.1% vs 1.6%; $P=0.046$). This may in part be explained by the requirement of

some guidance systems to verify the optimal site through the use of acute haemodynamic evaluation, which requires additional arterial access.

9.3.3 Clinical Response

Follow up data regarding clinical response was available in 76 patients (empirical site selection: 53, guided site selection 23), see Figure 47.

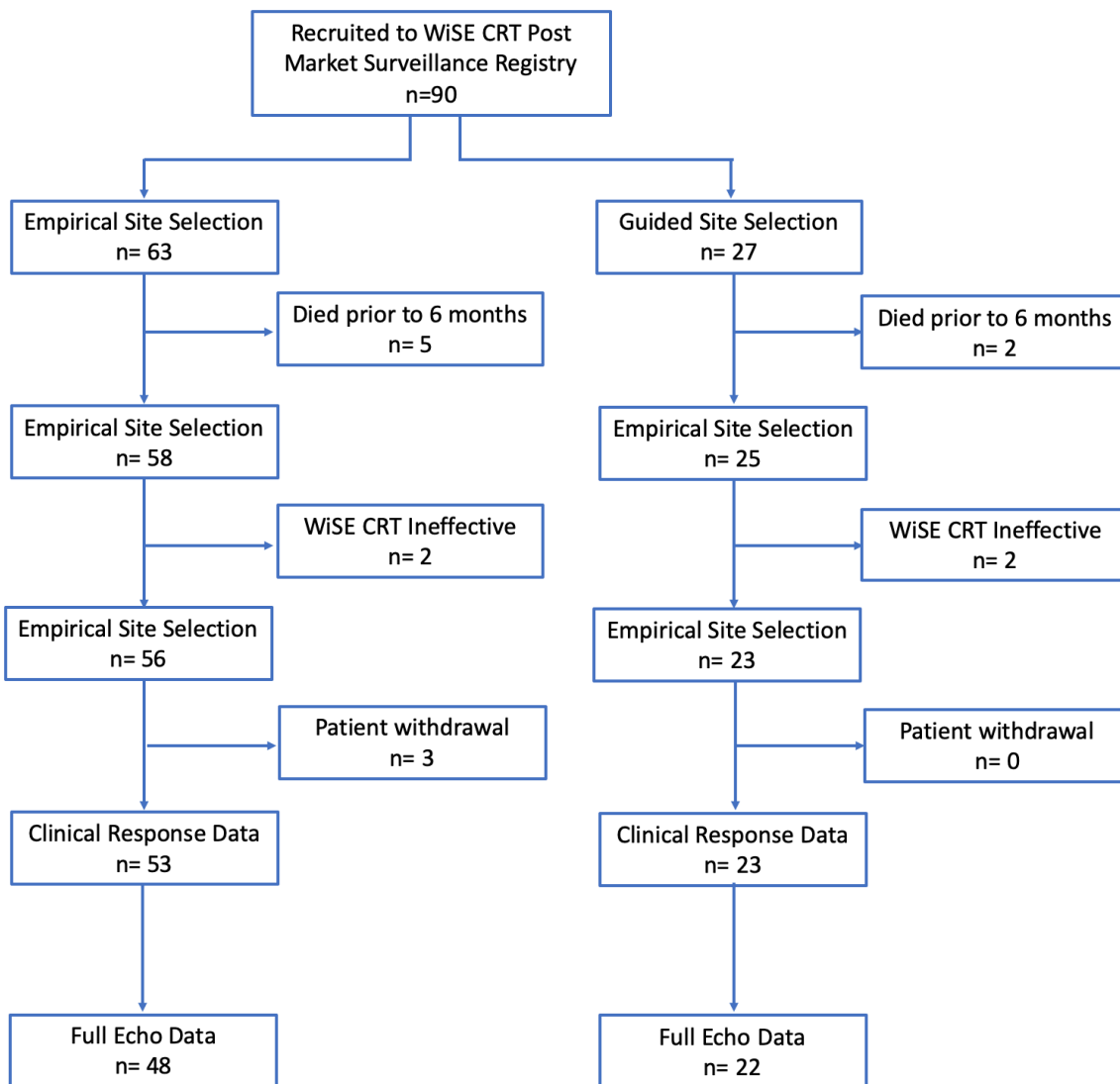


Figure 47. Patient recruitment diagram

Seven patients died prior to the collection of six month follow up data; two patients coming from the guided cohort and five coming from the empirical group. No deaths were a direct result of implant related complications. More detail regarding these events can be found in Chapter 6: The Safety & Efficacy Of Leadless LV Endocardial CRT Using The WiSE CRT Pacing System. Three patients who underwent empirical site selection withdrew from the Registry after undergoing

implantation with the system, meaning no follow up data was recorded. In addition, WiSE CRT pacing proved ineffective/inconsistent in in four patients (two from empirical group and two from guided group). In total, 60/76 patients had a complete data set including an echocardiographic assessment of ejection fraction and LV volumetric reverse remodelling (48 patients in the empirical implant group, 22 in the guided cohort). Overall, no significant difference was observed in symptomatic response metrics between those patients undergoing guided implantation vs empirical site selection, see Figure 48. In addition, no statistically significance difference in LV end systolic volumetric reverse remodeling was identified between the empirical/guided implant cohorts, see **Error! Reference source not found..**

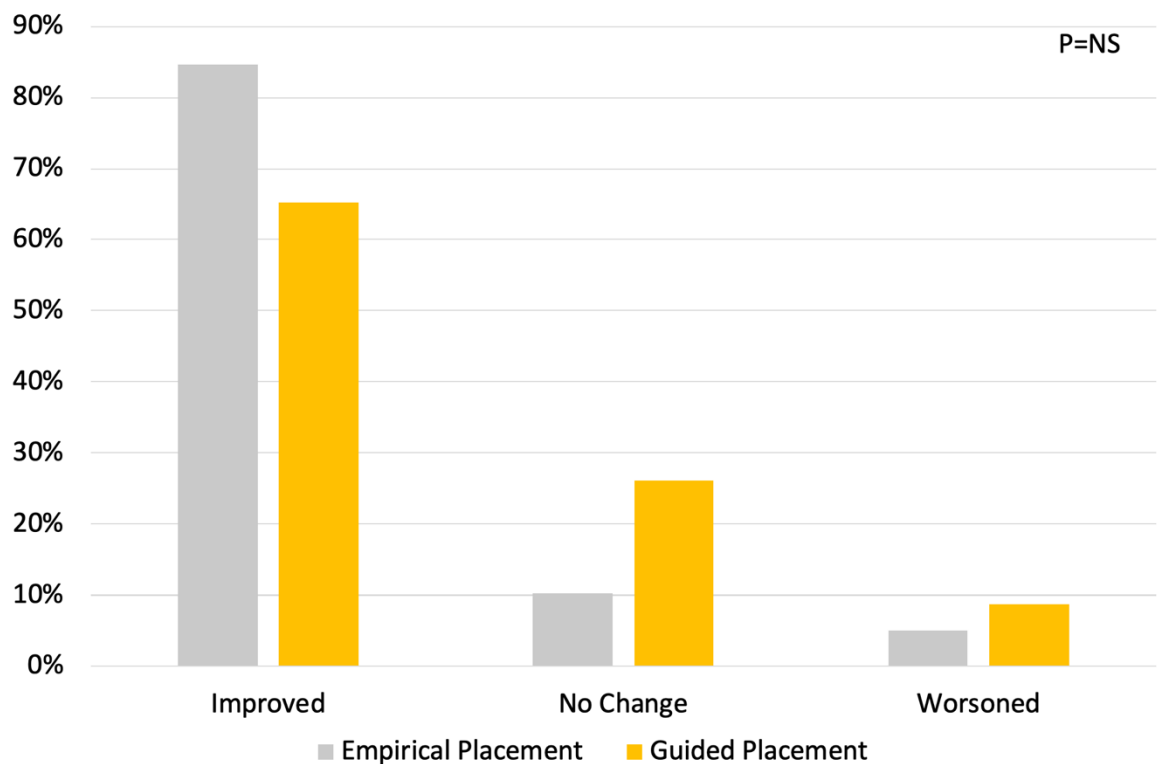


Figure 48. Clinical response comparison between empirical and guided LV endocardial site selection

Table 14. LVESV remodelling following empirical and guided LV endocardial site selection

	Empirical Placement	Guided Placement	P Value
LVESV Change (ml)	-20.4 ± 38.7	-23.3 ± 32.2	NS
LVESV Change (%)	-6.0 ± 21.5	-13.9 ± 25.4	NS

When echocardiographic response rates were analysed, a trend was seen favoring the use of pre and peri-procedural guidance however this signal failed to achieve statistical significance (47.2% vs 63.6%; P=NS), see Figure 49. These findings were confirmed using univariate binary logistic regression, see Figure 50.

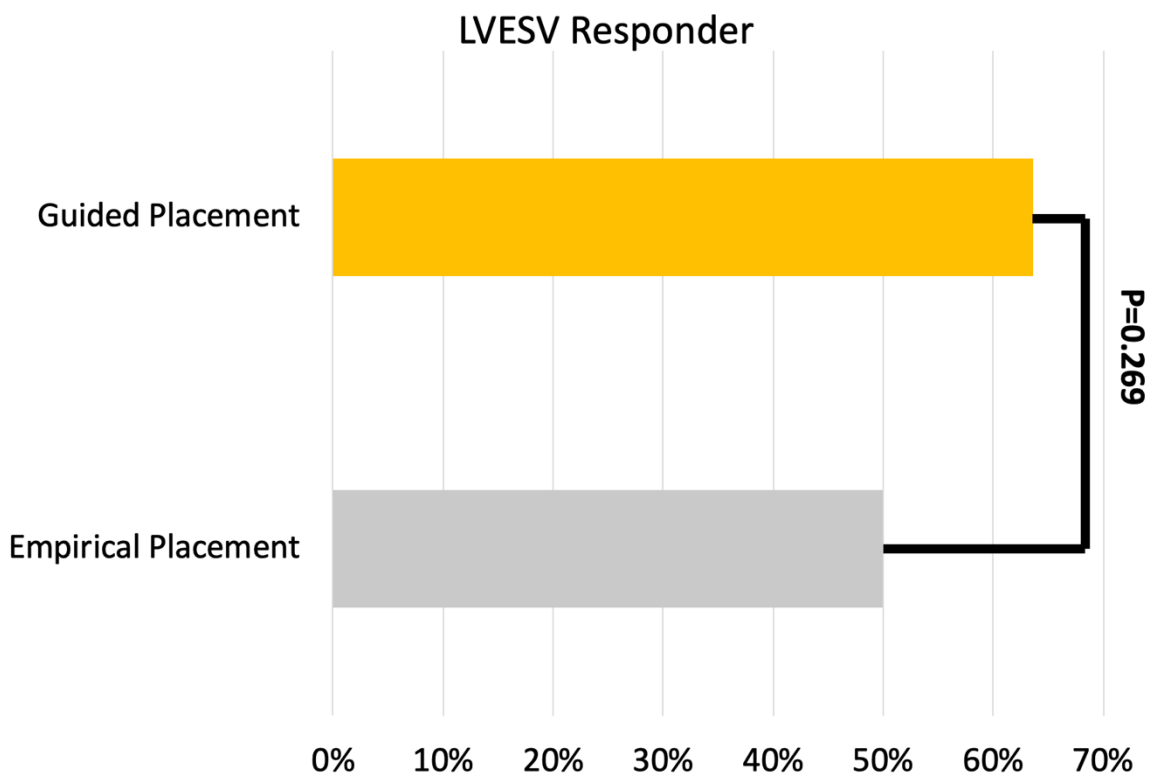


Figure 49. LVESV echocardiographic response rates to guided vs empirical LV electrode placement

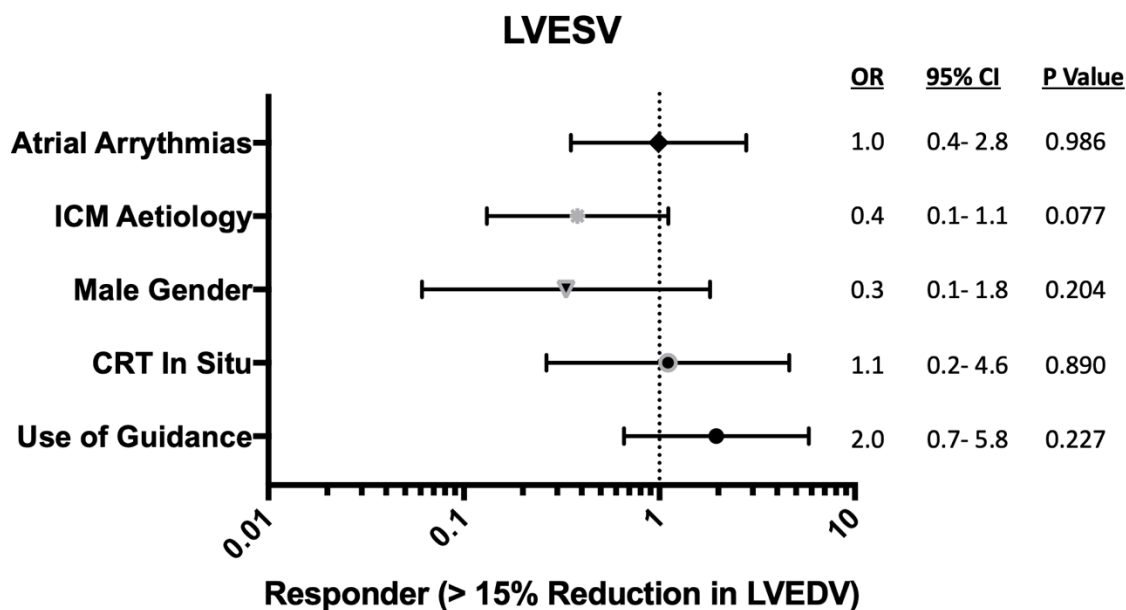


Figure 50. Binary logistic regression evaluating LVESV response

9.3.4 Presence of atrial arrhythmias

AF is associated with several deleterious effects which prevent optimal resynchronisation pacing. These include accelerated ventricular rates, the prevention coordinated AV pacing as well as making biventricular capture challenging to confirm. In patients undergoing epicardial CRT, AF confers a worse prognosis [75,295,296] however, in our analysis, the presence of atrial arrhythmias was not associated with a significant trend towards less LV remodelling, as shown in Figure 50.

9.3.5 Aetiology

Sub-analysis of randomised studies has consistently shown greater LV reverse remodelling occurs amongst DCM patients [297–300]. Following implantation with the WiSE CRT pacing system we observed a trend toward greater LV remodelling in DCM patients although this was not statistically significant (ICM: 41.7% vs DCM:63.6%; P=NS). This finding was confirmed following binary logistic regression, see Figure 50.

9.3.6 Gender

Male gender has previously been identified as an independent predictor of non-response to CRT [301,302]. Differences in physiological and pathological remodelling during end stage ischaemic heart failure [303], aortic stenosis [304] and hypertension [305] have also been widely described; potentially attributable to the higher rate of myocyte death identified in failing human male hearts [306]. Whilst a trend was observed showing male gender was associated with less LV remodelling- this was not significant, suggesting males may respond better to endocardial activation than has been observed in previous analyses of epicardial CRT.

9.3.7 Indication for WiSE CRT pacing

We assessed chronic response in two groups of patients; those with a functional CRT system in situ who had not-responded to transvenous epicardial CRT (Non-Responders) and those without a CRT system in situ including complex upgrades or patients where LV lead implantation had failed (No CRT). Rates of LV remodelling were similar in both cohorts (Non responders: 55.6% vs No CRT: 54.2%; P:0.619). Binary logistic regression confirmed no statistically significant difference in reverse remodelling between these sub-groups, see Figure 50.

9.4 DISCUSSION:

This sub-analysis of the WiCS Post Market Surveillance Registry set out to investigate whether biventricular endocardial pacing is equally effective amongst all patient cohorts. In particular we wanted to focus on whether the use of pre and peri-procedural guidance to identify and target the optimal LV endocardial pacing site would be associated with superior outcomes when compared to a strategy of empirical site selection.

The principal findings were:

- 1) The use of guidance was not associated with a statistically significant improvement in LV reverse remodelling. Trends were observed however, suggesting this approach may be beneficial.
- 2) Other metrics including presence of atrial arrhythmias, aetiology, gender, indication for endocardial pacing were not associated with any significant difference in LV remodelling.

LV endocardial activation may confer an additional benefit over epicardial activation as a sequelae of the increased access to viable, late activating tissue in those patients with ICM, as well as the enhanced conduction velocities associated with stimulation of endocardial tissue [224,252,253]. The optimal LV endocardial pacing site has been shown to display large inter and intra-patient variability [291]. In our analysis, the use of procedural guidance to identify and target a specific optimal pacing site, was associated with trends favoring greater echocardiographic response although these failed to achieve statistical significance.

The presence of atrial arrhythmias [75,295,296], male gender [64–67] and ischaemic aetiology [69,70] are all independently associated with poor response to biventricular epicardial CRT. Our sub-analysis of the WiCS Post Market Surveillance Registry is the first large scale examination of leadless endocardial CRT and suggests that rates of LV remodelling amongst these high risk groups appear non-inferior when endocardial stimulation is delivered via the WiSE CRT system.

9.4.1 Limitations:

The current analysis is limited by the fact that it is an unblinded, retrospective registry and was thus not randomised. It should be remembered that both the equipment and expertise required to perform pre-procedural advanced image guidance were only available at certain centres and so it would not have been possible to randomise patients evenly. Despite this limitation, our two sub-groups were well balanced with significant differences occurring in baseline QRSD and LVEF only. In addition, whilst each centre performing image guidance was targeted late activating, viable tissue, the precise method used varied at each centre. There is data to support targeting electrical latency [125,126], mechanical latency [119,122] and CMR guidance [234] and as no head-to-head comparison has been performed, each approach was deemed to be equivalent.

A further limitation is the small sample size of our cohort. Despite the WiSE CRT Post Market Surveillance Registry reflecting the largest population of patients so far implanted with the WiSE CRT device, in total this amounts to just 90 patients- 27 of whom underwent a guided implant. Given the small population, it would be unwise to draw definitive conclusions from our results as our observations are not adequately powered to confirm statistical significance. Despite this, trends were observed which may prove helpful in guiding future work.

Finally, various surrogate end points for mortality were employed in our study. We assessed both functional and LV volumetric changes. Whilst functional assessments can be subject to considerable interobserver variability and can lack the necessary sensitivity required to detect crucial changes in functional capacity, LV dimensions are significantly related to prognosis with LV

remodelling proportionally associated with changes in mortality. As such, LV dimensions are widely considered to be one of the most promising surrogate endpoints available [307].

9.5 CONCLUSION:

This is the first sub-analysis of the WiSE CRT Post Market Surveillance Registry. Our findings confirm that even amongst cohorts who typically exhibit lower less LV remodelling, rates of response were not significantly worse amongst any specific group. The use of pre and pre and peri-procedural guidance to identify and selectively target the optimal pacing site was achieved with a similar complication profile to that associated with empirical site selection. Finally, whilst trends were observed which appeared to suggest patients receiving a guided implant exhibited greater remodelling, ultimately these results failed to achieve statistical significance.

Chapter 10 Conclusion

The overall aim of this thesis was to assess the practice of biventricular endocardial CRT.

Specifically, there were five main objectives;

- 1) Assess whether indiscriminate BiV ENDO pacing is superior to BiV EPI CRT and whether there are any constraints where endocardial stimulation may prove inferior to traditional, transvenous epicardial CRT.
- 2) Assess the safety and efficacy of a leadless, endocardial CRT system during real world use.
- 3) Evaluate which metrics may be useful when looking to identify the optimal LV Endocardial pacing site.
- 4) Analyse the use of advanced image guidance in an effort to improve the response rate of endocardial CRT.
- 5) Compare the efficacy of empirical LV ENDO stimulation to a strategy of image guided ENDO activation.

10.1 Original contributions

10.1.1 Endocardial Activation Can Prove Superior to Epicardial Stimulation, But Sub-Optimal Endocardial Activation Can Also Be Worse

Stimulating the endocardial surface of the heart is associated with several advantages over epicardial CRT including greater potential for site selection, less phrenic nerve stimulation and lower capture thresholds. LV activation also occurs more rapidly due to the shorter conduction path length but also due to the intrinsic properties of endocardial tissue. Despite these benefits, our findings confirm that when stimulation is delivered at identical sites on opposing sides of the myocardium, endocardial pacing does not achieve superior improvements in acute LV contractility.

However, our findings also confirm that if a robust examination of the LV epicardial surface is performed in order to find the optimal site, rather than just the site of the chronically implanted LV lead, delivering BiV ENDO stimulation at this location does appear to be associated with

significant improvements in LV contractility. Equally, it is important to note that whilst optimally delivered BiV ENDO pacing is also frequently superior to BiV EPI, sub-optimal BiV ENDO can yield inferior changes in LV contractility.

10.1.2 LV Endocardial Pacing Can Be Effectively Delivered Via The WiSE CRT Leadless LV Pacing System

Activation of the LV endocardial surface can be achieved in a number of ways. The most basic involves the use of conventional pacing technology and passing a pacing lead across either the atrial or ventricular wall and implanting it within the LV cavity. However, this approach is associated with an increased thromboembolic risk as well as the possibility of adverse interaction between the mitral valve and the LV lead. A novel leadless approach using acoustic energy to wirelessly stimulate the LV has been devised and achieved near universal procedural success. Biventricular capture was confirmed in virtually all patients. In total, roughly 80% of patients reported an improvement in their clinical symptoms with over 55% showing evidence of significant LV remodelling.

We observed a similar complication rate during real world use, to that previously described. Acute complications occurred in three patients with one case of cardiac tamponade requiring emergent drainage. Chronic complications (24hrs to 6 months) occurred in 20% of patients. Most of these related to femoral arterial access issues however, trans-septal deployment of the pacing electrode may eradicate this complication.

A limitation of this system in its current format is the reliance on USS to activate the receiver electrode. Generating the USS signal requires a large amount of energy and as such battery longevity is less than for conventional lead based pacing systems. However, refinements in battery and USS technology in conjunction with improvements in screening techniques have already led to improved battery longevity with further gains predicted over the coming years.

10.1.3 The Optimal LV Endocardial Pacing Site Displays Marked Inter & Intra-Patient Variability Requiring Individual Tailoring Of The Lead Position

The optimal LV endocardial pacing site exhibits a marked degree of variability, across both non-ischaemic and ischaemic patients. Despite the favourable properties associated with stimulating the endocardial surface of the heart, improvements in LV contractility are not consistently associated with delivering stimulation at any one location. Instead, the optimal location in one patient was capable of being the least favourable in other. The ideal pacing location appears as

unique as the patient's own pathology and ultimately, individualised lead positioning is likely to be required in order to maximise the benefits associated with LV endocardial pacing.

10.1.4 Targeting Viable Myocardial Tissue Is Critical When Looking To Improve LV Contractility

Locating and avoiding non-viable, fibrotic myocardium has been shown to be beneficial during both epicardial and endocardial biventricular pacing. Crucially, endocardial pacing provides access to the entire surface of the LV, allowing greater access to available viable tissue. Our analysis confirmed these findings. The presence of non-viable tissue was confirmed via both real time electroanatomical mapping and CMR. Significant improvements in LV contractility were observed when stimulation was performed at viable sites whilst, haemodynamic response was much lower when scarred or fibrotic myocardium was stimulated.

10.1.5 Stimulating Late But Not Excessively Delayed Activation Appears An Optimal Strategy

Cardiac Resynchronisation Therapy (CRT) aims to restore regional activation synchrony thus improving the mechano-energetic efficiency of the heart. Intuitively, the site of latest activation should exhibit the most dyssynchrony and should consistently represent the optimal pacing site. Improvements in LV contractility displayed a linear relationship when stimulation was performed at sites displaying progressive electrical delay.

The site of latest activation was not however, synonymous with the optimal pacing site regardless of which metric was used to define electrical latency. In just 60% of cases was the latest activating site- also associated with the greatest improvement in LV contractility. Electroanatomical mapping has allowed us to visualise islands of viable tissue, which can exist within areas of ischaemic scar and display extremely late activation but when stimulated, do not result in effective depolarisation wave front propagation. Even amongst patients with non-ischaemic, dilated cardiomyopathy tissue characterisation displays heterogeneity. When evaluated using non-contact mapping, even patients with no evidence of late gadolinium enhancement on their CMR were observed to display evidence of conduction block.

10.1.6 QLV and LVLED Appear Useful Metrics When Looking To Identify The Optimal LV Endocardial Pacing Site However, Narrowing Of The Paced QRSd Appears Less Reliable

QLV and LVLED appear useful markers when looking to identify and target the optimal LV endocardial pacing site. Stimulating sites exhibiting late electrical activation is associated with beneficial improvements in LV contractility. The role of narrowing of the paced QRSd to guide site selection is less clear. Electrical and mechanical resynchronisation are not necessarily synonymous. Such electro-mechanical uncoupling means that it is possible for stimulation to achieve a narrow QRS but sub-optimal mechanical activation. This appears particularly common when pacing is delivered in the region of the LV septum.

10.1.7 The Distribution Of Late Activating Tissue Displays Greater Heterogeneity in Patients With Ischaemic Cardiomyopathy

Postero-lateral LV pacing locations are typically thought to represent an ideal site to deliver LV stimulation given the underlying substrate being corrected is typically left bundle branch block, which results in delayed electrical activation of the postero-lateral wall. This finding was consistently observed amongst patients with non-ischaemic, dilated cardiomyopathy where delay in activation progressively increased, in proportion to the distance from the septum. However, such a finding was not replicated amongst ischaemic patients however, due to the impact of scar tissue disrupting wave front dispersion.

10.1.8 A Pilot Assessment Of Optimal Site Selection During LV Endocardial Pacing Confirms This Strategy Is Both Safe & Appears To Result In Highly Effective CRT

Two facets of endocardial pacing imply the use of site selection is crucial; firstly, the high degree of variability in the location of the optimal site and secondly, that indiscriminate endocardial pacing can prove inferior to traditional transvenous epicardial CRT. The optimal site was successfully located using a combination of either pre-procedural imaging and/or electro-anatomical mapping and it proved both safe and technically feasible to selectively target and implant the pacing electrode at that location in 92% of cases. Guided biventricular endocardial pacing with the WiSE system was associated with both significant improvements in acute LV contractility and in turn, a chronic echocardiographic response rate of 71%.

10.1.9 The Use Of Pre & Peri-Procedural Guidance To Identify & Target The Optimal LV Pacing Site Did Not Improve Response In A Small Cohort

Endocardial CRT is associated with several advantages over traditional, transvenous epicardial CRT however, the haemodynamic response to endocardial stimulation varies enormously depending on the site of stimulation. The optimal pacing site appears patient specific and varies considerably. Previous work has shown that delivering pacing at sites exhibiting electro-mechanical delay is associated with greater improvements in haemodynamics. In addition, pilot work has also shown that a specific site can be safely targeted during deployment of the pacing electrode. During a direct head-to-head comparison of guided vs empirical electrode deployment, the use of pre and peri-procedural guidance to identify and target the optimal pacing site did not result in a significantly higher rate of echocardiographic response. However, the approaches used remain of interest and provide the basis for further work exploring the use of pre and peri-procedural guidance to inform LV Endocardial site selection.

10.2 Implications & Limitation

Heart failure remains a significant cause of both morbidity and mortality with few effective therapies. The introduction of resynchronisation pacing led to a dramatic improvement in suitable patients however, this therapy has been plagued by a persistent non-responder rate of between 30 and 50%. The potential causes for non-response are numerous and are outlined in Chapter 2. In response, novel approaches to CRT have been devised. One approach is to optimise the site of LV stimulation, as outlined in Chapter 3. CRT aims to improve the mechano-energetic efficiency of the heart by delivering stimulation at sites of delay in order to restore efficient activation. Unfortunately, approximately 10-15% of patients are unable to receive effective biventricular epicardial CRT; either due to issues with lead implantation, persistent lead displacement, concurrent phrenic nerve stimulation during LV pacing or the coronary sinus tributaries overlying areas of non-viable scarred myocardium.

Activation of the endocardial surface of the heart offers an alternative resynchronisation strategy, allowing direct access to fast endocardial conduction tissue and benefitting from the shorter endocardial activation route. LV endocardial pacing can be achieved in a variety of ways, as discussed in Chapter 4. The benefits associated with endocardial pacing led many investigators to believe that indiscriminate endocardial activation would prove superior to conventional transvenous epicardial CRT. However, as our findings in Chapter 5 illustrate, endocardial pacing is not a panacea for the issue of non-response. Instead, great care must be taken when selecting an

endocardial pacing site as while endocardial stimulation can yield superior changes in acute LV haemodynamics, delivering stimulation at an inferior site can in fact result in inferior outcomes.

Traditionally, endocardial activation has been performed in a similar way to conventional epicardial CRT via pacing leads which must cross either the atrial or ventricular septum, limiting the options for customised tailoring of the LV pacing site. In addition, this approach was associated with a risk of stroke and damage to the mitral valve. The introduction of a novel wireless approach, which employs acoustic energy to activate a small piezoelectric crystal tipped electrode embedded within the LV endocardium reflects a dramatic step forward. This pacing strategy is uniquely customisable and was found to be both safe and highly effective in our analysis outlined in Chapter 6.

Given the response to endocardial stimulation is highly variable and dependant on the site of stimulation, it is critical that operators are able to identify and target a preferable site whilst avoiding unfavourable locations. Our analysis in Chapter 7 outlines our work on evaluating different metrics which aid identification of the optimal pacing site. We assessed the ability of these metrics to locate the optimal pacing site in a small pilot study in Chapter 8. Our results confirmed that optimal site could indeed be located and accurately targeted using the leadless pacing delivery system.

Our final analysis in Chapter 9 represents a direct head-to-head comparison of two contrasting site selection strategies; empirical vs guided deployment of the pacing electrode. It reveals that in this small cohort, the use of guidance to inform pacing site selection was not associated with a greater echocardiographic response rate. However, trends were observed which showed site selection may prove beneficial and this analysis may help direct further research in this area.

10.3 Future Directions

10.3.1 LV EPI CRT Remains The Mainstay Of Resynchronisation Treatment

Transvenous epicardial CRT will continue to function as the default strategy for the delivery of CRT and remains the optimal therapy for those patients who exhibit a remediable underlying substrate and whose anatomy is amenable to allow adequate correction. Unfortunately, the constraints of CS anatomy in conjunction with the limitations of BiV EPI CRT mean that this approach is frequently unable to deliver effective resynchronisation pacing.

A novel approach to CRT involves attempting to selectively capture the His-Purkinje network of fast conducting fibres via LV only pacing. Rather than trying correct underlying electro-mechanical dyssynchrony, this approach aims to replicate healthy intrinsic biventricular depolarisation. New delivery mechanisms allow stimulation of the LV septum via trans-venous access [229] meaning this approach may well become increasingly widespread. Whether similar results can be achieved through selective His capture in the RV remains to be seen, although initial studies of this promising pacing modality appear promising [309].

10.3.2 Greater Use of Pre-Procedural Imaging Could Identify Patients Less Likely To Respond to BiV EPI CRT

Pre-procedural imaging and modelling [308] have the potential to allow physicians to identify those patients who may benefit from an alternative pacing strategy; either due to a lack of suitable targets or recognition that the target area cannot be accessed via the epicardial coronary venous system. Endocardial LV pacing results in a more physiological, endocardial to epicardial activation pattern, a greater reduction in total LV activation time (LV_{TAT}) and an improved haemodynamic performance (greater increases in $LV DP/dt_{max}$) in both the LV [224,265] and RV [255]. It is also associated with a higher implant success rates, less phrenic nerve stimulation and far greater access to different pacing sites.

More widespread recognition of cases where this is the case will result in greater use of endocardial pacing, and in particular leadless endocardial pacing systems such as the WiSE-CRT system (WiSE-CRT System, EBR Systems, Sunnyvale, California) which have proved safe and effective and do not require long-term anticoagulation [270]. Growth in endocardial pacing will mandate increasing use of site selection and guidance given the optimal LV endocardial pacing displays such a high degree of variability.

10.3.3 Identifying The Optimal LV Pacing Site Is Critical To Delivering Effective BiV ENDO CRT

The optimal LV endocardial pacing site displays marked inter and intra-patient variability and whilst some argue that any endocardial pacing site will invariably prove superior to epicardial stimulation, research has shown that sub-optimal BiV ENDO CRT can achieve haemodynamic improvements inferior to those associated with empirically positioned BiV EPI CRT [196]. As such,

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whilst endocardial pacing affords the freedom to perform LV stimulation at a customisable location, site selection is even more critical in order to maximise the potential benefits associated with this technique.

Tissue characterisation remains an integral parameter when looking to optimise CRT delivery. Targeting viable tissue is clearly beneficial and this can be achieved using a variety of modalities. Undertaking a direct head-to-head comparison of these diagnostic approaches would aid the development of future LV lead guidance systems. Whilst it is clear targeting viable myocardium is beneficial, it remains to be seen precisely how the presence of discrete areas of scar affects the location of the optimal pacing site.

Assessing mechanical dyssynchrony can also be achieved through a variety of modalities however, the prospective evidence proving dyssynchrony assessments can improve patient selection for CRT is lacking [183,184]. The use of CMR based dyssynchrony indexes may offer a more reliable solution [124], however larger scale, prospective, randomised validation of these techniques is required before they can be comprehensively endorsed. In the mean-time, mechanical dyssynchrony assessments aimed at identifying viable sites exhibiting late mechanical activation do appear to aid LV site selection. It's not clear whether this approach is superior to targeting sites of electrical latency or even whether these two sites are synonymous [208]. Both Q-LV [125] and LVLED [126] appear particularly useful markers to aid site selection. Neither technique requires sophisticated electro-anatomical mapping or additional pre-procedural image processing and instead can be calculated by the operator at the time of LV lead deployment. A more integrated approach is likely to be necessary however, than simply targeting the site of latest electrical activation, particularly in ischaemic patients. Instead, the focus should be on targeting a site which displays late activation in the absence of myocardial scar.

Narrowing of the paced QRS during pacing appears a less reliable marker of the optimal pacing site and we would urge caution with this approach given the potential for electro-mechanical uncoupling. Optimising the RV pacing site by identifying electrical delay also appears to be beneficial [218], especially when revising a previously implanted system where the position of the LV lead is relatively fixed.

10.3.4 Effective Site Selection Requires Accurate Guidance Technology To Ensure Optimal Positioning Of The Pacing Stimulus

Site selection remains only as good as the adjunctive guidance system given the technical limitations of spatial orientation using conventional fluoroscopy [233]. Co-registration between 2D and 3D modalities is challenging with the simplest solution integrating pre-implant imaging data with peri-procedural coronary sinus balloon venography. However, these systems are unable to determine whether a suitable tributary of the coronary sinus subtends the target segment until the procedure has begun highlighting a limitation of the transvenous, epicardial CRT. Guidance systems which can accurately visualise the entire coronary sinus network pre-procedurally, allow decisions to be made regarding not just the most appropriate target but also the most suitable means of targeting this area.

10.3.5 As Leadless Pacing Technology Becomes More Widespread, Venous Access Will Become The Primary Deployment Route

The WiSE-CRT system has been developed with trans-femoral arterial access in mind, however, arterial access complications remain an issue. The SOLVE CRT study (ClinicalTrials.gov identifier NCT02922036) is a prospective, multicentre, randomised, controlled, double-blinded clinical trial designed to robustly assess the safety and efficacy of leadless endocardial CRT. Given the arterial access issues highlighted in our work, trans-septal implants represent a method of reducing the procedural risk of WiSE CRT pacing. In time, as entire pacing systems become leadless with atrial and right ventricular activation coordinated via communication between the various components, venous implantation approaches will become increasingly de rigour.

10.3.6 The Evolution Of Imaging Technology Will Continue With Higher Resolution Scans Better Able To Define Key Anatomical Structures

CMR remains the pre-eminent imaging modality for assessing both tissue characterisation and mechanical activation and increasing experience with ultrahigh field CMR will inevitably result in improved image quality [310,311]. Greater spatial resolution will allow detailed visualisation of the entire coronary venous tree allowing pre-procedural planning to be performed entirely from one, non-ionising imaging modality.

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Other non-invasive imaging techniques which may become increasingly adopted are electrocardiographic imaging & Holographic imaging systems. ECGi allows an assessment of tissue characterisation and can be used to locate areas exhibiting late electrical activation. Refinement of body surface mapping systems now means that instead of multiple electrode vests, a more straightforward ECG belt [312] can derive information on local electrical delay in order to guide LV lead implantation. Holographic imaging systems like the Hologscope (Real View Imaging, Yokneam, Israel) allow users to interact directly with a live 3D digital hologram. Physicians can manipulate the image (rotating, slicing, measuring and marking) [313] fostering a greater understanding of the patients own unique anatomy.

Grants & Awards

British Heart Foundation Project Grant. 2017

- BHF Project Grant: PG/16/108/32593. £183,756

European Heart Rhythm Association-EUROPACE-CARDIOSTIM. Vienna, Austria. 2017

- Young Investigator Award: Clinical. Runner Up

Magnetic And eLectric Technologies (MALT) Meeting. Krusenburg, Sweden. 2018

- Young Investigator Award. Winner

Heart Rhythm Congress. Birmingham, UK. 2018

- Young Investigator Award: Clinical. Winner

British Society of Heart Failure. London, UK. 2018

- Young Investigator Award. Runner Up

Published Papers

- [1] **Sieniewicz BJ**, Gould JS, Rimington HM, Ioannou N, Rinaldi CA. Transseptal Delivery of a Leadless Left Ventricular Endocardial Pacing Electrode. *JACC Clin Electrophysiol* 2017;3:1333–5. doi:10.1016/j.jacep.2017.04.020.
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Oral Presentations

Wireless LV Endocardial Cardiac Resynchronisation Therapy Improves Response; Results From A Multicentre International Study

Presented: British Society of Heart Failure, London, UK. 2018

A Multicentre International Study Examining the Safety and Efficacy of Wireless LV Endocardial Pacing During Real World Use

Presented: Asia-Pacific Heart Rhythm Sessions, Taipei, Taiwan. 2018

Safety and Efficacy of Wireless LV Endocardial Pacing; A Multicentre International Study Examining Real World Use of the WiSE CRT Pacing System

Presented: Heart Rhythm Congress, Birmingham. 2018

LV Lead Electrical Delay Aids Identification Of The Optimal Endocardial Pacing Site; Results From An International Multi-centre Registry

Presented: Heart Rhythm Sessions, Boston, USA. 2018

Identifying and targeting the optimal site for LV endocardial CRT using electrical markers of latency & advanced imaging

Presented: MALT Meeting, Uppsala, Sweden. 2018

Variability in the optimal location for LV endocardial pacing: results from a multicentre international registry

Presented: EHRA-EUROPACE-CARDIOSTIM, Vienna, Austria. 2017

Identification of the optimal LV endocardial pacing site using paced QRS duration

Presented: Heart Rhythm Sessions, Chicago, USA. 2017

Identifying the optimal location for LV endocardial pacing: results from a multicentre international registry of acute LV endocardial pacing

Presented: Heart Rhythm Congress, Birmingham. 2017

Poster Presentations

Real World Experience of Leadless LV Endocardial CRT with the WiSE CRT Pacing System; An International Study

Presented: Heart Failure Society of America, Nashville, USA. 2018

Patient Etiology Predicts The Distribution Of Late Activating LV Myocardium; Results From A Multi-centre International Registry

Presented: Heart Rhythm Sessions, Boston, USA. 2018

Targeted Electrode Deployment During Biventricular Endocardial Pacing Improves LV Reverse Remodelling: A Multi-centre UK Study

Presented: Heart Rhythm Sessions, Boston, USA. 2018

Optimal site selection during biventricular endocardial pacing improves acute haemodynamic response and chronic remodelling: A multi-centre UK study

Presented: EHRA-Congress, Barcelona, Spain. 2018

Safety and efficacy of optimal site selection during biventricular endocardial pacing: A multi-centre UK study

Presented: EHRA-Congress, Barcelona, Spain. 2018

Cardiomyopathic aetiology affects the distribution of endocardial electrical latency; results from a multi-centre registry

Presented: EHRA-Congress, Barcelona, Spain. 2018

Does targeting the site of maximal electrical delay result in the optimal haemodynamic improvement; results from an international multi-centre registry

Presented: EHRA-Congress, Barcelona, Spain. 2018

Poster Presentations

Identification of the optimal LV endocardial pacing site using paced QRS duration

Presented: EHRA-EUROPACE-CARDIOSTIM, Vienna, Austria. 2017

Prediction of optimal LV endocardial pacing site with Q-LV in ischemic and non ischemic patients

Presented: EHRA-EUROPACE-CARDIOSTIM, Vienna, Austria. 2017

Predicting the optimal site for LV lead deployment using epicardial non-invasive mapping

Presented: EHRA-EUROPACE-CARDIOSTIM, Vienna, Austria. 2017

Variability in the optimal location for LV endocardial pacing: results from a multicentre international registry

Presented: Heart Rhythm Sessions, Chicago, USA. 2017

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