Thesis for Doctorate of Medicine

Optimising the left ventricular lead for endocardial and epicardial cardiac resynchronisation therapy

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Thesis Abstract

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Cardiac Resynchronisation Therapy (CRT) is an effective treatment for selected patients with heart failure. The left ventricular (LV) lead used to achieve this can be hard to place via the coronary sinus in a proportion of patients, and in addition may not be in an optimal position in others.

In this thesis, I initially discuss CRT and its technical limitations. Using a large meta-analysis, I elucidate contemporary rates of LV lead placement failure. An alternative method of LV lead placement is endocardial, and I discuss results to date, again using a meta-analysis to summate prior trials and the technique's risks and benefits. The main subject of the thesis is assessing a novel method of LV endocardial pacing via the interventricular septum. I report a trial of 19 patients in whom conventional CRT was not possible or unsuccessful, showing clinical response to CRT delivered in this manner to be similar to conventional CRT, with acceptable risks.

LV lead location in endocardial CRT has been little studied. I go on to investigate optimal LV lead positioning in this group, by assessing acute haemodynamic response (AHR) to CRT with a high-fidelity pressure wire and a multi-level modelling analysis. I show that this technique is reproducible. I compare placement at sites of late mechanical activation and late electrical activation, showing little difference in this cohort or in a parallel study of AHR in 22 patients undergoing conventional CRT. With a multivariate analysis I show that only electrical delay is a consistent predictor of acute response.

These results support the use of this novel technique for CRT as a second-line procedure, and I discuss future directions for this. Lead site selection at a site of late electrical activation is supported by my work, and again I summarise the context of this.

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Aims of thesis

- To assess the need for endocardial LV pacing by investigating the current rate of failure to place a LV lead via the coronary sinus
- To assess the results to date of LV endocardial pacing
- To investigate the safety and efficacy of LV endocardial pacing via the interventricular septum
- To investigate the optimal position for coronary sinus and endocardial LV leads

Publications arising from this work

At the time of writing, the following publications by the author include elements of the content of this thesis.

Journal articles

- Gamble, James H.P., Yaver Bashir, Kim Rajappan, and Tim R. Betts. Left Ventricular Endocardial Pacing via the Interventricular Septum for Cardiac Resynchronization Therapy: First Report. 2013, Heart Rhythm 10:1812–14.
- Betts, Gamble, Khiani, Bashir, and Rajappan. Development of a Technique for Left Ventricular Endocardial Pacing via Puncture of the Interventricular Septum. 2014, Circulation: Arrhythmia and Electrophysiology 7: 17–22.
- Gamble, Herring, Ginks, Rajappan, Bashir, and Betts. Procedural Success of Left Ventricular Lead Placement for Cardiac Resynchronization Therapy: A Meta-Analysis. 2016, JACC: Clinical Electrophysiology 2:69–77.

- Gamble, Herring, Ginks, Rajappan, Bashir, and Betts. Endocardial left ventricular pacing for cardiac resynchronisation– systematic review and meta-analysis. Under review by Heart Rhythm.

Selected conference abstracts

- Gamble, Khiani, Ginks, Rajappan, Bashir, and Betts. Assessing Response to Biventricular Pacing: Non-Invasive Cardiac Monitoring Does Not Consistently Detect Acute Response. Europace 17:iii92. Europace 2015 Poster
- Gamble, Khiani, Ginks, Rajappan, Bashir, and Betts. Left Ventricular Endocardial Pacing across the Interventricular Septum - Medium-Term Results. Europace 17:iii20. Europace 2015 Poster
- Gamble, Herring, Khiani, Foley, Ginks, Rajappan, Bashir, and Betts. Differential relationship of electrical delay with endocardial and epicardial left ventricular leads for Cardiac Resynchronisation Therapy. Oral presentation; won Young Investigators Award at British Heart Rhythm Congress 2015
- Gamble, Herring, Khiani, Foley, Ginks, Rajappan, Bashir, and Betts. An acute comparison of different strategies for targeting the left ventricular lead for Cardiac Resynchronisation Therapy. British Heart Rhythm Congress 2015 Poster
- Gamble, Herring, Khiani, Foley, Ginks, Rajappan, Bashir, and Betts. Safety and Efficacy of Endocardial Left Ventricular Pacing for Cardiac Resynchronisation Therapy - a Meta-Analysis. Heart Rhythm Society scientific sessions 2016 poster
- Gamble, Herring, Khiani, Foley, Ginks, Rajappan, Bashir, and Betts. Endocardial Left Ventricular Pacing across the Inter-Ventricular Septum for Cardiac Resynchronisation Therapy - Clinical Results. Heart Rhythm Society scientific sessions 2016 poster

Chapter One – **Background Part I: CRT epicardial and endocardial LV pacing**

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Abbreviations

BiVP	BiVentricular Pacing
CRT	Cardiac Resynchronisation Therapy
EF	Ejection Fraction
HF	Heart Failure
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVP	Left Ventricular Pacing
NYHA	New York Heart Association
RV	Right Ventricle
RVP	Right Ventricular Pacing

Introduction

In this chapter I will try and build up background on heart failure and concurrent cardiac conduction tissue disease, cardiac resynchronisation therapy as a treatment for this, and techniques to achieve it, including conventional epicardial and endocardial left ventricular pacing. I will then discuss left ventricular endocardial pacing in detail, including a review of progress in this technique so far.

In the subsequent second background chapter I will go into more detail on left ventricular lead placement and methods to optimise this.

Heart failure

Heart failure (HF) is defined mechanistically as an inability of the heart to deliver oxygen at the rate required by the tissues, or clinically as a syndrome of signs and symptoms due to this inability. These symptoms can be classified according to severity, most commonly using the New York Heart Association (NYHA) classification. The severity of cardiac dysfunction underlying heart failure is most commonly assessed using the ejection fraction (EF). EF has become the predominant measure of cardiac dysfunction, although it is known to be inconsistently measured by many techniques, and does not clearly identify the

benefit of therapies, for example Cardiac Resynchronisation Therapy (CRT) (Kaufmann 2013, Kutyifa 2013a, McMurray 2012). Furthermore, the correlation between the degree of cardiac dysfunction and symptoms is poor, such that asymptomatic patients can have significant myocardial dysfunction and a relatively poor prognosis (McMurray 2012).

The scale of the problem is significant – about 2% of the adult population has HF, with a much higher prevalence in the elderly of up to 6-10% (McMurray 2009). Many patients with HF have limiting symptoms resulting in a poor quality of life, and 30-40% die within one year of diagnosis (McMurray 2009).

Ejection fraction has been used to dichotomise HF into those patients with a normal EF (although these patients tend to have many other cardiac abnormalities) and those with a reduced EF. Although the majority of patients with HF do not have a reduced EF, the vast majority of heart failure therapies have been developed for the reduced EF group, who are easier to identify.

Current medical therapies focus on interrupting the maladaptation to abnormal cardiac function that underlies HF. They are effective in reducing mortality and improving symptoms, although there is a remaining high mortality and burden of symptoms even in many patients with optimal treatment (McMurray 2012).

Cardiac Resynchronisation Therapy

The underlying pathophysiology

The development of CRT began in the 1980s, as investigators noted that electrical conduction delay was seen in many patients with severe heart failure. This delay includes slow electrical conduction at several levels, including between the atria and the ventricles, between the ventricles, and within the left ventricle (LV). The latter phenomenon of LV

intra-ventricular delay is closely associated with left bundle branch block (LBBB). The prognostic importance of this is illustrated by the observation that the QRS duration on ECG correlates closely with the risk of death in patients with heart failure (Gorcsan 2012).

These factors of intra-ventricular dys-synchrony within the LV, between the left and right ventricles, and between the atria and ventricles all act to significantly worsen the overall cardiac function. This wastes a significant proportion of cardiac work due to contraction of regions of the myocardium at inefficient points in the cardiac cycle and without the benefits of coordinated contraction with the other chambers (Hu 2013, Nelson 2000, Yu 2009).

The function of the LV in LBBB is known to be abnormal in several ways, shown in several early experiments to include a different mechanical contraction pattern and abnormal perfusion, as well as the abnormal electrical conduction pattern (Vassallo 1986). Prinzen et al expanded on this work in a study in 1999, in which they assessed the overall cardiac work and thus cardiac efficiency in a dog model (Prinzen 1999). They used right ventricular pacing (RVP) as a model of LBBB, as a roughly similar activation pattern is known to result (Eschalier 2015). They showed that RVP reduced cardiac work to 40% of that found in right atrial pacing, and that LV pacing improved this to 60%. This work was in a dog model, and used several complex equations and associated assumptions to derive cardiac work from MRI tagging images, but it illustrates the principle that LV pacing can *partially* restore normal cardiac function compared to RV pacing or LBBB (Nelson 2000).

Nelson et al confirmed this finding in a small cohort of patients with LBBB and dilated cardiomyopathy. They placed a temporary pacing wire in a lateral branch of the coronary sinus and used this to pace the LV. They found that this increased LV dP/dt max (the maximum rate of change of LV pressure, a marker of LV contractile function) but without

an increase in heart rate or myocardial oxygen consumption. This elegant experiment showed the "rather unique" property of LV pacing to improve cardiac mechano-energetics, apparently without a cost in terms of myocardial energy consumption (Nelson 2000).

Helm et al illustrated the time-course of LV dyssynchrony in a dog model (Helm 2005). They used cardiac MRI to follow LV wall movement and the temporal pattern of strain, as illustrated in Figure 1 below.

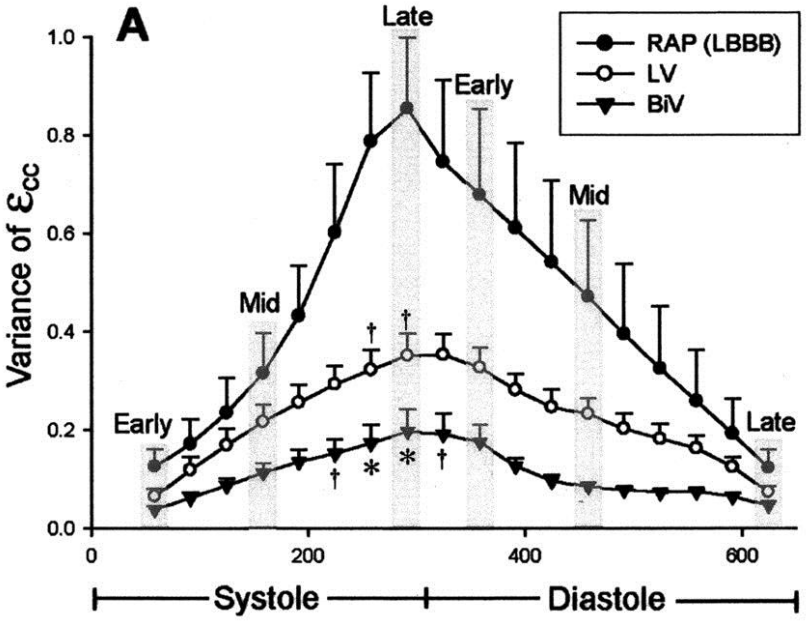


Figure 1- Time-course of left ventricular contraction, with a measure of LV dyssynchrony on the y axis. RAP represents right atrial pacing, used as a model of LBBB. LV and BiV represent LV pacing modes. It can be seen that LV dyssynchrony peaks at end-systole and gradually improves over diastole. Both LV and BiV pacing improve the dys-synchrony, BiVP significantly more. From Helm et al (Helm 2005).

Restoration of more normal LV conduction and the resultant improvement in LV function produces improvements in multiple dysfunctional cellular and electrophysiological processes, including calcium handling, action potential duration, ion-channel expression, and myocardial energetics (Cho 2012, Kirk 2013). As shown in the studies discussed

above CRT does not entirely normalise electrical dyssynchrony, but does very significantly improve it. The degree of LV dyssynchrony resulting from LV and BiV pacing is more than normal, but less than LBBB (Ploux 2015).

The first clinical descriptions of CRT were in the mid-1990s (Cazeau 1994). There was a steady progression to crossover trials (Auricchio 1999) and subsequently to larger multi-centre trials (Abraham 2002) showing a clear clinical benefit of the therapy.

Clinical results of CRT

Several studies have shown that CRT is an effective treatment of heart failure in appropriate patients (Holzmeister 2011). These studies are now well-known but it is worth summarising the results briefly. CRT has been shown to decrease both hospitalisations (Cleland 2005, Moss 2009) and mortality (Cleland 2005, 2006, McAlister 2007) as well as improving symptoms and quality of life (Cleland 2005, McAlister 2007), as shown in clinical results in Figure 2 below. It is additive to medical therapy for HF (Schmidt 2014).

Patients with LBBB seem to benefit the most from CRT. This has been a topic of much discussion and research, but in summary the evidence suggests that there is either only a limited benefit or no benefit of CRT in patients without LBBB. The degree of response increases with QRS duration, from about 120ms up (Cleland 2013, Leyva 2014), and patients with a QRS duration of less than 120ms do not appear to benefit, and are probably harmed by CRT (Ruschitzka 2013). CRT is now widely supported by guidelines for appropriate patients (Dickstein 2010, Epstein 2008, UK NICE 2014, Vardas 2007).

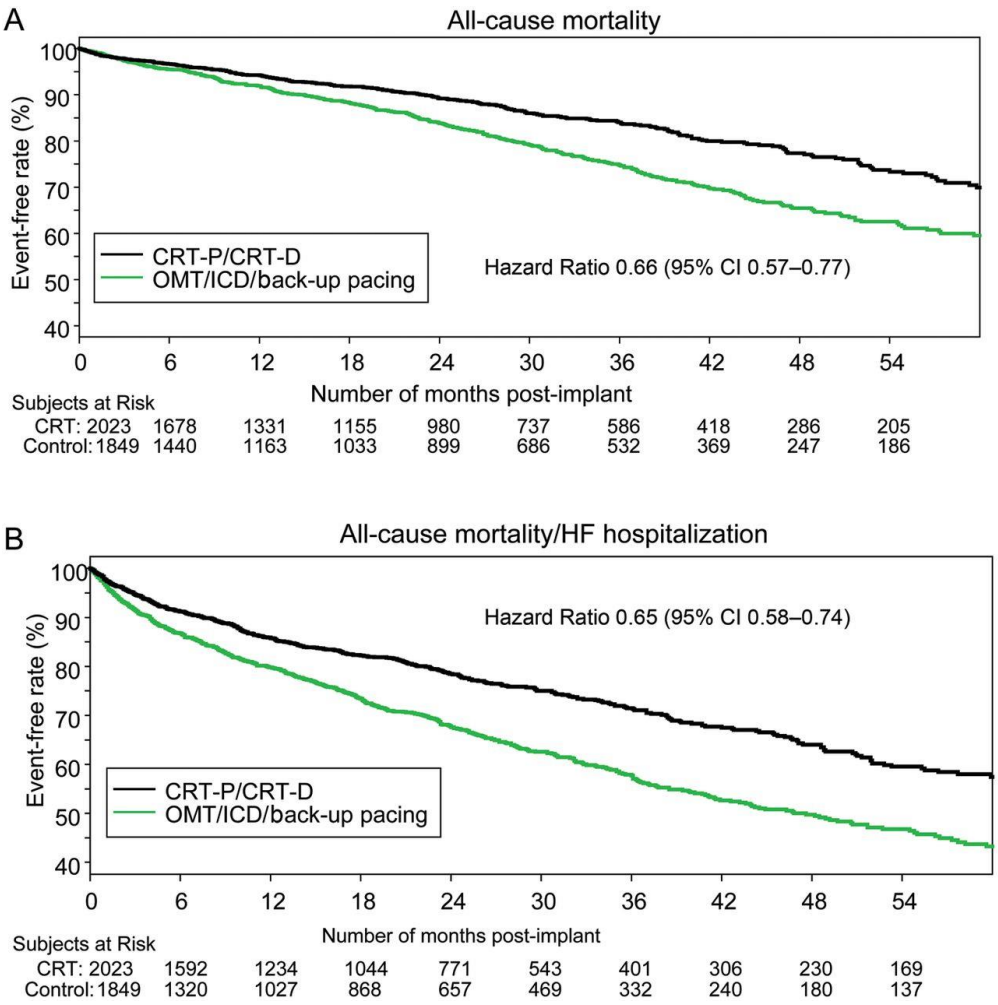


Figure 2 – Clinical benefit of CRT, figures from a 3872-patient meta-analysis of most of the larger clinical trials of CRT (Cleland 2013). Panel A shows all-cause mortality, and panel B mortality and heart failure hospitalisation rates. The results are both durable over time, and statistically and clinically significant.

Technique

The initial studies of CRT used a temporary LV endocardial lead in order to assess the benefit of biventricular pacing (BiVP), but then a surgically placed epicardial LV lead for long term LV stimulation (Leclercq 2000). After these early studies showed a clear benefit of CRT, there was a rapid development of techniques and technology over the subsequent few years, evolving the technique of transvenous implantation of leads into the epicardial LV veins via the coronary sinus (Daubert 1998). There is now a wide spectrum of guide

and inner catheter shapes available to assist in the intubation of the coronary sinus and then of the targeted coronary vein.

Left Ventricular Pacing Leads

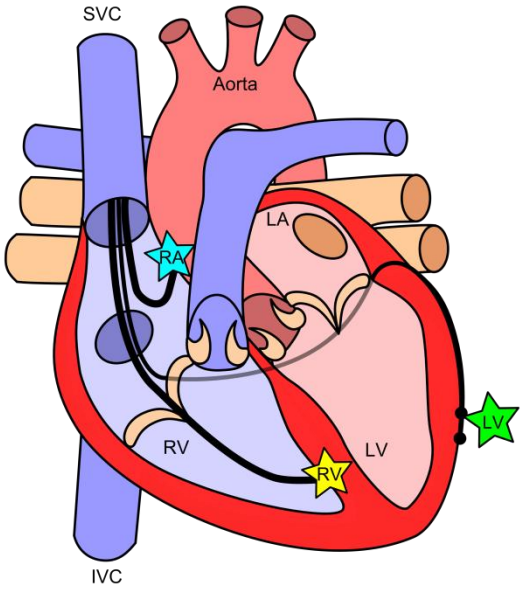


Figure 3 – Illustration of CRT leads.

LV pacing leads are now specifically designed for this purpose. Early leads were unipolar, with one pacing pole at the lead and the anode being the pulse generator. These were replaced by bipolar leads with two electrodes, allowing stimulation over a smaller area and generally lower capture thresholds. The LV lead, a right ventricular lead and in most cases a right atrial lead are connected to a CRT pulse generator. This can incorporate a cardioverter-defibrillator if required (CRT-D system) or can be a pacemaker only (CRT-P).

More recently LV leads with four electrodes have been developed. These quadripolar leads allow the stimulation of the LV myocardium from any of the four electrodes. The pulse generator can be programmed to use various combinations of one of the electrodes as the anode or cathode, and another of the electrodes, the right ventricular lead, or the generator itself as the anode. This allows for many possible stimulation vectors, although the number available on each device is dependent upon the specific device hardware.

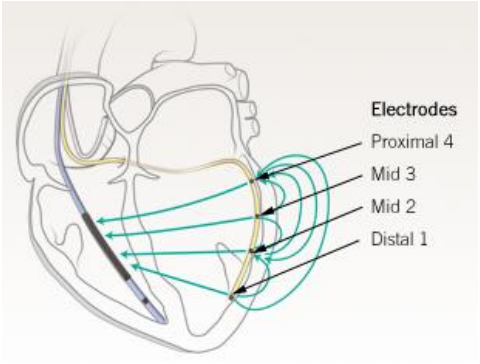


Figure 4 – St Jude Medical Inc. (SJM) were first to market with a quadripolar LV lead (and thus this lead has been used in much of the prior research), which has an "S" configuration with three ring electrodes located 20, 30 and 47 mm from the distal tip electrode. The electrodes on the SJM quadripolar lead are termed D1, M2, M3 and P4 as shown. All four electrodes on the LV lead can be programmed to act as the cathode, and M2 and P4 may be programmed to act as an anode. This allows 10 possible pacing configurations. Other manufacturers produce similar leads, some of which allow more potential configurations (Gamble 2014). Image courtesy of SJM.

Non-response to CRT

The issue of 'non-response' to CRT has been extensively discussed and investigated. Non-response is loosely defined as a lack of improvement after CRT. It is quickly apparent that this is extremely dependent upon how 'improvement' is measured. Different measurements of response will give a different proportion of patients in whom the chosen measure improves. Fortwalt et al found that 26 publications on CRT response used 17 different primary response criteria. They applied these criteria to a large study population, and found that response rates varied between 32% and 90%, and that 99% of patients showed a positive response according to at least one of the criteria. There was particularly poor correlation between clinical and echocardiographic criteria (Fornwalt 2010).

Thus attempts to improve the rate of CRT response and to treat patients who are perceived to be non-responders are challenged by this lack of definition. To some extent, this may reflect the heterogeneous population of patients labelled as non-responders to CRT, which includes a wide variety of different subtypes. Mullens attempted to define this in a widely-cited paper in which their group worked to identify the primary reason for non-response in each patient (Mullens 2009a).

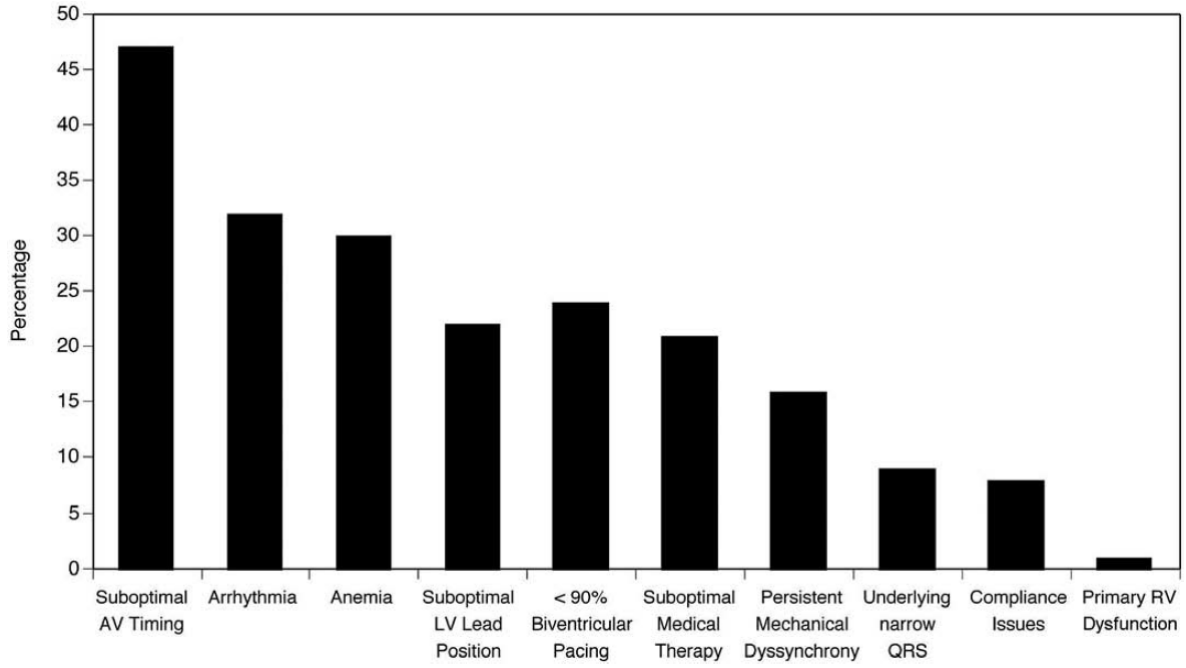


Figure 5 – Identified reasons for non-response to CRT in a group of patients referred to a specialist CRT non-response clinic. From Mullins et al (Mullens 2009a)

The conclusions drawn as to the primary cause of non-response were, in many cases, subjective to the assessors. Many of the causes of non-response cited cannot be proven, or are suggested by techniques such as echocardiographic optimisation of CRT which have limited reproducibility and have not been shown to improve clinical outcomes (International Working Group on Quantitative Optimization: 2013). The paper does however illustrate the breadth of cardiac problems present in this group. It is also important to note that the paper makes limited mention of the importance of other non-cardiac comorbidities in this group. Although older and more comorbid patients do benefit from CRT, they still have a higher mortality and morbidity (Bogale 2012, Guha 2013, Verbrugge 2013a).

Despite the limitations of the concept and classification of non-response, there does seem to be a relatively consistent group of about 30-40% of CRT recipients who derive less benefit and are at increased risk for poor outcomes, and it seems from Mullens' data and

other work that in at least some of these cases improvements can be made that result in better outcomes (Zhang 2015).

Another important part of the cause of non-response is patient selection. As mentioned above, QRS width is a primary determinant of the efficacy of CRT (Leyva 2014). Selection of patients without a wide QRS is likely to result in non-response. The potential benefit of CRT in patients with a narrower QRS has been an area of much discussion and research. In brief, although earlier studies suggested a benefit of CRT in this group, this has not been borne out by a large randomised study (Jabbour 2015, Ruschitzka 2013, Sohaib 2015). Similarly, RBBB patients seem to benefit significantly less often from CRT, although there is benefit in some, which may reflect heterogeneity within the RBBB group (Cleland 2013).

Assessment of acute haemodynamic response to cardiac pacing

Many studies, including many of those referenced in this thesis, have attempted to assess the acute cardiac response to changes in pacing stimulation. It is worth discussing the theory and techniques used to measure this now, as this assessment is used by many studies discussed below.

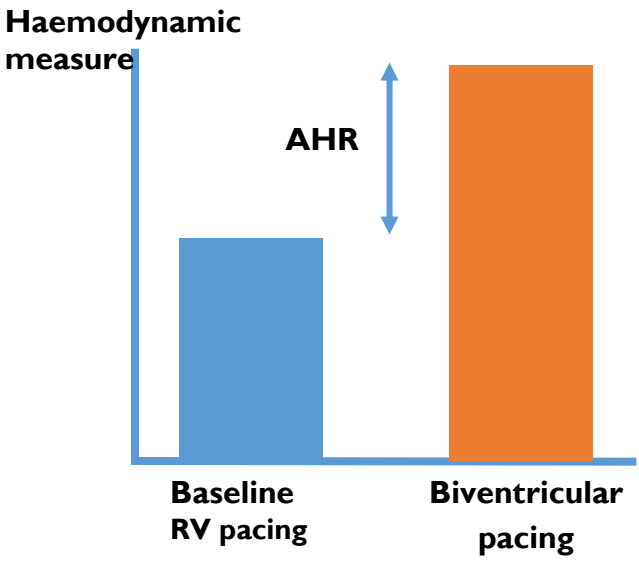


Figure 6 – Acute haemodynamic response

Each subject's heart will have a different baseline level of function, in terms of cardiac contractility, which will also be influenced by cardiac afterload, preload, heart rate, valvular regurgitation, and potentially by cardiac ischaemia. Accordingly almost all

experimental protocols have fixed the heart rate, which can easily be achieved in the situation of cardiac pacing. The other cardiac parameters cannot easily be fixed, and will vary both within the patient and between patients. In order to standardise as much as possible, most comparisons are expressed as percentage change from a baseline state to an intervention state. This allows the measurement of the acute haemodynamic response (AHR) to a pacing intervention.

Multiple measures of cardiac function are known to be changed by CRT, as shown in Table 1 below. These changes occur within seconds after activating CRT (Auricchio 1999, Delnoy 2011, Manisty 2012, de Roest 2013) and mostly persist over months (Steendijk 2006). Blood pressure changes seem to occur acutely with CRT but do not persist in the longer term (Manisty 2012, Steendijk 2006).

Parameter	Expected change	Notes and references
LV dP/dt max	Increase, 10-50%	Most commonly used. (Auricchio 1999, Dekker 2004, Delnoy 2011, Duckett 2011, Pappone 2015, de Roest 2013, Steendijk 2006, Suzuki 2010, Zanon 2014)
LV dP/dt min	Increase (i.e. more negative), 10-50%	Assesses diastolic function. (Dekker 2004, Delnoy 2011, de Roest 2013)
LV systolic pressure, blood pressure	Increase, 0-10%	Rapid small amplitude change, often not maintained. (Dekker 2004, Manisty 2012, Steendijk 2006)
Stroke volume	Increase, 5-40%	(Dekker 2004, Delnoy 2011, Manisty 2012, de Roest 2013, Steendijk 2006)
Stroke work	Increase, 10-50%	(Dekker 2004, Delnoy 2011, de Roest 2013, Steendijk 2006)
Cardiac output / index	Increase, 5-20%	(Dekker 2004, Delnoy 2011, de Roest 2013, Steendijk 2006)

Table 1 - Selected cardiac parameters improved by CRT and their expected range of change.

LV dP/dt is the rate of change in LV pressure, and thus the first derivative of LV pressure. LV dP/dt max, the maximum dP/dt obtained in each cardiac cycle, has been much used for

the assessment of CRT (Auricchio 1999, Dekker 2004, Delnoy 2011, Duckett 2011, Pappone 2015, de Roest 2013, Steendijk 2006, Suzuki 2010, Zanon 2014). It has been shown to be reduced in the context of reduced LV systolic function due to dyssynchrony, and to be a sensitive marker of this abnormal cardiac function in both animal models and humans (Yu 2009). It is dependent upon cardiac preload but is not affected by afterload (Kass 1987, Mason 1971, Wallace 1963). The cardiac preload state would be expected to be relatively constant over a short timescale during the haemodynamic evaluation of pacing.

Techniques of AHR measurement

Several techniques have been used to assess AHR to CRT. In order to measure dP/dt max, a precise measurement of LV pressure is required, which can be obtained using a pressure manometer wire. This device was designed to be used in coronary arteries to assess pressure drop across a coronary lesion, but is simple to insert within a catheter into the LV to measure pressures and dP/dt max. This simplicity has meant that it is widely used for research.

A conductance catheter allows measurement of both LV pressure and volume, and thus derivation of full pressure-volume loops. This is more complex both procedurally and in interpretation, so although it provides more data it has been used less often.

Finally, several authors have investigated a variety of non-invasive techniques to measure cardiac function and thus AHR. These have included using echocardiography to derive stroke volumes, blood pressure, and various impedance-based measures. This is discussed in more detail in a subsequent chapter.

Limitations

As mentioned above, many of these parameters are dependent upon LV preload and afterload (Kass 1987, Mason 1971, Wallace 1963). Pressures will be particularly dependent upon filling status and vasodilatation. Accordingly, most experimental protocols attempt to minimise variation in these factors, but this cannot be entirely removed, even by normalising to baseline values. This physiological variation will combine with measurement error to produce significant variability between measurements. This variability can compete with the effects being measured, making them impossible to detect or producing spurious results, particularly in protocols with short recording periods or a lack of repeatability (Francis 2013). The issue of measurement error has plagued the optimisation of CRT atrioventricular and ventriculo-ventricular intervals, alterations in which produce very small physiological changes. These changes are often of less magnitude than the error in the variables used to measure them, resulting in meaningless optimisation protocols (International Working Group on Quantitative Optimization: 2013).

The other major limitation of most of these techniques is that they are invasive, requiring arterial access to place a pressure wire or conductance catheter, which has attendant risks.

Technical limitations of CRT

Placing an LV lead for CRT remains challenging, and in a significant proportion of patients a LV lead cannot be implanted. This proportion has generally been quoted in the literature as about 6-8%, based upon the large multi-centre trials of CRT that started in the early 2000s (Curtis 2013, Gras 2007, Moss 2009, Tang 2010), although these figures do not take account of changes in success rates in contemporary trials. In the next chapter I will assess

the historical and contemporary rates of failure to place an LV lead using meta-analytical techniques.

The reasons for failure to place a lead include obstructing valves, tortuosities in the venous branches, coronary sinus dissection, phrenic nerve stimulation and areas of LV scar. A discussion of the functional anatomy of the coronary venous anatomy will help explain these reasons.

The coronary venous anatomy

The coronary venous system drains predominantly via the coronary sinus (CS) into the right atrium. The anatomical features of the CS and its branches explain many of the challenges of LV lead placement.

A Thebesian valve is found at the os of the CS in a proportion of patients. One group used a fibreoptic endoscope to view the CS os in 100 patients, and found a visible Thebesian valve in 54%. In 6 patients the valve obstructed more than 70% of the os (Anh 2008). Other groups found a valve in 74% (Mak 2009) and 64% (Randhawa 2013) of autopsy specimens, suggesting that a valve is probably present in most patients but can be vestigial. Further valves, including the valve of Vieussens are present within the CS body in about 60% of cases (Randhawa 2013), and can obstruct passage up the CS.

The further CS anatomy is highly variable, and may provide limited options for placement of an LV lead, as illustrated in Figure 7 below.

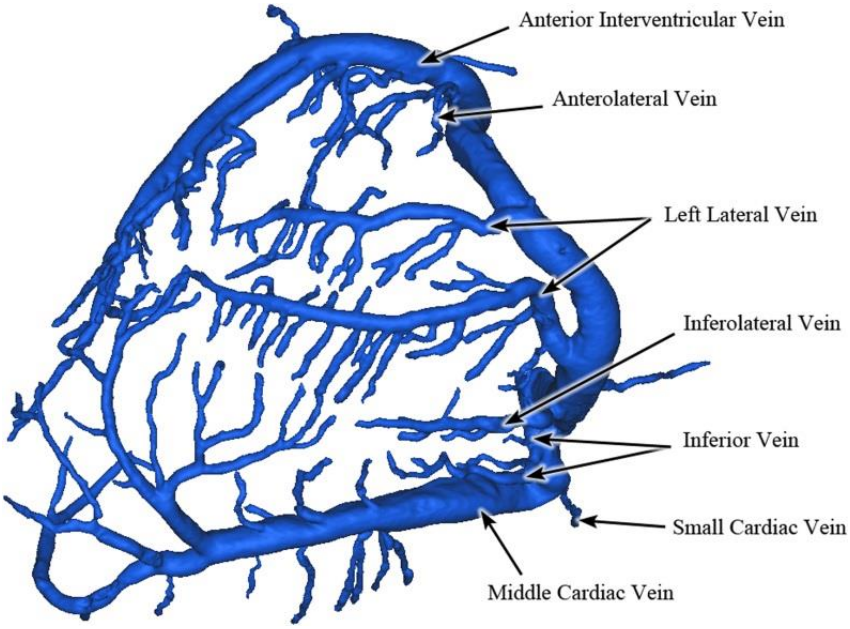


Figure 7 – Left lateral view of a representative coronary sinus specimen, from Spencer et al who made an exhaustive post mortem assessment of 121 human hearts, and found that all normal anatomies have a middle cardiac branch and an anterior interventricular vein (also known as the great cardiac vein), but that there is very significant variation in the veins present in between these (Spencer 2014). 11% of the specimens did not have a vein overlying the inferolateral region of the heart, which has been most commonly targeted for LV lead placement, and the diameters of 20% of the veins overlying this area were too small to place a 5 French pacing lead. The inferolateral vein is often called the posterolateral vein by other authors.

Khan et al retrospectively reviewed the coronary venograms of 133 patients, and attempted to classify the suitability of veins seen for LV lead placement. Using this unavoidably subjective process, they found that although almost all patients had at least one potential target for an LV lead, only 44% of patients had more than one, and there was a non-significant trend for patients with ischaemic cardiomyopathy to have less suitable veins than those with dilated cardiomyopathy (Khan 2009).

Other issues with LV lead placement

The venous anatomy can also be problematic due to tortuosities in the veins, such that placing a lead in them is extremely challenging. Dissection of the CS occurs in a proportion of procedures. The frequency of this occurrence is assessed in the subsequent chapter, although an older meta-analysis reported it as occurring in about 2% of cases (van Rees 2011). A significant dissection generally necessitates aborting LV lead placement, but it is often possible to place a lead on a subsequent attempt (Fatemi 2008).

Phrenic nerve stimulation can be a further problem. The phrenic nerve courses over the lateral portion of the left ventricle, and is thus located within the target area for CRT in most patients. Problematic phrenic nerve stimulation occurs in up to 13% of patients with CRT and can limit CRT effectiveness (Biffi 2013).

Myocardial scar is common in CRT candidates, more so in ischaemic cardiomyopathy but also present in some of those with dilated cardiomyopathy. If there is significant scar in the region of LV lead placement, capture thresholds are often high and it may not be possible to obtain a viable lead position in this area.

Alternatives to LV lead placement via the coronary sinus

The above discussion illustrates some of the problems with placing an LV lead via the coronary sinus route, resulting in a rate of failure to place an LV lead and a need for alternative routes. In addition, as use of CRT expands and patients survive longer the need for LV lead replacement has increased, however it is not feasible to replace the lead via the CS in 20-50% of cases due to venous branch or CS occlusions (Burke 2005, Rickard 2012).

Surgical epicardial lead placement

Before the development of techniques for CS lead placement, all permanent leads for CRT were placed surgically. The most common technique used for this has been open cardiac surgery using a lateral thoracotomy to place a lead directly onto the epicardium. This is a major procedure with significant morbidity as well as a risk of death in heart failure patients. Alternative surgical techniques include mini-thoracotomy, endoscopic approaches, and robotic-assisted surgery.

Miller et al reported a series of 48 surgically placed leads and 432 transvenous CS leads. The transvenous group were older and included more men. They found a higher incidence of a composite endpoint of death, ventricular assist device or transplant in the surgical group over the subsequent 7 years. This risk was predominantly over the first few post-operative months (Miller 2011). Another series reported similar results, with a slightly higher long term mortality rate in the surgical group and a short term peri-procedural risk (Ailawadi 2010). Neither study was randomised, and the long term risk differential may simply reflect different baseline populations. Both studies used a variety of surgical techniques.

Rickard reported a series of 96 surgically placed leads, with low surgical complication rates and identical long term survival and response to a cohort of patients with transvenous lead placement (Rickard 2015).

A small randomised study has been published comparing transvenous lead placement to robotic-assisted surgical placement in 21 patients. This found no outcome differences and no difference in echocardiographic response to CRT at 6 months. The authors concluded that although surgical lead placement appeared to be technically successful, it was not superior to a transvenous lead (Garikipati 2014).

The largest study to date looked retrospectively at 216 patients implanted with epicardial leads in the Leiden Medical Centre between 2004 and 2013 (Buiten 2015). Only 9 leads were implanted as a 'sole' procedure due to failed transvenous placement; the rest were placed at the time of a concurrent cardiothoracic operation, mostly bypass grafting. Results were good with low reported complication rates due to the lead placement. Lead durability was excellent, with 5-year cumulative lead failure rates of 1.6%. There have been some concerns about the long term durability of epicardial leads. In the paediatric population epicardial leads do seem to have a high failure rate (Kwak 2012), but evidence is lacking that this applies to adults, although a French study of 62 patients found a 10% failure rate of epicardial leads by 36 months (Cousin 2015).

A potential problem with surgical lead placement is that access to the posterolateral basal aspect of the LV, where leads are probably optimal in most patients, is relatively difficult. A small study found that many leads were placed anteriorly by surgeons, which could results in worse outcomes, although this is clearly very dependent upon the local practice (Polasek 2015).

Patients who are candidates for CRT by definition have poor LV function and symptomatic heart failure. This patient group are known to be high-risk for surgery, and so a significant proportion of CRT candidates are not felt to be candidates for a surgical epicardial lead. This limits the application of this technique, although there is little published data on what proportion of CRT candidates would be candidates for open surgery.

Endocardial left ventricular pacing

Given the limitations of both transvenous epicardial pacing via the coronary sinus and of surgical epicardial pacing, alternative techniques have been investigated. Endocardial pacing has been proposed as an alternative. There is a body of pre-clinical evidence suggesting potential benefit of endocardial CRT, which is worth reviewing.

Possible pro-arrhythmic effects of epicardial left ventricular pacing

Animal studies

There is a long-standing concern that CRT might be pro-arrhythmic, with the theory being that additional stimulation of the heart might induce arrhythmia. In 2004 Fish et al reported that in a dog heart slice model, epicardial pacing elongated the QT interval and broadened QRS width (Fish 2004). It also increased the transmural dispersion of repolarisation, the duration of intramyocardial repolarisation and conduction through the layers of myocardium (Antzelevitch 2001). Increases in this repolarisation time are thought to underlie pro-arrhythmic effects seen in Brugada syndrome and long QT syndromes (Antzelevitch 2001, 1999, Salama 2011). Although this is a model some way removed from human hearts, it does provide a suggestion of concern.

Similar results were found by two other groups, who also showed that biventricular epicardial pacing prolonged transmural dispersion of repolarisation (Bai 2005) to a greater degree than endocardial pacing (Xu 2012). Medina-Ravell et al further investigated this phenomenon in humans (Medina-Ravell 2003). They found that epicardial pacing of the LV alone prolonged the QT interval, although this effect was less prominent in biventricular pacing. All of these papers do not confirm that biventricular pacing is pro-arrhythmic, but show that it changes repolarisation, which would be expected from extraneous stimulation of the myocardium. Their methods cannot confirm a pro-arrhythmic effect.

Human results

Several studies have found a neutral effect of CRT on arrhythmia (Fish 2005, Lin 2008), although this appears to be due to a differential effect across the population of CRT recipients, with those patients who have benefited from CRT in terms of positive response and reverse LV remodelling displaying a reduction in ICD shocks (Di Biase 2008, Gold 2011a) and the rate of sudden cardiac death (Anand 2009), but with non-responders to CRT having no benefit or an increased risk (in particular in those without underlying LBBB (Gold 2011a, Ruschitzka 2013)). Whether these effects are due to LV reverse remodelling or to CRT itself is not known, although it seems most likely that it is the reverse remodelling that reduces arrhythmic risk.

This is supported by the recent ECHO-CRT study, in which CRT was assessed in patients with a narrow QRS. The study recruited patients with a near-normal QRS duration (mean 105ms) but reduced EF and echocardiographic evidence of dys-synchrony, based on a series of prior single-centre and small studies showing an apparent benefit of CRT in this population. In this patient group CRT significantly *increased* the rate of death and had no effect on symptoms (Ruschitzka 2013). Other work has shown that CRT increases dys-synchrony from normality, but decreases it relative to LBBB (Ploux 2015). One interpretation of this data would be that epicardial CRT is intrinsically pro-arrhythmic, but that this effect is offset in patients who respond to CRT by the associated reverse remodelling, which is anti-arrhythmic.

Endocardial stimulation may reduce the pro-arrhythmic effect of CRT

There is some evidence that endocardial stimulation may improve the abnormal stimulation patterns induced by epicardial stimulation. Xu et al measured transmural duration of repolarisation in a canine wedge LV preparation, and showed that LV endocardial and mid-myocardial pacing reduced this significantly relative to epicardial

pacing (Xu 2012). In a dog whole-heart model of a dilated LV with LBBB, endocardial stimulation reduced duration of repolarisation relative to epicardial stimulation (Van Deursen 2009). The same group measured LV activation patterns, and showed significantly shorter electrical activation times and more complete repolarisation of the heart with endocardial pacing (Strik 2012a).

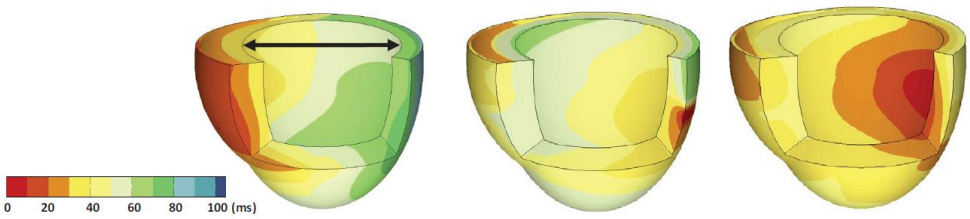


Figure 8 – LV activation maps. On the left is baseline activation in LBBB in a dog heart failure model, in the middle epicardial pacing, and on the right endocardial pacing, showing a shorter activation time. From Strik et al (Strik 2012a).

Contrary to these results, Osadchii paced epicardially and endocardially in a guinea pig model, and found a reduced transmural duration of repolarisation with *epicardial* pacing (Osadchii 2012), although he did suggest that differential expression of ion channels through the myocardium in dogs and guinea pigs might explain these differences. An expression gradient in multiple ion channels between endo- and epicardium is also seen in human hearts (Soltysinska 2009) and is one explanation for the differential effects of endocardial and epicardial pacing.

Scott et al showed results consistent with the majority of these animal findings in a small human study. In 8 patients with LV endocardial pacing leads, QT dispersion and several T wave features (further measures of repolarisation) were improved relative to a group of 28 patients with epicardial leads (Scott 2011). Özcan et al were able to show a similar result by comparing ECG parameters in 7 patients with coronary sinus leads before and

after lead replacement with endocardial LV leads (due to CS lead displacement) (Özcan 2015).

There are no clear conclusions as to how significant the possible pro-arrhythmic effects of epicardial pacing are clinically, and so this evidence for the potential benefit of endocardial pacing is largely theoretical at the moment. It does suggest one mechanism of potential superiority of endocardial pacing by a reduction in arrhythmic events, which are common in CRT patients.

Haemodynamic response to endocardial pacing

Animal studies

There is a further body of evidence that suggests LV endocardial pacing may be superior to epicardial pacing at improving haemodynamic response to CRT. Similarly to the potential benefits in terms of arrhythmia reduction, this comes initially from animal models. Van Deursen et al, in a dog model, showed that endocardial biventricular pacing resulted in a 90% increase in LV dP/dt max and a 50% increase in LV stroke work compared to epicardial BiVP (Van Deursen 2009).

Bordachar et al produced a similar dog model by embolising the left anterior descending artery and then ablating the left bundle branch, to end up with dogs with an EF below 35% and LBBB (Bordachar 2012). They then placed both epicardial and endocardial LV leads, as well as an RV lead. They found that LV endocardial to RV BiVP increased LV dP/dt max significantly more than LV epicardial to RV pacing, as shown in Figure 9 below. Both of the above studies used a dog model, and although this is a relatively good model of human physiology, as discussed above the gradient in the expression of ion channels through the myocardium varies between animals, which could mean that these results are not generalizable to humans (Osadchii 2012, Soltysinska 2009).

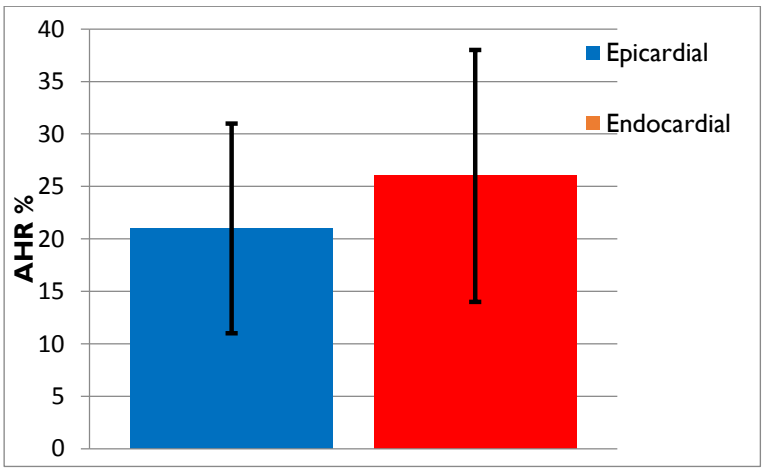


Figure 9 - Acute haemodynamic response to biventricular epicardial and endocardial pacing, data from Bordachar (Bordachar 2012). The difference between epicardial and endocardial was reported as significant at a P value of <0.01.

Similarly, another group found that in a dog model the increase in dP/dt max with endocardial BiVP correlated with the extent of electrical delay (i.e. the time for the electrical depolarisation started at a right ventricular electrode to reach the LV pacing site) (Howard 2011), which was not found for epicardial pacing. This result would suggest that the best place to pace endocardially would be the site of latest LV electrical activation. The finding of no such correlation in epicardial pacing is however surprising, as several other authors have suggested a correlation between epicardial electrical delay and response in humans (Singh 2006, Zanon 2014).

Human results

Derval et al compared endocardial to epicardial biventricular pacing in 35 patients. They placed (temporary) catheters in the RV and a lateral CS branch, and moved another between several LV endocardial sites (Derval 2010). They recorded LV pressures with a conductance catheter, and at each site they assessed the AHR to pacing by dP/dt max. They measured response at 9 sites, once each for 20 seconds. They found that the best site was variable and extremely patient-specific. Pacing at the site immediately endocardial

to the epicardial coronary sinus lead was not superior, but they found that the best available endocardial site in each patient was significantly better than epicardial pacing. The large number of assessments and lack of repetition may mean that it is hard to discriminate the differences between sites from measurement noise.

Spragg et al used a similar protocol in 9 patients, measuring AHR based on dP/dt max using a conductance catheter (Spragg 2010). They assessed AHR at 50 different endocardial sites per patient measuring over 15-20 beats, comparing to a baseline value recorded about every 10-15 measurements. 7 patients had CRT devices in situ, and in these they paced at the endocardial aspect of the myocardium below the epicardial CRT LV lead. They found no difference in the dP/dt max at these sites, suggesting that there is no intrinsic benefit to pacing endocardially at the same site. Despite this, they did find that the best endocardial site was on average 13% better than the AHR using the CRT system, suggesting that endocardial pacing allows access to optimal sites not achievable epicardially. They also found that the optimal pacing site varied between patients, and concluded that accordingly pacing site optimisation was important, even on the LV endocardium.

Similarly to Derval et al, they took a very large number of measurements without repetition, and assessed percentage change against a very infrequently assessed baseline. They report a mean baseline coefficient of variation of 7.6%, which implies a 95% confidence interval for random variation of approximately ±15%, such that the 13% difference between endocardial and epicardial pacing could well represent chance variation (Wichterle 2011). The order of pacing sites was also not (reported to be) randomised, potentially introducing order bias.

Garrigue et al used Doppler echocardiography to compare permanent endocardial pacing in 8 patients with epicardial pacing in 15 patients (Garrigue 2001). They found a significantly greater reduction in electromechanical delay, and increases in lateral wall

systolic motion, and mitral flow with endocardial pacing. Despite this all patients in both groups were reported to have improved clinically.

This does neatly illustrate a more general problem in assessing response to CRT, which is that many studies have focused on quite simple 'hard' outcome measures such as change in NYHA class or HF morbidity and mortality. This makes it hard to assess the *extent* of improvement. For example, in the Garrigue study above the echo data suggests that endocardial CRT may be superior, but this was not correlated with any clinical outcomes other than an improvement in NYHA class, a measure too insensitive to identify a significant change in response between the groups.

Ginks et al assessed AHR to endocardial and epicardial pacing in 15 patients with predominantly non-ischaemic cardiomyopathy, using a pressure wire in the LV (Ginks 2011). Endocardial pacing was performed at four different sites per patient, and epicardial pacing in one lateral or posterolateral vein.

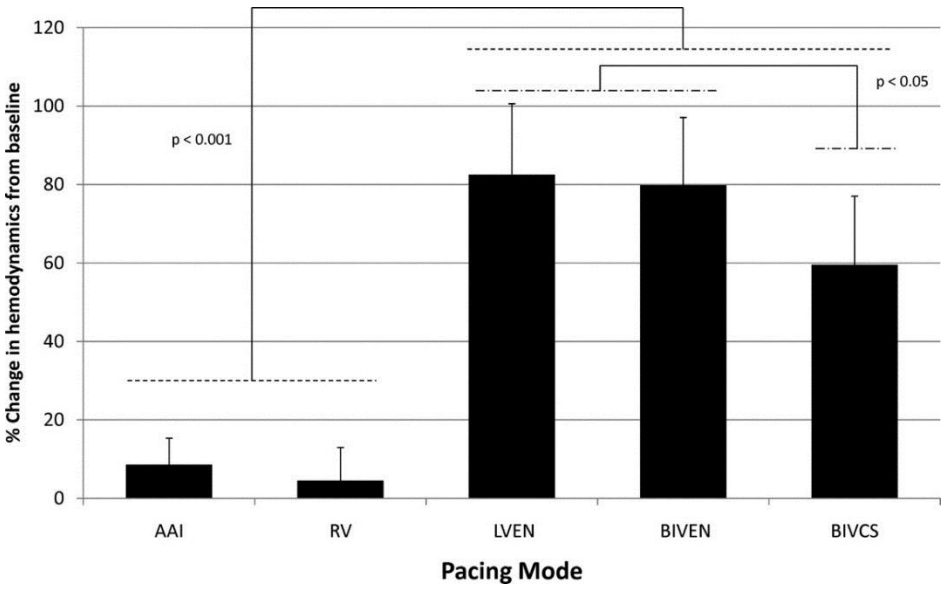


Figure 10 – Effect of endocardial and epicardial pacing on AHR compared to AAI and RV only standard pacing. LVEN: LV endocardial only, BIVEN: biventricular LV endocardial and RV pacing (at the best of four sites), BIVCS: biventricular LV epicardial (in a lateral branch of the CS) and RV pacing. From Ginks et al (Ginks 2011).

As shown in Figure 10, pacing including the LV endocardium was superior to pacing involving the coronary sinus lead. They also found that a lateral position of the LV lead was generally superior.

The same group showed similar results in another cohort of 10 patients, although in this smaller sample there was not a significant effect of LV endocardial pacing site between patients (Ginks 2012a). In both studies they also assessed LV scar with cardiac MRI, and showed in this small number of patients that pacing within a site of scar or slow conduction reduced the AHR. Endocardial pacing allowed selection of pacing sites outside these scars.

Most recently the same group assessed the AHR to pacing in 15 men (Shetty 2014). In a similar protocol they compared biventricular epicardial (via CS) pacing both at one site and at two sites (using two epicardial leads) with endocardial pacing. Again multiple endocardial sites were assessed, including the endocardial aspect of the LV to an epicardial lead. Similarly to previous studies, the AHR at the best available endocardial position (of multiple sites tried) was superior to conventional epicardial CRT, as shown in Figure 11.

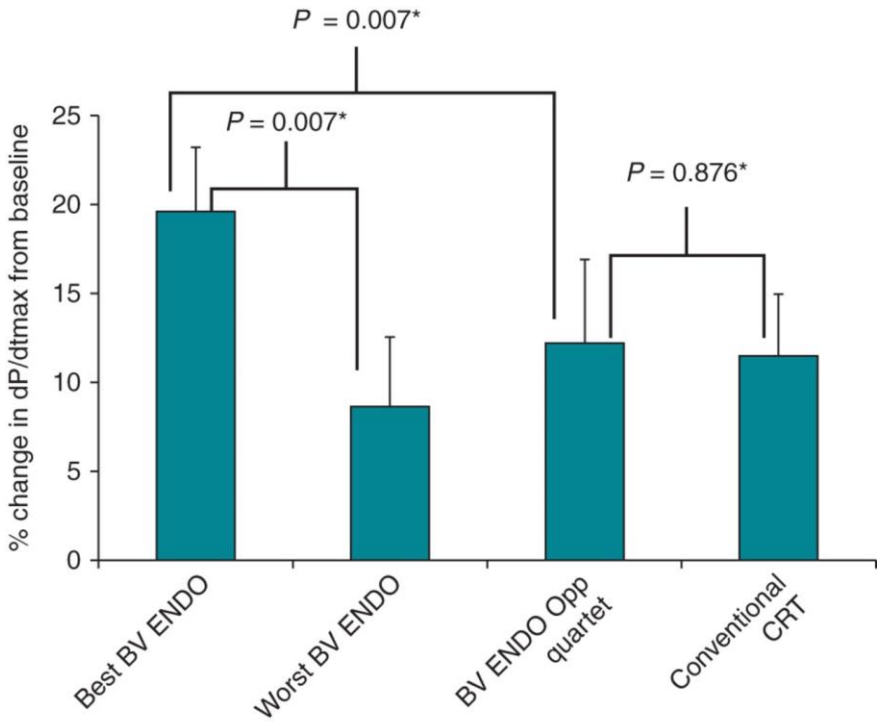


Figure 11 – Endocardial and epicardial pacing effects, from Shetty et al (Shetty 2014). BV ENDO denotes biventricular endocardial pacing at the best and worse site tried. BV ENDO Opp Quartet denotes biventricular endocardial pacing at the endocardial aspect of an epicardial lead, and conventional CRT denotes standard biventricular pacing from that epicardial lead.

Testing the endocardial aspect of the epicardial lead allowed them to again show that there was no apparent intrinsic benefit of endocardial pacing. All three of these studies found a benefit of endocardial biventricular pacing over epicardial. They suggest that this is explained by greater freedom to choose an optimal LV endocardial pacing site, rather than any intrinsic benefit of endocardial pacing of itself. As they assessed several endocardial and only one epicardial site, their results could also be at least partly explained by the larger number of sites tested endocardially randomly happening to produce a greater response than the single site tested epicardially. If they had been able to subsequently pace at the endocardial aspect of the optimal endocardial site that might have allowed more valid comparison.

An Italian group used a conductance catheter to measure pressure-volume loops and assess AHR to pacing based on the stroke volume in ten patients (Padeletti 2012). They tested four different endocardial pacing sites, and found a statistically similar mean increase in stroke volume (as well as dP/dt max) at all endocardial sites versus AAI pacing. Most notably, they found that the optimal site in each patient was anatomically near to, and had a comparable AHR to, the one with the greatest RV-LV electrical delay. After this assessment protocol they placed a permanent LV lead via the CS, but due to the restrictions of CS anatomy were only able to place the lead at the selected optimal site in four out of ten patients.

This again illustrates the potential benefit of endocardial pacing in allowing less restricted access to optimal LV pacing sites. Furthermore, it again suggests that the pacing site is specific to the patient, as there was a similar mean response in all endocardial pacing sites across the whole group, but an optimal site could be chosen in each patient.

Techniques to achieve endocardial pacing

Atrial trans-septal endocardial lead placement

The majority of permanent LV pacing has been performed epicardially, surgically for most of the very early studies and since then predominantly as transvenous epicardial pacing via the coronary sinus.

The atrial transseptal approach to LV endocardial pacing was initially described by Jaïs in 1998, the early days of CRT (Jaïs 1998). He first performed a puncture of the inter-atrial septum from right femoral access (as this was the access point the equipment was designed for) and then placed a guidewire in to the LV. This guidewire was then pulled intravascularly up to the right internal jugular vein and used to pass a sheath back across

the inter-atrial septum. The sheath was then used to deliver a lead into the left atrium, which was manipulated across the mitral valve and attached.

Multiple modifications of the technique have been described over the past decade, but it has remained complex, with most groups using a combined femoral and superior approach to puncture the atrial septum and deliver a lead from the subclavian vein (Elencwajg 2012, van Gelder 2011, Jaïs 1998, Morgan 2009, Nuta 2007). The use of snares to feed guidewires or pacing leads across into the left atrium has been a common feature in many techniques (Elencwajg 2012, van Gelder 2011, Jaïs 1998, Morgan 2009, Nuta 2007). All these groups have used equipment designed for other purposes in order to perform the procedure. All studies have reported results on small numbers of patients with relatively limited follow-up.

More recently one of the device companies (Medtronic Inc) has developed LV lead implant equipment specifically designed to allow puncture of the inter-atrial septum and delivery of an LV lead from the left subclavian/axillary vein access typically used for CRT procedures. This was used in the large ALSYNC study, which included 138 patients and is thus by some way the largest and most rigorously conducted study of endocardial pacing (Morgan 2016).

A series of 20 cases of a hybrid surgical/endocardial procedure was described by Kassai et al, in which the LV apex was accessed and punctured surgically, and then an endocardial lead placed into the LV apex (Kassai 2008, 2009, 2011).

These studies are discussed in more detail in a subsequent chapter.

Leadless pacing

For some time the designers of pacing technology have been working on systems that do not require leads, as it is well established that many pacing complications are lead-related.

Recently the first few patients have been included in studies assessing right ventricular endocardial pacing (Reddy 2014), but these devices do not yet have any way to coordinate and so remain unsuitable for LV pacing.

A system has been designed for LV leadless pacing, using ultrasound to deliver energy to an endocardial transducer, which converts it to electrical energy to activate the myocardium (EBR systems WISE). The transducer is only 9mm long and is inserted trans-arterially. The ultrasound pulse generator and battery units are implanted over the apex of the heart, but require a suitable acoustic window. The ultrasound pulse (and thus LV pacing) is triggered by detecting pacing from an implanted RV pacemaker or ICD.

In the initial trial of 17 patients, the system could be implanted in 13 (~75%). These patients had a 66% response rate based on improvement in NYHA class, comparable with standard CRT. In three of the failed implants pericardial effusions occurred, one of which resulted in the patient's death (Auricchio 2014). There were no thrombotic strokes or transient ischaemic attacks (TIA) however, and these would not be expected as the transducer is designed to endothelialise rapidly, minimising the risk of thrombus formation. The company have subsequently redesigned the implant equipment to reduce the risk of LV perforation.

Other techniques

Reinig tried retrograde aortic valve access to the LV endocardium in pigs, with good acute success rates (Reinig 2007). The pigs were given aspirin and clopidogrel; on necropsy at 6 months two pigs were found to have thrombus on the LV lead tip. I am not aware of any human implants using this technique.

A trial based in Maastrict (Vernooy 2012) is investigating LV septal pacing from a lead tunnelled into the LV endocardium but not entering the left ventricle, but are recruiting

candidates for pacemakers, aiming to achieve capture of residual sub-atrioventricular nodal conducting tissue and thus physiological pacing. Early results are positive (Rad 2015a).

Key research questions

I think that from the above text several questions emerge.

Firstly, what is the likely current demand for non-standard LV pacing techniques – i.e. how often does LV pacing fail in the contemporary era of CRT? In the next chapter I will assess this in a meta-analysis.

Secondly, I have discussed multiple techniques of endocardial pacing above, but have not reported their results. In the subsequent chapter I will assess the clinical results to date of endocardial pacing, again using meta-analysis to summate the results of multiple trials. One of the key themes of the thesis is the clinical results of a trial of endocardial pacing, and so this data will assist in setting this in the context of prior results.

Finally, I have not discussed where precisely within the LV the pacing lead should be placed. This topic is the other key theme of my results, and accordingly I will discuss the background literature on this in a subsequent second (and shorter) background chapter.

Chapter summary

- CRT is an effective treatment for heart failure and conduction disturbance, exemplified by LBBB
- Non-response to CRT is frequent and multi-factorial, but can be linked to poor LV lead position
- Acute haemodynamic response to CRT can be used to measure acute physiological changes resulting from biventricular pacing
- CRT can be limited by difficulties in access to the coronary sinus or its branch vessels, or a lack of suitable pacing sites
- Alternatives to conventional CRT via the coronary sinus include surgical epicardial pacing as well as endocardial pacing
- There is evidence to suggest that LV endocardial pacing may have physiological and practical benefits over epicardial pacing
- Clinical results of endocardial LV pacing to date suggest the technique is viable

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Chapter Two – **Procedural success of left ventricular lead placement for cardiac resynchronization therapy – a meta-analysis**

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Introduction

As discussed in the prior chapter, CRT is an effective therapy for suitable patients with heart failure (Abraham 2002, Bristow 2004, Cleland 2013, 2005, Linde 2008, Tang 2010, Young 2003). LV lead implantation can be technically demanding and may fail due to a variety of procedural or anatomical challenges. When writing the background material in the prior chapter, it rapidly became evident that the contemporary rate of failure to place a LV lead for CRT is not well documented. In particular, I wanted to establish the likely extent of the need for a second-line procedure such as endocardial pacing. Accordingly, I performed a meta-analysis of the published data to assess the success rates, causes of failure, and procedural characteristics of CRT implantation both during the evolution of this procedure and in the modern era.

Methods

The meta-analysis was conducted according to the PRISMA statement (Moher 2009). A systematic search of PubMed, Web of Science and the Cochrane Library was performed to identify relevant articles published until the end of 2014. I used the keywords 'cardiac resynchronization therapy', 'cardiac device', and 'CRT'. Hand searching of the reference lists of included publications allowed identification of articles not found in my primary search strategy. I also searched relevant United States Federal Drug Administration (FDA) device pre-market approval summary reports, which are the publically available documents reporting data submitted to the FDA at the time of device approvals or modifications in the USA.

All publications reporting the results of attempted implantation of LV leads for CRT via the transvenous CS route were included, whether within a formal trial design or as part of a case series or similar report. Where studies compared conventional CRT to a different

procedure or control, the conventional CRT arm was included. I excluded publications that only reported outcomes after the implant procedure; that did not make it clear if any implants had failed; or that were entirely or largely duplicates of previously reported data. I was deliberately inclusive, in order to include the maximum number of patients to assess procedural success rates.

The titles of all publications identified were screened and those that did not meet my criteria were excluded. Subsequently I reviewed the abstracts of remaining publications, and if necessary the publication text. Methodological quality was not assessed, but publications were dichotomized into randomized controlled trials (RCT) and others.

I recorded the number of patients in whom the implant procedure failed. Reasons for failure to place a left ventricular lead were recorded as absolute numbers in one of a series of pre-defined categories. In addition, I recorded reported population parameters from the trials, as absolute numbers when provided or as mean and standard deviation. LV lead revision, when reported, was assessed as a secondary data point. I recorded the absolute numbers of revised LV leads and the study follow up time

Given the large number of trials included over a long time period, significant heterogeneity was expected, and so a random effects meta-analytical approach was applied to all analyses. I analysed the logarithm ratio of the rate of failure. Results are presented back-transformed as the median percentage of implant failures. For the investigation of temporal trends, studies were considered according to the starting year of recruitment, which was estimated from provided data if unavailable. This was used to dichotomize included studies, using the mid-point of the total time period of all studies as the dividing point and to assess temporal changes and trends using meta-regression. Subgroups were compared using mixed-effects logistic meta-regression, allowing for differential heterogeneity between subgroups. Meta-analysis of event count data with relatively rare

events, like this data, is considered to be best performed using the binomial-normal model, which provides appropriate weight to studies with low event numbers (Stijnen 2010).

I also used random-effects meta-analysis to estimate the mean of population parameters, using the logarithm transform to estimate population proportions, and treating continuous variables in the standard meta-analytical manner; subgroups were similarly compared using meta-regression. I analysed lead revision as a mixed-effects logistic regression meta-analysis of the incidence rate of revision, again using a binomial-normal model.

Several different LV lead classification schemes have been used to describe the anatomical location of the final LV lead position, including a broad classification as anterior, lateral or posterior; by the vein or vein territory used; or by segment as anterior, lateral, posterolateral or posterior (Vardas 2007). I recorded the absolute numbers of leads in the positions described, and the proportion of leads in the lateral-posterolateral region generally considered to be optimal (Vardas 2007), when this could be estimated from the provided data, and estimated proportions using similar meta-analytical techniques to above.

Statistical analysis was performed using R version 3.1 and the Metafor package, with use of the ggplot2 package for graphs (R Core Team 2015, Viechtbauer 2010). A significance level of 0.05 was used, and all testing was two-tailed.

Results

Studies included

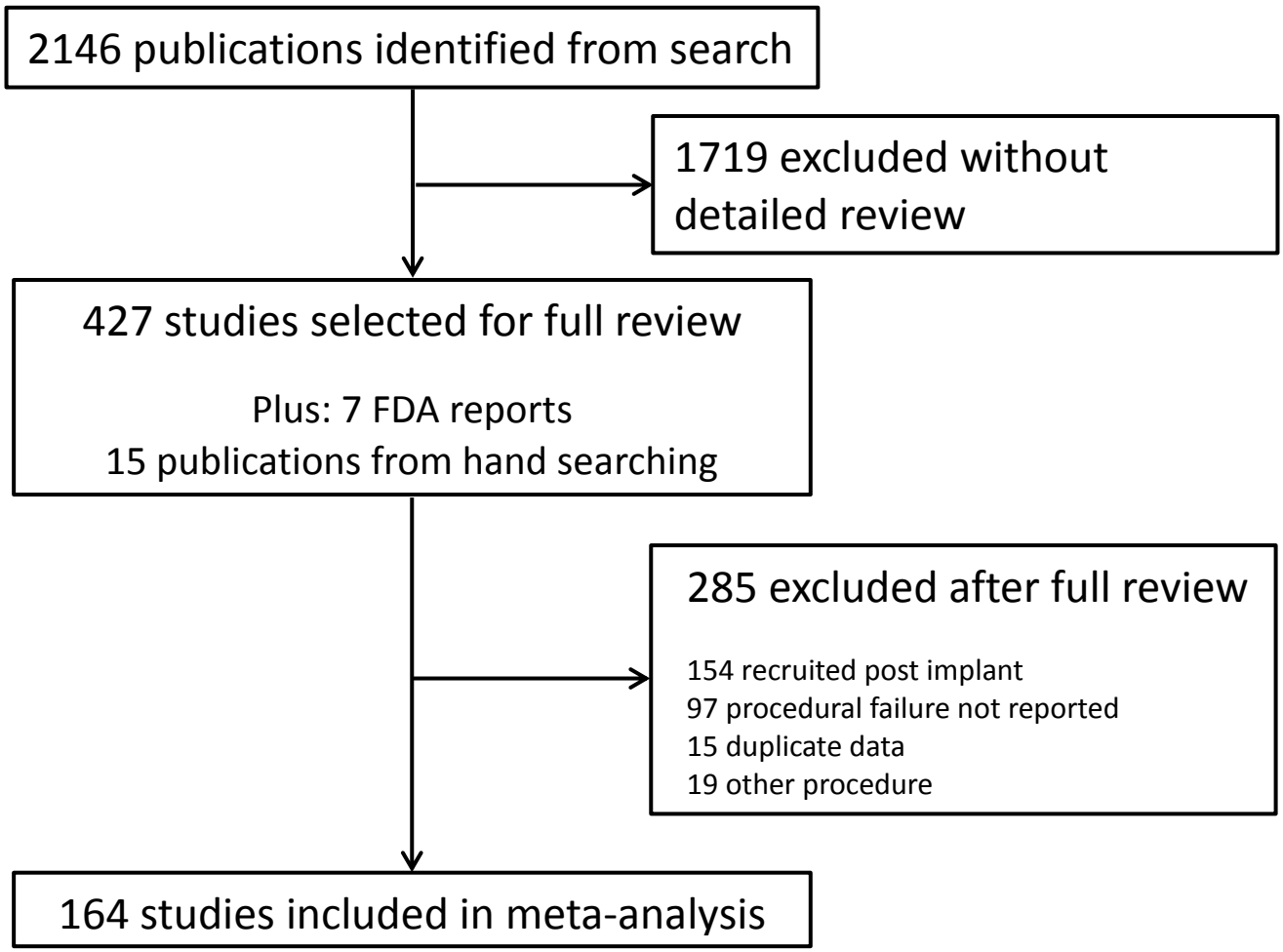


Figure 12 – Flow of publications through the review process.

Figure 12 above summarizes the selection of the 164 included studies, which commenced recruitment between 1997 and 2012, and were published between 2000 and 2014. 7 additional studies were found for which the only available report was in FDA documents. A full list of included studies is detailed in the appendix. Included studies involved 29,503 patients in whom implantation of a LV lead for CRT was attempted.

Characteristics of included patients

Summary characteristics of all included patients are detailed in Table 2 below and are also further separated into early studies commencing recruitment before the midpoint of 2004, and later studies commencing recruitment from January 2005 onwards. The start and end dates of recruitment were estimated for 20% of studies.

Reporting of baseline patient details was inconsistent between studies, although some data was reported for 99% of patients. Several studies did not include those patients in whom implantation of a left ventricular lead failed within their reported number, and in other studies data was reported for those who were excluded before implant. The percentage of patients included in the studies in which each data point was reported is included in Table 2. This was over 80% for all parameters. There was prominent heterogeneity in the data for all parameters, with I^2 values (a measure of study heterogeneity) over 95% for all parameters except the sex distribution (80%). There was a significant decrease in mean QRS duration between the early and late time periods, although if the 9 studies specifically including patients with a narrow QRS were excluded, this difference was reduced (after exclusion, early 163 (159-167), late 156 (152-160; P=0.003).

	All	Early	Late	P value (early vs late)	Available data N, (%)
Studies	164	86	78		
Patients	29,503	17,042	12,461		
Median patients per study (range)	102 (9-1164)	123.5 (9-1089)	83.5 (12-1164)	0.07[a]	
Mean study duration in years	2.5 (0-11)	2.8 (0-11)	2.0 (0-7)	0.001[a]	
Median centres (range)	1 (1-128)	6 (1-128)	1 (1-126)	0.001[a]	
All below are median plus 95% Confidence Interval					
Percentage male	74.1% (72.4-75.8%)	74.4% (72.1-76.8%)	73.6% (71.2-76.1%)	NS (0.66)	28,220 (96.6%)
Age, years	66.3 (65.3-67.3)	66.7 (65.6-67.9)	65.8 (64.2-67.3)	NS (0.33)	28,114 (96.2%)
Percentage ischemic aetiology	50.3% (46.6-54.2%)	51.7% (46.2-57.8%)	48.2% (43.8-52.9%)	NS (0.35)	25,886 (88.6%)
Percentage of device upgrade procedures	0.6% (0.4-1.1%)	0.4% (0.2-0.8%)	1.6% (0.8-3.2%)	0.01	25,886 (88.6%)
LV EF	26% (24.5-27.7%)	26% (23.3-28.1%)	27% (24.5-28.9%)	NS (0.53)	25,953 (88.8%)
NYHA Class	2.8 (2.7-2.9)	2.8 (2.6-2.9)	2.9 (2.9-3.0)	NS (0.06)	24,326 (83.3%)
QRS duration, ms	155.1 (150.0-160.2)	160.1 (154.4-165.8)	148.9 (140.6-157.1)	0.03	23,240 (79.5%)

Table 2 – Summary features of patients in included studies. ([a]Mann-Whitney U test, other comparisons by meta-regression).

Occurrence of failure to place an LV lead

The proportion of patients in whom it was not possible to place a LV lead is shown in Table 3 below and as a forest plot in Figure 13 below.

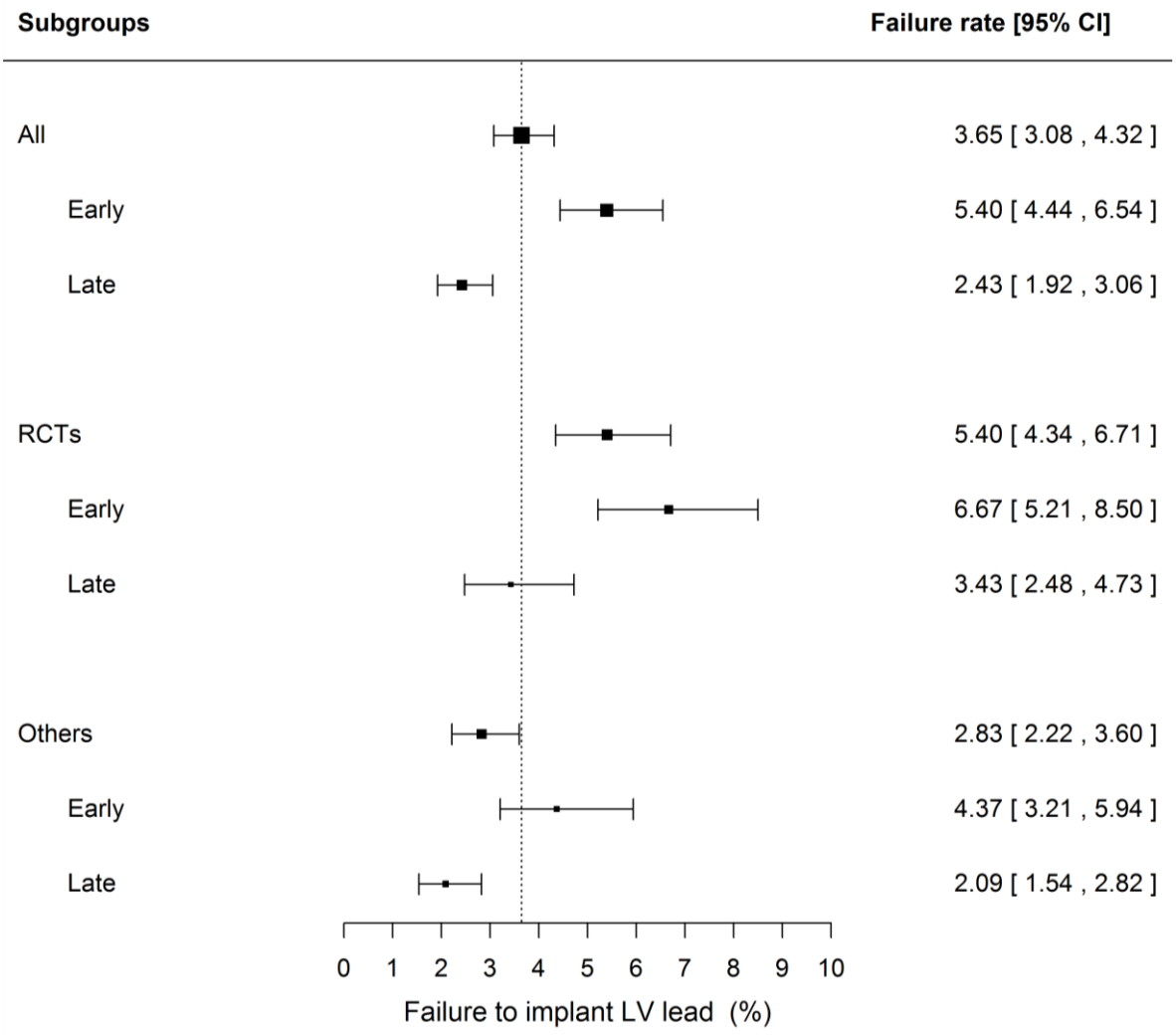


Figure 13 – Forest plot of subgroup estimates and 95% confidence intervals of the proportion of patients in whom LV lead placement failed.

	All	Early	Late	P value (early vs late)
Patients	29,503	17,042	12,461	
Failure rate (95% CI)	3.6% (3.1-4.3%)	5.4% (4.4-6.5%)	2.4% (1.9-3.1%)	<0.001
Failure rate range	0-17.9%	0-17.9%	0-12.0%	

Table 3 – Failure to place a LV lead (Comparison by meta-regression)

The proportion of failed LV lead placement decreased steadily over the time period by 0.48% per year (95% CI -0.28 to -0.69%, P<0.001). Meta-regression of each half of the time period separately showed a trend towards a significant decrease over the early period of 0.51% per year (CI -1.1 to +0.09%; P=0.095)) but no significant change over the late period (+0.032% per year; CI -0.03 to +0.04%; P=0.86).

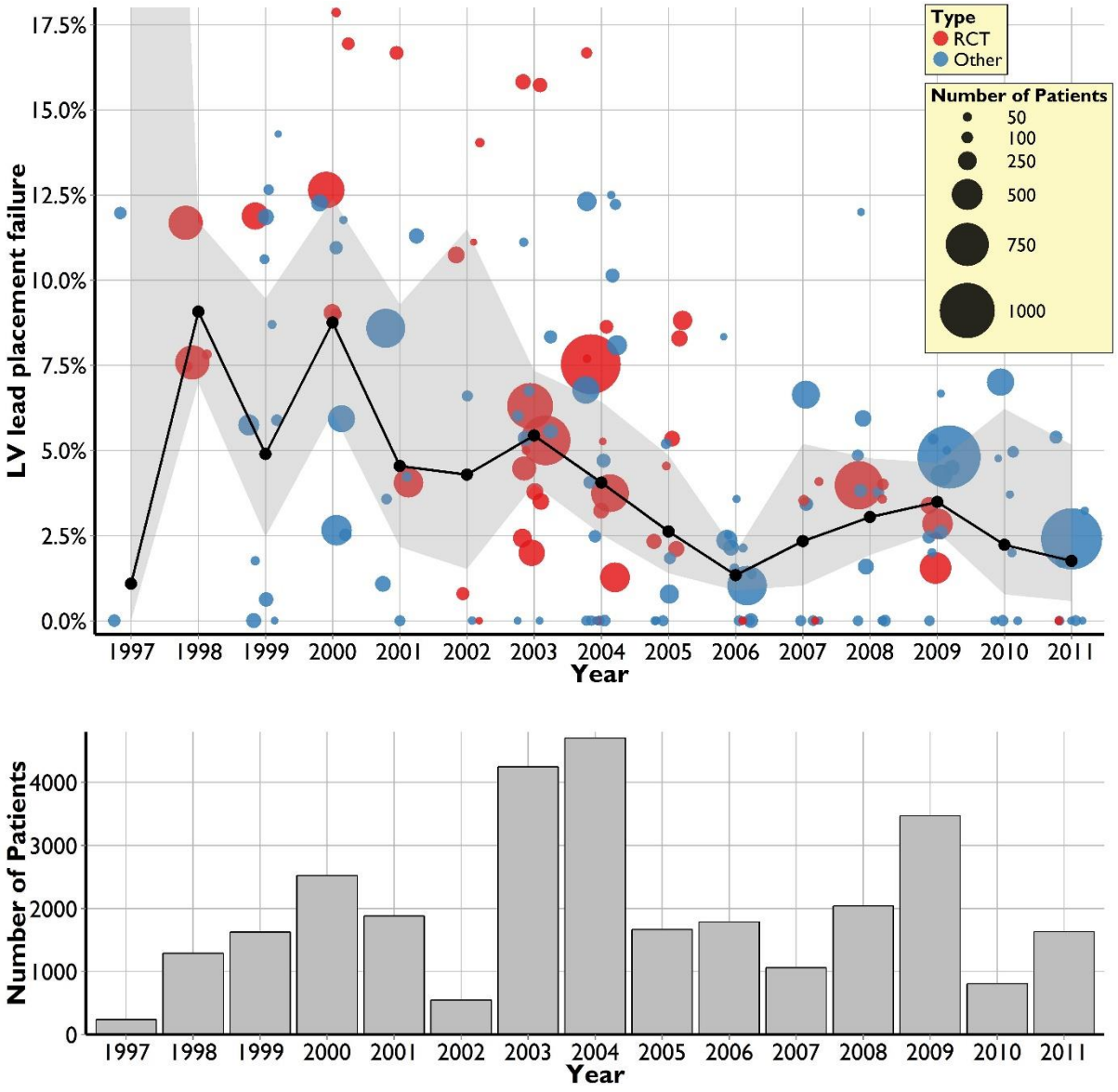


Figure 14 – The top panel shows percentage failure rates by the starting year of recruitment, the study type and number of patients. The line shows the mean failure rate and the 95% CI (in grey). The bottom panel shows the total number of subjects included.

As expected, and as is illustrated by the wide distribution of dots representing studies in Figure 14, there was significant heterogeneity between studies in this analysis. I^2 values were high at 79% across the whole time period, although this decreased from 89% in the early period to 69% in the later period. There was a strong trend towards a decrease in I^2 across the time period.

33% of included studies were RCTs, which were larger than non-randomized studies (median patients 175 vs 89.5) and more likely to be multi-centre (median centres 19 vs 1) and included 46% of patients. Failure rates in RCTs are also shown in the forest plot in Figure 13. A more detailed breakdown of the differences between RCT and other trials is shown in Table 4 below.

	All	RCT	Others	P value (RCT vs Others)	Available data N, (%)
Studies	164	54	110		
Patients	29,503	13,579	15,924		100%
Median patients per study (range)	102 (9-1164)	174.5 (9-1089)	89.5 (0-1164)	0.007[a]	100%
Mean study duration in years	2.5 (0-11)	2.6 (1-8)	2.4 (0-7)	0.04[a]	100%
Median centres (range)	1 (1-128)	19 (1-128)	1 (1-126)	<0.001[a]	100%
All below are median plus 95% Confidence Interval					
Percentage male	74.1% (72.4-75.8%)	73.8% (70.5-77.2%)	74.3% (72.6-76.1%)	NS (0.76)	28,220 (96.6%)
Age, years	66.3 (65.3-67.3)	65.8 (64.2-67.3)	66.8 (65.6-68.0)	NS (0.28)	28,114 (96.2%)
Percentage ischaemic aetiology	50.3% (46.7-54.2%)	52.3% (45.9-59.6%)	48.2% (44.4-52.2%)	NS (0.27)	25,886 (88.6%)
Percentage of device upgrade procedures	0.6% (0.4-1.1%)	0.3% (0.1-0.7%)	1.6% (0.9-2.8%)	0.001	25,886 (88.6%)
LV EF	26% (24.5-27.7%)	27% (22.7-30.6%)	26% (24.6-26.5%)	NS (0.49)	25,953 (88.8%)
NYHA Class	2.8 (2.7-2.9)	2.7 (2.6-2.9)	2.9 (2.9-3.0)	0.02	24,326 (83.3%)
QRS duration, ms	150 (150-160)	150.1 (139-161)	160 (156-164)	0.05	23,240 (79.5%)

Table 4 – Summary features of patients in included studies, stratified by study type ([a]Mann-Whitney U test, other comparisons by meta-regression). Similarly to the early/late analysis, if the studies specifically recruiting patients with narrow QRS are excluded, there is then no difference in QRS duration between RCTs and other studies (160.6 vs 160, P=0.86).

Funnel plots of the rate of failure to place a lead suggests significant under-reporting of events in small studies (Figure 15). A modified Egger's test also suggested significant under-reporting (p<0.001 of no under-reporting) (Moreno 2009). A trim-and-fill analysis, a method of estimating the likely result in the presence of additional hypothetical studies,

suggests that 30 further studies with more events would have been expected to be reported, which would have increased the overall failure rate estimate to 5% (4.3-5.9%).

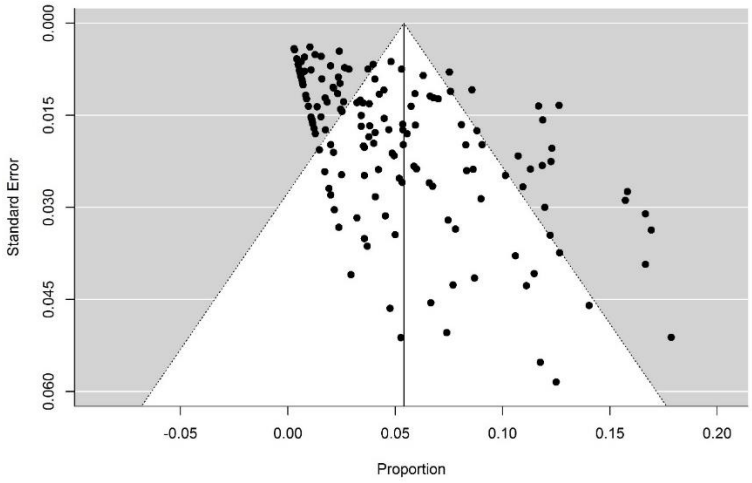


Figure 15 – Funnel plot, shown for illustration as the un-transformed proportion of failures to place a LV lead in each study on the x-axis. The y-axis shows the corresponding standard error of the estimate, the vertical line the overall population estimate, and the white triangular area the pseudo-confidence interval into which 95% of studies would be expected to fall. The group of studies in the top left of the plot outside the confidence interval are those reporting no or very few failures. It is also notable that several studies report higher than expected failure rates, in the area to the right of the triangle.

Reasons for failure to place an LV lead

The reasons for the inability to place an LV lead were reported in 44 (27%) of studies and for 613 patients (39% of LV lead placement failures); they are shown in Figure 16 below. Inability to place an LV lead due to difficulties with CS access and navigation decreased significantly from 53% (95% CI. 43-63%) to 30% (18-46%; P=0.01) of failures, and failure due to a lack of an anatomically suitable site (no suitable vessel, no acceptable threshold, lead instability or phrenic nerve stimulation) increased significantly from 39% (29-49%) to 64% (49-77%; P<0.001).

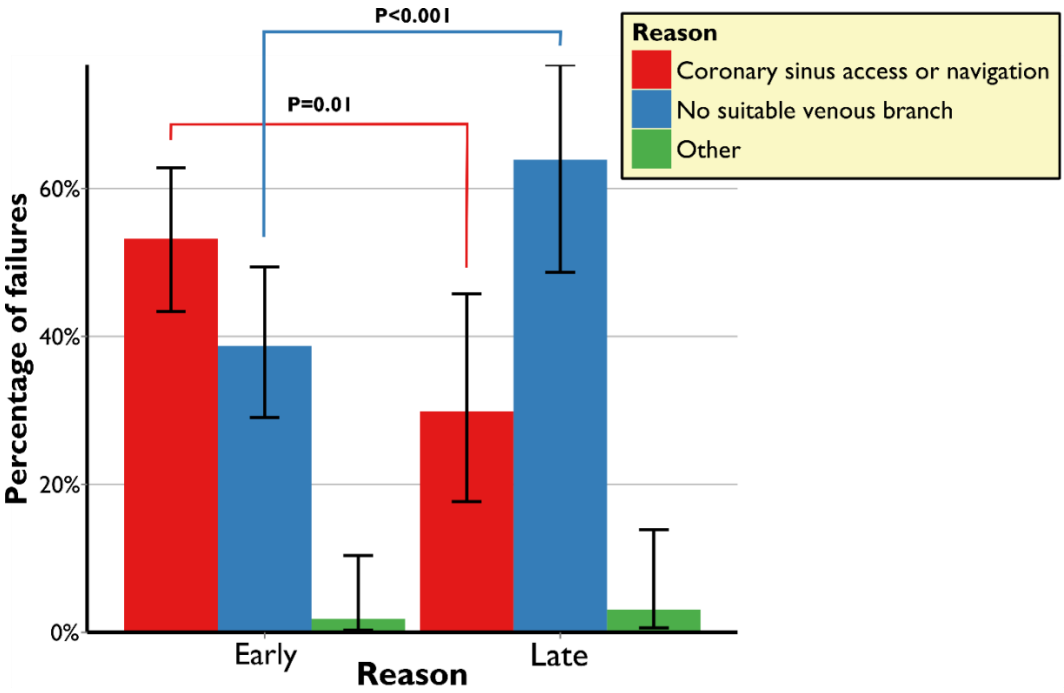


Figure 16 – Reasons for failure to place a left ventricular lead. P values from meta-regression.

19 (12%) of trials, including 6455 (22%) patients, reported the failure rate at each LV lead implant attempt. The failure rate for the first attempt was 7.2% (95% CI. 5.8-8.9). The results of a second attempt were recorded for 187 (34%) of these attempts, which failed in 41% of patients.

LV lead position

The final transverse plane location of the LV lead was reported for 29% of studies and for 7695 leads (26% of successful procedures). 46% of lead positions were reported using the vein territory (summarized in Figure 17 below), 23% used the anterior/posterior/lateral classification, 13% used the segment, and 19% reported the position only for some leads.

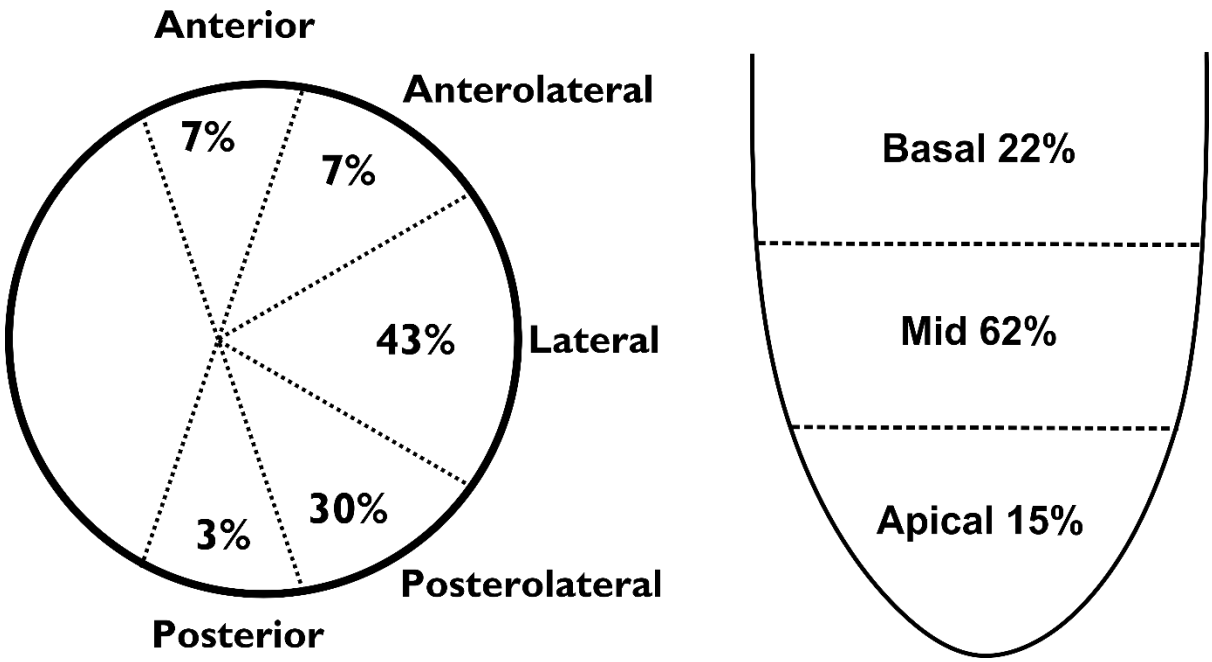


Figure 17 – Final LV lead positions reported, as estimated by meta-analysis. The transverse plane location is shown on the left, as reported in the 21 studies using the ESC vein territory classification for 3565 leads. The possible venous tributaries of the coronary sinus and their territories as seen in the LAO 40° radiographic view are shown. On the right the cranio-caudal lead position is shown, as reported in 10 studies and 1463 leads, and as seen in the right anterior oblique 30° view.

Overall, 68% (95% CI 56-79%) of leads were reported as being lateral or postero-lateral. In the early period 63% (48-76%) of leads were placed laterally or postero-laterally, and in the late period this increased to 81% (74-87%; P=0.01). The proportion of lateral or posterolateral leads was not a significant predictor of success rates by meta-regression (p=0.1).

Lead and device design

The only lead used frequently enough to make comparisons was the St Jude Medical quadripolar lead (1458Q), which was used in 14 non-randomized studies, including 1,327 patients, commencing between 2009 and 2011. The rate of failure to implant an LV lead in

the quadripolar lead arms of these studies was 3.8% (2.9-4.9) , which was not significantly different from other studies recruiting in the late time period (P=0.19 by meta-regression).

LV lead revision

	All	Early	Late	P (early vs late)
Studies reporting LV lead revision rates	83	48	35	
Patients	15,222	8,732	6,490	
Mean months follow-up	8.2	8.3	8.2	NS (0.84)[a]
Lead revision rate, revisions per 100 patient-years	6.9 (5.4-8.7)	7.9 (5.8-10.7)	5.7 (4.0-8.1)	NS (0.18)

Table 5 – LV Lead revision rates ([a] Mann-Whitney U test, other comparison by meta-regression; 95% CI in brackets)

83 studies (including 15,222 patients, 52% of total) reported LV lead revision rates over a mean follow up of 8.0 months (range 1-24 months), including a total of 10,501 patient-years of follow-up. These were used to derive the rate of LV lead revision per 100 patient-years, summarized in Table 5 above. Figure 18 below shows lead revision rates over time. LV Lead revision did not change significantly over the whole time period (P=0.18) or over either half of the time period (P=0.16).

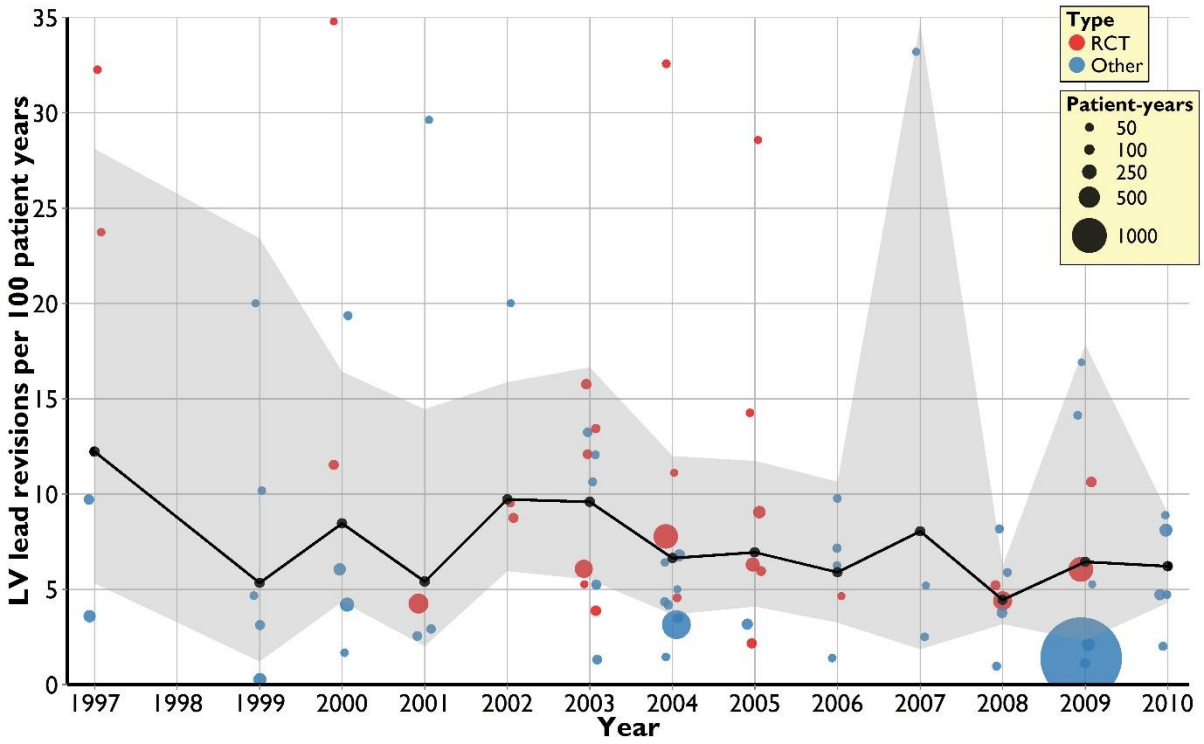


Figure 18 – Lead revision rates per 100 patient-years over time by starting year of study recruitment, the type and size. The line shows the mean failure rate and the 95% CI.

When lead revision was considered as a simple proportion of patients, studies following patients for 1-3, 3-6 and 6-12 months reported similar LV lead revision proportions (4.7%, 4.7%, 4.4% respectively), but studies with over 12 months follow up reported a higher proportion of lead revision (6.3%, P<0.001 versus others); however when considering lead revision rates as a function of study follow-up time, studies with shorter follow up time had significantly higher rates of displacement per 100 patient years(p<0.001). There was not sufficient available data to assess differential revision rates of LV lead designs. There was significant heterogeneity in study outcomes across the whole time period, with I^2 87%, which did not significantly change between the early and late periods.

Discussion

I report data on success rates of LV lead implantation in a very large population of patients, including the majority of patients included in the landmark RCTs of CRT. The main finding of my analysis is that the rate of failure to implant a LV lead via the CS route has fallen consistently since the introduction of the technique, with a reduction in the rate of decrease in the last few years. The predominant reasons for failure to implant an LV lead have changed from those relating to access and navigation of the CS to there being no suitable target vessel. The need for revision of the LV lead has not apparently changed significantly over the whole time period.

Failure rates for implantation of an LV lead

The improvement seen in success rate over time would be expected for many procedures. The techniques and equipment available for CRT have developed markedly over the time period included, initially as equipment specifically designed for CRT was developed, and latterly as it has been refined (Gellér 2011, Giannola 2011, Jackson 2013). There is also undoubtedly an operator learning curve that applies to this procedure, seen both within studies and within centres (Ahsan 2013, Gras 2007, Kirkfeldt 2011, León 2005, Macías 2007). All of these effects would be expected to have been more prominent over the earlier years of the technique.

The apparent slowing of the improvement in success rates seen over the second half of the study period might be due to increasing numbers of cases in which the limiting factor becomes patient anatomy, rather than operator skill and equipment. This is supported by the changes in reasons for implant failure, in which failures caused by difficulty accessing and navigating the CS were a major issue in the early period, but less so in the late period. This problem is less likely to be amenable to further technical developments that utilize a

CS approach to implantation, which supports the need for alternative techniques such as LV endocardial pacing, in which the LV can be paced without the need for CS access.

Further lead design improvements, such as an increased variety of lead shapes, profiles and multiple electrodes, might be expected to result in a further limited reduction in failed implants, although I did not find any such benefit from quadripolar leads in this study. The recently presented, but as yet unpublished, MORE-CRT study did show a benefit of quadripolar leads, driven apparently by easier implants, but with a similar rate of failure to place a LV lead to contemporary studies in my analysis. A publication from my group has shown reduced phrenic nerve stimulation, LV lead revision and displacement in patients with quadripolar leads, also without an apparent reduction in procedural success (Behar 2015). A further factor in this lack of decline could be additional operators starting to implant LV leads, at a lower point in their individual learning curves.

It is notable how LV lead revision rates, after the initial years of CRT, appear to have changed very little, unlike the rate of failure to place a LV lead. The analysis of lead revision rates is limited as this was a secondary outcome, but this still represents a large data-set.

The very infrequent occurrence in contemporary studies of failure to place a left ventricular lead suggests that second-line procedures to place leads surgically or endocardially will need to be refined and centralized into super-specialist centres in order for operators to have adequate experience and skills in these techniques (Betts 2014, Bordachar 2010). This suggestion is supported by the extremely high 41% failure rate of repeat attempts at LV leads in those patients in whom the first procedure had failed.

LV lead position

My data suggest that a significant proportion of patients receive an LV lead that is positioned either anteriorly or apically where it may be less likely to benefit them, and that some successful implants might be at the cost of a poor lead position (Singh 2011, Ypenburg 2008). Reporting of lead positions and reasons for failed implants were inconsistent across studies, and so this data is from a sub-selection of included papers. Lead position in almost all studies was reported by the investigators, rather than centrally adjudicated, which is likely to reduce the accuracy of this data as it has been previously shown that investigator reporting of lead position is variable (Wilton 2014). It is possible that certain types of study are over-represented in this group, which could bias the data. In particular, studies reporting base to apex lead position were frequently investigating quadripolar leads, which due to their design could be placed at the apex but set up to pace from a more proximal pole located basally. It is also not possible definitively to state that lead position was not optimal in those in whom leads were placed in a non-classical position, as at least some included studies that targeted leads based on imaging data to positions optimized on a patient-specific basis (Khan 2012, Saba 2013).

Characteristics of patients undergoing CRT implantation

There were only very small shifts in patient characteristics over time and these were largely of such small magnitude as to be clinically and statistically insignificant. A decrease in QRS duration was seen through the studies included, even after those studies specifically including narrow-QRS patients were excluded, but no clinically relevant change in NYHA class or LVEF was noted.

Overall it is notable how highly represented men in their sixth and seventh decade are in the CRT study population, and how the research population is younger than the heart failure population commonly seen clinically. Some reported 'real-world' CRT implant data

is not dissimilar to that seen in the current meta-analysis (Dickstein 2009) but it is notable that recent US data shows that 'real-world' patients are older and include more women (Borne 2014). I did not attempt to make any links between study population parameters and success rates, as these were not consistently reported for all patients in whom implants were attempted, and in particular those in whom implants failed were often excluded from study reporting. Hence these population parameters can only provide a snapshot of practice of CRT within trials.

Limitations

The conclusions of my analysis are limited by its meta-analytical nature and by the variable completeness of data reporting in the included studies. The significantly lower failure rate in non-randomized studies could reflect under-reporting of failed implants, due to either omission of reporting these or to publication bias. This is supported by my statistical assessment of a likely bias towards under-reporting, although an alternative explanation would be that these studies were largely single-centre series performed by experienced operators. It is also possible that reporting of the reasons for failed implants was inconsistent, with operators reluctant to report certain complications such as coronary sinus dissection or perforation. These limitations may make the failure rate estimate from the RCT sub-group more reliable. It is notable in the graph of LV lead failure rates over time (Figure 14) that there is a significantly lower failure rate in 2006, despite a reasonable sample size in the year. No clear explanation for this anomaly was found, although it is possible that the reasons discussed above might apply.

Almost no studies reported the characteristics of patients with failed LV lead placement, so it was not possible to assess if any particular features of this population might have predisposed them to failed LV lead placement.

Chapter conclusions

The rate of failure to implant a left ventricular lead for CRT has fallen very significantly since the introduction of this procedure, but the rate of change seems to have slowed or stopped. The reasons for failure to place a lead have changed to be predominantly due to adverse anatomy rather than technical limitations, supporting a need for alternative techniques for left ventricular pacing. Lead revision rates have changed little since the introduction of CRT.

An appendix to this chapter is in the thesis appendices, including a full list of included papers and their references.

With many thanks to Dr Jacqueline Birks of the Oxford Centre for Statistics in Medicine for invaluable assistance with the statistical analysis.

Chapter Three – Results of left ventricular endocardial pacing – systematic review and meta-analysis

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Introduction

As I have discussed in the prior background chapter, several techniques to achieve LV endocardial pacing have been described, and within these techniques there are multiple variations. All of these techniques have been investigated in small studies. In order to assess the relative benefits and risks of this LV endocardial pacing, I will make a systematic assessment of the studies so far and their results.

Methods

The review and meta-analysis was conducted according to the PRISMA statement (Moher 2009). A systematic search of PubMed, Web of Science and the Cochrane Library was performed to identify relevant articles published until the end of February 2016. I used the keywords 'endocardial pacing' and 'endocardial LV pacing', and excluding reviews and other secondary publications. Hand searching of the reference lists of included publications allowed identification of articles not found in my primary search strategy. The broader search described in Chapter 4, which attempted to capture almost all studies investigating cardiac resynchronization therapy, also assisted in the identification of additional studies.

All publications reporting the results of endocardial implantation of LV leads for CRT were included. I excluded publications that were entirely or largely duplicates of previously reported data. The titles of all publications identified were screened and those that did not meet my inclusion criteria were excluded. Subsequently I reviewed the abstracts of remaining publications, and if necessary the publication text. Methodological quality was not assessed. Where CRT response rates were provided, I recorded these in a standardised method, defining clinical response as ≥ 1 point decrease in NYHA class (this was the most commonly reported response parameter1) and echocardiographic response as >5% increase in LV ejection fraction (EF).

A random-effects meta-analysis was performed, with similar methods to the prior chapter. I used a binomial-normal model to analyse the incidence rate of complications and a normal-normal model for response rates (Stijnen 2010). I also used random-effects meta-analysis to estimate the mean of population parameters where appropriate. The logarithms of the incidence rates and response rates were used to normalise the data. I used R version 3.1 (R Core Team 2015) with the metafor package (Viechtbauer 2010).

Rate comparisons are made with a chi-squared test of the incidence rate ratio. A significance level of 0.05 was used for testing and confidence intervals (CI), and all testing was two-tailed.

Review

Atrial trans-septal endocardial lead placement

The most used method of endocardial pacing is the atrial transseptal approach initially described by Jaïs in 1998 (Jaïs 2000). Multiple modifications of the technique have been described over the past decade, but it has remained complex, with most groups using a combined femoral and superior approach to puncture the atrial septum and deliver a lead from the subclavian vein, and using modifications of existing equipment to allow this (Calvo 2014, Domenichini 2015, Jaïs 2000, Lau 2011, Mondoly 2013, Pasquié 2007). The experience of this technique is reported in several small single centre publications, often focused more on technique than on clinical outcomes, with limited reporting of response parameters. Complications appear to be more consistently reported, although follow-up length was often limited.

Most studies used standard 6 French pacing leads, although since the availability of the Medtronic SelectSecure lead, which is a 4.2 French bipolar lumenless lead delivered through a catheter, this has been frequently used, on the basis that the smaller surface area may be less thrombogenic. Practice around anticoagulation has varied, but most studies report using an INR target of 2.5-3.5.

Trans ventricular apical pacing

A series of 20 cases of a hybrid surgical/endocardial procedure was described by Kassai et al (Kassai 2011). This constituted surgical access to the LV apex via a mini-thoracotomy,

followed by placement of an endocardial LV pacing lead through the apex. The 6 French lead was then tunnelled up to the generator in a standard left subclavicular position, with RV and RA leads implanted in the standard transvenous method. They used an INR target of 3-3.5. Initial clinical results in 12 patients were encouraging with a response rate reported as 100% (Kassai 2011). The same group went on to compare these 12 patients in a non-randomised, non-blinded manner with an apparently reasonably well-matched group of 12 patients who had standard surgical epicardial LV lead placement (Mihalcz 2012). They reported better response parameters in the trans-apical group.

Larger studies

Rademakers et al report the cumulative experience of 2 centres over 7 years, with 45 patients in whom an atrial transseptal approach was used, and 6 in whom a transapical approach was used (3 due to failed atrial transseptal and 3 due to the presence of a mitral valve prosthesis) (Rademakers 2014). In the majority of cases they used the 4.2 French lumenless lead. Their centres used a relatively high INR target of 3.5-4.5. The 51 patients were followed up for a median of 24 months, representing a significant cumulative exposure. They reported 8 thromboembolic events in 7 patients, although the CHADS-VASc or similar score was not reported, making it difficult to assess baseline risk. A persistent concern about placing leads across the mitral valve has been the potential for worsened mitral regurgitation (MR), but they did not observe this.

Recently Medtronic (Minnesota, USA) has developed LV lead implant equipment specifically designed to allow puncture of the inter-atrial septum under guidance by transoesophageal echocardiography and delivery of an LV lead, with access solely from the left subclavian/axillary vein access typically used for CRT procedures. This was used in the large ALSYNC study, which included 138 patients and is by some way the largest and most rigorously conducted study of endocardial pacing (Morgan 2016). Patients were recruited

from 18 centres on the basis of failed attempts at conventional CRT or non-response to CRT (22.5% of patients). The study includes a minimum of 12 months of follow-up for all included patients, a mean of 17 ± 6, and up to 36 months for some patients. The 4.2 French Select Secure lead was again used, and they used an INR target of 3 with a range of 2-4. Again, they did not observe worsening of MR, and in fact report improvement in 33%.

With this larger patient group they were able to assess thromboembolic risk in more detail. 5 strokes (all reported to be non-disabling) occurred in patients with endocardial leads, as well as 14 TIA events in 9 patients.

Results

Studies identified and patient population included

1560 studies were identified, of which 28 studies met initial inclusion criteria. 6 of these studies were excluded as they included duplicate data, leaving 22 valid studies published between 1999 and 2015. 20 studies used the trans-atrial septal technique with various modifications (Calvo 2014, Domenichini 2015, Garrigue 2001, Geller 2013, Jaïs 2000, Ji 2004, Lau 2009, 2011, Leclercq 1999, Mondoly 2013, Morgan 2009, 2015, Nuta 2007, Pasquié 2007, Patel 2013, Rademakers 2014, Shalaby 2013, Wright 2012), and one used the trans-apical surgical hybrid technique (Kassai 2011, Kis 2015). I have also included one study using the trans-ventricular septal technique (Karpenko 2015) which was developed in Oxford and is the subject of other parts of this thesis. I have not included the early reports from our group as they will be discussed elsewhere. An additional study used the wireless endocardial ultrasound transducer (Auricchio 2014), but was not included in the analysis as this technique is significantly different to all other studies.

Parameter	Result	Available in
Studies	22	
Patients included	365	
Median patients per study (range)	8 (1-136)	
Proportion of male patients	66%	93%
Age (years)	66.2 (61.9-70.5)	97%
EF (%)	26.4 (23.8-29.0)	91%
NYHA class	3.0 (2.8-3.2)	98%
CHADS-VASc score	3.4 (2.9-4.0)	47%

Table 6 - Summary features of included studies and patients. The age, EF and NYHA results are based on meta-analysis of the parameters quoted in the studies, and are mean and 95% CI. The proportion of male patients is a simple percentage based on the numbers reported in each study. The proportion of total patients in whom this data was reported in shown to the right.

As shown in Table 6 above, the range of numbers of patients included in each study was very wide. The ALSYNC study (Morgan 2016) contributed 38% of the total patients; the median patients per study in the remaining studies was 6. Most included patients had undergone a failed coronary sinus implant of an LV lead for CRT, but across all studies, 10% of patients were reported as being included on the basis of non-response to CRT.

Although this is not well-illustrated by the demographics, narratively it is clear from included studies that the majority of patients were not straightforward patients but tended to be complex and high risk. Given the third-line status of these techniques in most centres (behind surgical epicardial placement for suitable candidates), and their novel nature, this would be expected.

No studies were randomised or had any comparator group. As mentioned above, other than ALSYNC (Morgan 2016) and the Rademakers study (Rademakers 2014) they were small and predominantly single centre. Reporting quality was generally poor, with blinding not used for response determination.

Study outcomes

Response to CRT

15 studies, including 241 patients (74% of total patients), reported clinical response outcomes. Positive response (≥ 1 decrease in NYHA class) was reported for 178 patients, giving a crude response rate of 74%, although the range of reported response rates was wide and unevenly distributed between studies. ALSYNC reported an overall response rate of 59%, with 60% of failed implants and 52% of non-responders responding at 6 months. The estimate of response rate in the remaining studies was 93%. The random-effects meta-analysis produced an overall mean response rate of 84% (95% CI 73-91%), as shown in Figure 19 below.

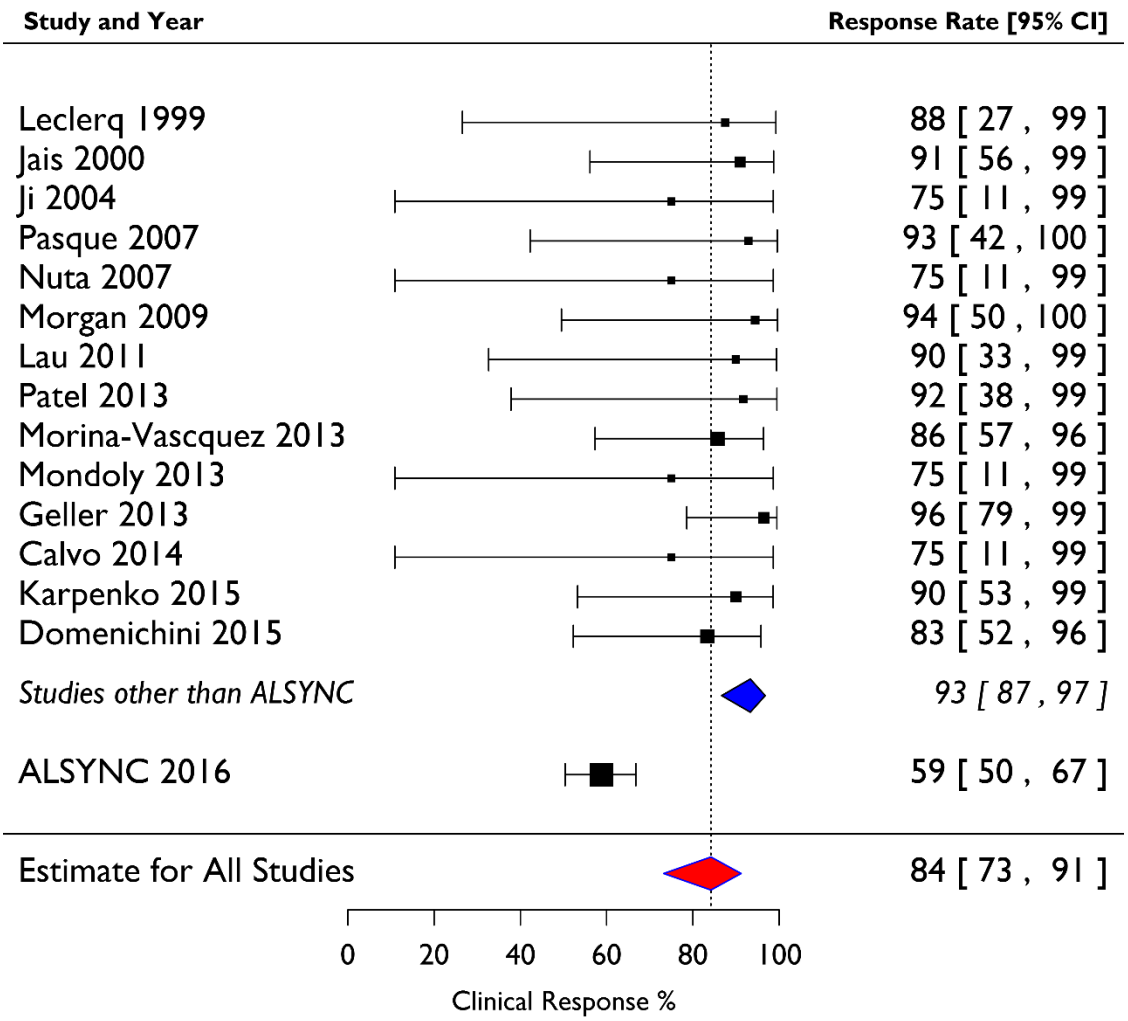


Figure 19 - Meta-analysis of response rates in trials of endocardial LV pacing for CRT. The error bars illustrate the 95% confidence interval for each study. The squares illustrate the mean estimate response rate, with the size of the square proportional to study size. The divergence of ALSYNC from other studies is clearly shown.

Only 3 studies reported echocardiographic response as defined by >5% increase in EF.

The estimate for echocardiographic response rate was 64.3% (56.8-71.2).

Adverse outcomes

Thromboembolic complications were reported by all 22 studies, which followed up patients for 22.8 ± 32.7 months, representing 535 patient-years of follow up.

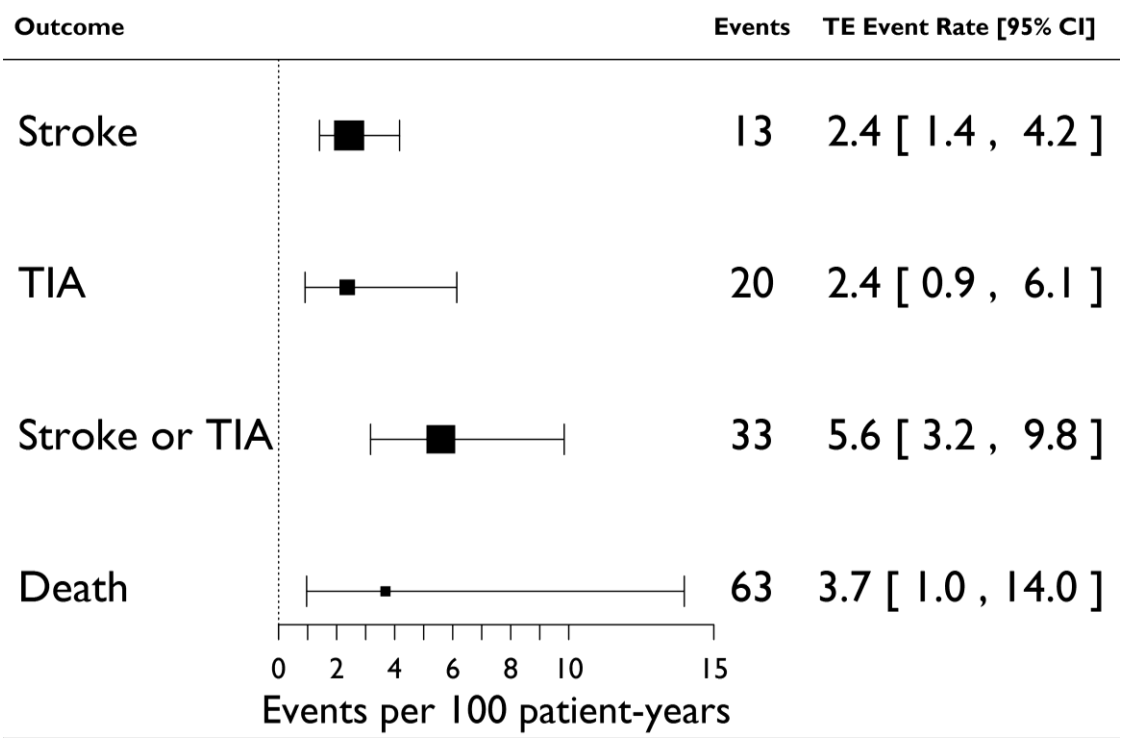


Figure 20 – Summary results of the meta-analysis of adverse outcomes in trials of endocardial LV pacing for CRT, including the total number of events recorded, the event rate per 100 patient-years, and the CI.

As shown in Figure 20, there were relatively small numbers of events reported. There was also considerable heterogeneity between studies, with 13/23 (57%) of studies reporting no events. Heterogeneity for any adverse outcome as measured by I^2 was 77.9%, representing moderate-severe heterogeneity. This heterogeneity can also be appreciated in Figure 21. Length of follow-up did not appear to predict the thromboembolic event rate.

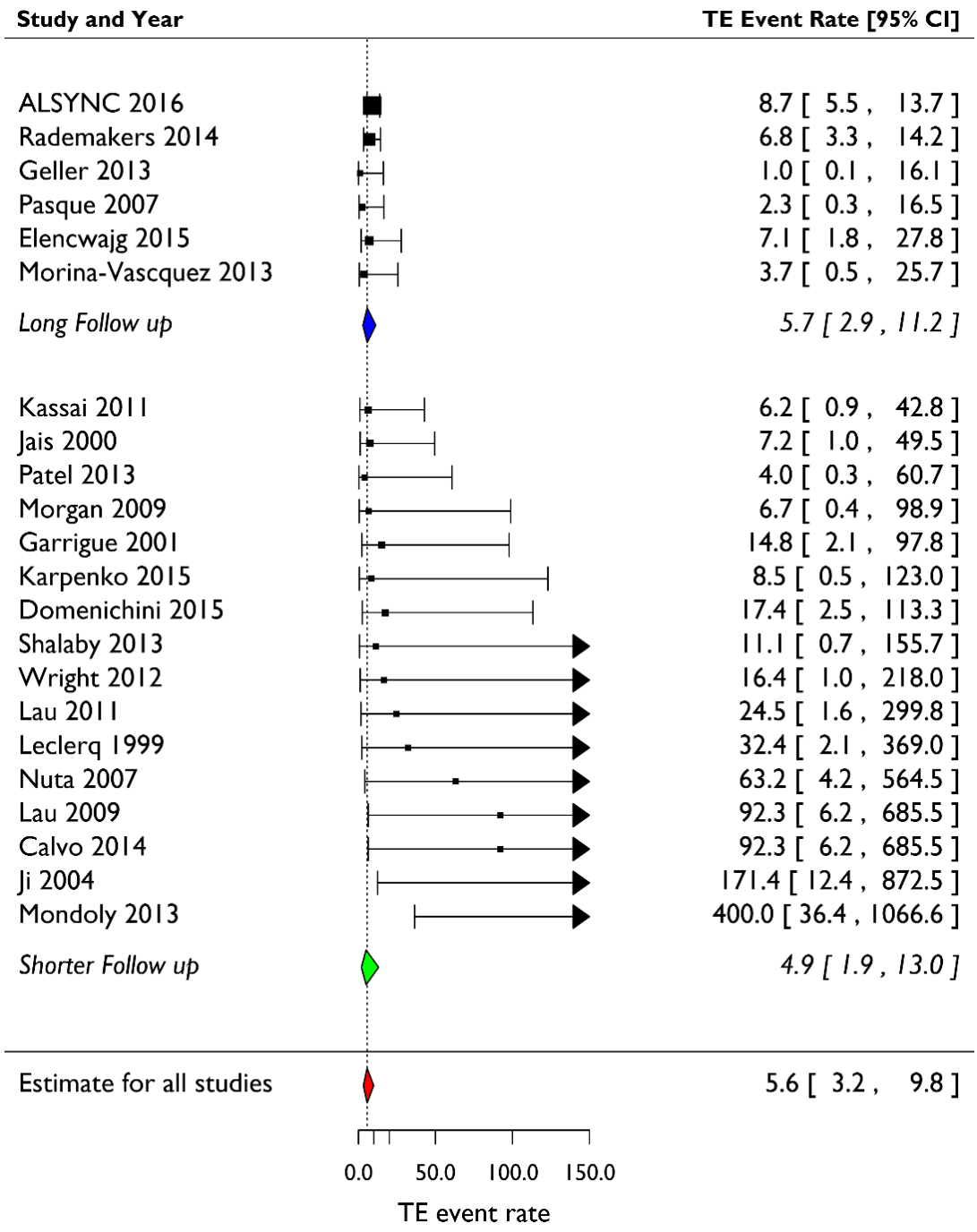


Figure 21 – Random-effects meta-analysis of stroke or TIA events, with all studies shown to illustrate heterogeneity and the wide confidence intervals for smaller studies. Studies are ordered by the number of patient-years follow up, and subgroup estimates are shown for the studies with long follow up, defined as the upper quartile of patient-years, and for the remaining studies.

The bulk of these events were from ALSYNC, contributing 38% of total patient-years of follow up, and Rademaker's study, contributing 19% (Morgan 2016, Rademakers 2014).

Narratively, many studies relate the majority of stroke and TIA events to periods of reduced anticoagulation and difficulty in maintaining a consistent INR level.

Discussion

Response rates

Some authors have suggested that endocardial pacing might increase response rates over standard CRT (Bordachar 2010), and as discussed above there is some evidence for better acute haemodynamic response to endocardial pacing relative to epicardial pacing. This effect appears from the literature to be predominantly due to the ability to choose a pacing site rather than to an intrinsic benefit of endocardial pacing. It appears from the response meta-analysis results that clinical response rates after endocardial pacing, at 84%, are better than those achieved using standard lead placement via the coronary sinus, where about 50-70% of patients are expected to improve their NYHA class (Birnie 2006, Chung 2008, Sohaib 2013). There is however a clear disconnect between the results of ALSYNC and the other studies. Part of this effect is likely to be the group of non-responders in ALSYNC, in whom there was only a 52% response rate. Non-responders to CRT are however a challenging population who are expected to be less likely to improve and are known to frequently have multiple reasons, such as comorbidities, that prevent functional improvement after CRT (Mullens 2009a), so that it could be argued that achieving a response even in this proportion is an excellent result.

Even without this group however, the high response rates reported in other studies were not seen in ALSYNC. This phenomenon of higher response rates being reported by smaller trials with less bias-resistant design features has been observed in other CRT trials (Jabbour 2015) and in similar areas (Nowbar 2014). Accordingly, I do not think the

response rate analysis here is convincing evidence that response rates are higher in the endocardial pacing population.

Thrombosis risks

All patients who have a LV endocardial pacing lead implanted will have a risk of thrombus forming on the lead, potentially causing systemic embolism and stroke. This is one of the significant downsides of LV endocardial leads.

It is reasonably well-established that there is a risk of thrombus forming on intracardiac leads. One study systematically examined the leads of patients with right-sided leads having ablation procedures with intracardiac ultrasound, finding some thrombus in 32% of patients. Thrombus was identified on right atrial leads in 29% of patients, on RV leads alone in 1%, and on both in 5%. The thrombus was noted to be transient from day to day (Supple 2011). Other groups have previously suggested that most lead-related thrombi occur on the right atrial lead, a potential problem of the trans-atrial puncture techniques (Korkeila 2006, Novak 2009, Seeger 1986). The frequency at which thrombi are identified varies depending on the technique used to identify them, from 9% on trans-oesophageal echocardiography (Korkeila 2006) to 29% using intracardiac ultrasound (Supple 2011) and up to 54% on post-mortem (Novak 2009).

The annualised thrombosis rates calculated from this dataset are undoubtedly significant. None of the trials have a control arm and so there is no definitive method to identify a comparison rate. The patients included in these trials, as mentioned above, were high risk patients with heart failure. Those recruited to studies of a novel technique are likely to have been particularly high risk. In the ALSYNC study 50% of patients had atrial fibrillation and 76% were on oral anticoagulation at the study start. Although only 4 studies reported

CHADS-VASc scores, in these the mean CHADS-VASc score was 3.4 as detailed above. Thromboembolism rates in this population would be expected to be high.

One comparison population would be the WARFCEF trial, which randomised 2305 patients with heart failure to warfarin or aspirin. The population was younger (mean 61 years), less sick with mean NYHA class 2.2, and only ~30% had an ICD or pacemaker. Over 42 ± 22 month follow-up the rate of ischaemic or haemorrhagic stroke in the warfarin arm was 0.84 per 100 patient-years (Homma 2013). This is significantly lower than the stroke rate in the endocardial pacing population (p=0.007). An analysis of data from the SAVE trial followed 2231 patients with myocardial infarction for 42 ± 10 months, mean age 59, mean LVEF 31%, 28% on warfarin (Loh 1997). They found a stroke rate of 1.5 per 100 patient-years (P for comparison = 0.11). They also noted a much increased rate of stroke in patients with EF <28% (as did >50% of patients in the current analysis), who had a stroke rate of approximately 2.5 per 100 patient-years. Neither of these studies reported TIA rates.

Another study investigating systemic thromboembolism in 202 patients with a significant intra-cardiac shunt due to congenital heart disease found an annualised risk of systemic thromboembolism of 2.1% in those with an intra-cardiac pacing lead, 27% of whom were on warfarin (Khairy 2006). A similar study found stroke or thromboembolism in 8.2% of 364 patients with a confirmed patent foramen ovale followed up for mean 4.7 years, reflecting an event rate of 1.7 per 100 patient-years (DeSimone 2013).

A recent large analysis of Danish registry data investigated the ability of the CHADS-VASC score to predict stroke in patients with heart failure, both with and without AF (Melgaard L 2015). Heart failure patients without AF (and not on warfarin) had an annual stroke rate of 2.0% with a CHADS-VASc score of 3 (a likely minimum for the endocardial pacing population) and 3.0% for a score of 4. With AF and not on warfarin, risks were 3.2% and

4.3%, although the addition of warfarin would be expected to approximately halve these risks (Ruff 2014).

In patients with atrial fibrillation there is extensive data on assessing stroke risk. The rate of stroke or embolism in patients with a CHADS-VASc score of 3 on warfarin can be estimated from published data at 1.4% per year, and with a CHADS-VASc score of 4 at 2.1% (Sprague 2003). These rates with a CHADS-VASc score of 3 or 4 are not significantly different from those seen in my analysis.

This would suggest that the added risk of endocardial pacing is of the order of 1 additional stroke per 100 patient years. It is also clear that anticoagulation in this population must be meticulous.

Mortality rates

In a large meta-analysis of trials of CRT the rate of death was approximately 6.5 per 100 patient-years (not significantly different from the rate in the current study), in a population who were lower risk than the one included here (Cleland 2013). Only one death (in ALSYNC) was reported as being due to the procedure. Similarly to the stroke rate, this will clearly be influenced by the length of study follow up and study size. 49/65 (75%) of the reported deaths were from the three studies with longer follow up (Kis 2015, Morgan 2016, Rademakers 2014). It appears that the mortality rate is similar to that expected in a CRT population.

Lead Extraction

Transcutaneous extraction of an LV lead inadvertently placed through a patent foramen ovale has been described (Trohman 1991). In ALSYNC, there were 6 LV lead dislodgements which are described as all receiving a further LV lead without complication, although I know that one of them displaced again and was subsequently referred to

Oxford for a trans-ventricular septal lead. This latter patient's event does not seem to be recorded in the ALSYNC paper. In 5 patients in ALSYNC, system infection occurred requiring extraction, without complication. This does seem to show that these leads can be extracted safely, at least when they have not been in place for a long time.

Limitations

This analysis is limited by the small numbers of patients included in the majority of studies. There is clearly a significant heterogeneity between study results, illustrated in particular by the differences in reported results from the multi-centre ALSYNC study and the other studies, which are all small and single centre. It is also challenging to accurately assess the expected risks of the patients included, who were likely to be very high risk and complex patients. Unfortunately, their risk profile is hard to capture from data provided, and there is a limited amount of comparison data available. This limits the accuracy of comparisons of stroke or other outcome rates. In addition the small numbers make effective comparisons between different approaches to endocardial LV pacing inappropriate.

There was also heterogeneity in the amount of outcome and complication data reported in studies. I collected all available data but this meta-analysis is still limited by the data reported in the studies. It is possible that there was under-reporting of adverse events in the smaller studies.

Conclusions

It would appear that the rate of thromboembolism in patients with endocardial LV leads is probably increased over that expected in a similar population, although it does not seem that the magnitude of the increase is large. The rate of death in this cohort appears to be as expected.

The results of the smaller studies would suggest that the rate of response to CRT may be greater than in conventional CRT, but study results are inconsistent, and most notably this was not confirmed by the only large study, ALSYNC.

This increased risk may be offset by significant improvement, although the only way to definitively assess the risk-benefit ratio of endocardial pacing would be a randomised trial comparing it to alternative therapeutic options. The development of leadless endocardial pacing technologies may well obviate the need for these techniques in the future.

Chapter Four – **Background Part II – Left ventricular pacing site selection for CRT**

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Optimal LV pacing sites

As discussed in the first background chapter, CRT uses biventricular pacing (BiVP) to restore coordination of the heart in the context of slow conduction within the left ventricle (LV), exemplified by left bundle branch block (LBBB). This relies primarily on stimulation of the LV, accompanied by either concurrent right ventricular stimulation or selection of CRT timing intervals to allow intrinsic RV activation and LV stimulation.

Where is the optimal pacing site?

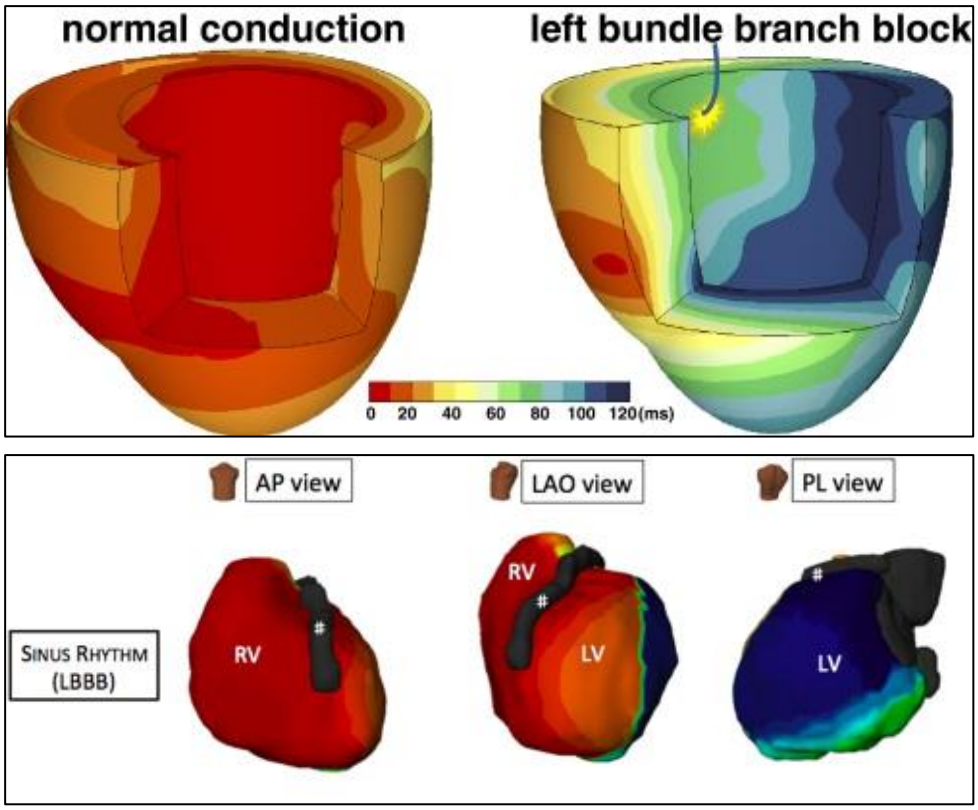


Figure 22 – Top panel: electrical activation patterns of the LV in normal conduction (left) and in LBBB (on right). Reds and oranges represent fast conduction, and blues and greens show electrical delay. From Strik et al. (Strik 2012b), who used a dog model. Bottom panel: similar data from a human study, showing slow conduction in the posterolateral part of the LV in a patient with LBBB (Eschalier 2015).

From first principles, it follows that the optimal position for LV pacing would be the site that was previously most dyssynchronous. Delivering a stimulus to the site in the left

ventricle that is the latest area to contract which would be expected to have the greatest chance of resynchronising the LV. In LBBB, in the absence of normal activation via the left bundle, LV activation must occur by spread of activation from the right heart, via the interventricular septum across to the lateral LV wall. This is confirmed by experimental data in both animal and human models, as shown in Figure 22 above and in the left panel of Figure 23 below. Accordingly, we would anticipate that the optimal stimulation site would be on the LV lateral wall, furthest from the septal breakthrough point, where electrical activation will be the latest and accordingly dyssynchrony the greatest. There are two relevant components of dyssynchrony: delay in the electrical activation of the myocardial tissue, and the resultant (greater) delay in contraction and mechanical activation. Although it would be expected that mechanical activation might follow electrical activation, the two may not necessarily be the same.

Computer Modelling

Computer modelling results support the hypothesis that the optimal LV pacing site is on the lateral wall.

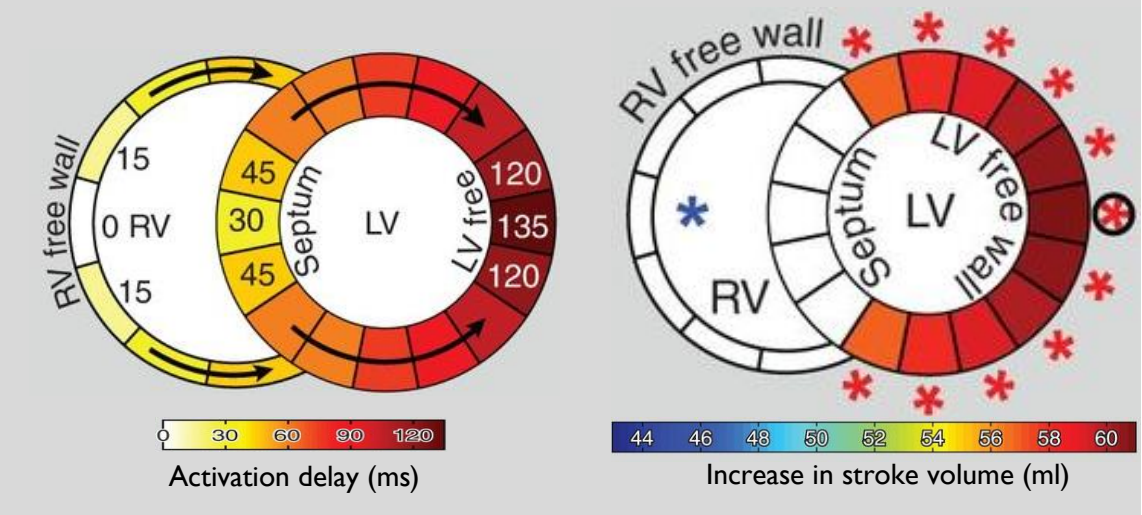


Figure 23 - Optimal LV pacing site from a high-fidelity computer model. Left: baseline LBBB model showing activation delay in ms and on a colour scale. Right: increase in LV stroke volume due to CRT from baseline LBBB, also illustrated in a colour scale, as produced by stimulation at each segment. The RV stimulation site is illustrated by a blue asterisk, the potential LV sites are illustrated by red asterisks, and the optimal site by the circled red asterisk. There was an optimal section of the far lateral wall in which stimulation provided the best possible improvement of a 21% increase in LV stroke volume, which as expected was the section with the greatest electrical delay. It is worth noting that the least optimal LV pacing site, on the interventricular septum, was still associated with a 12% increase in LV stroke volume over baseline, suggesting that at least in terms of stroke volume, the range between best and worse sites is not huge. From Huntjens et al (Huntjens 2014).

As illustrated in Figure 23 above, in one such modelling study the optimal stimulation site was in the lateral LV wall, as expected (Huntjens 2014). LV scar changes the optimal activation site in the computational model discussed above. Of note, as the scar moves more laterally in the LV and into the optimal pacing site, the magnitude of possible acute

response to CRT decreases, from 21% without scar to 11% with scar in the lateral segment , as shown in Figure 24 below.

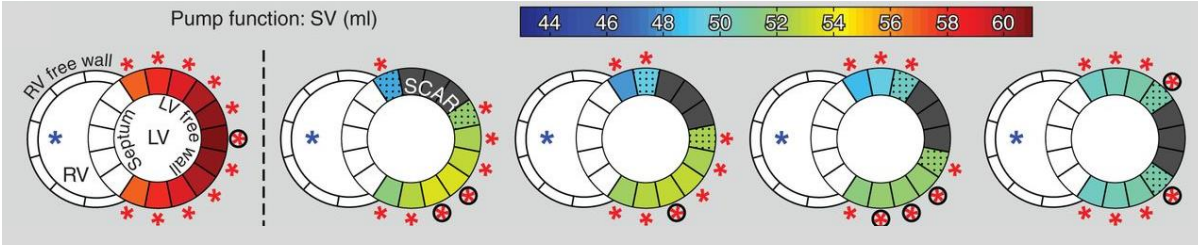


Figure 24- Acute response to CRT is dependent upon the extent and site of LV scar. On the left, CRT response is shown in an unscarred LV, with the extent of LV stroke volume (SV) increase illustrated by the colour scale as in Figure 23. On the right, different scar positions are modelled, with scarred segments in grey. The maximum potentially achievable AHR decreases as the scar moves more laterally. The optimal pacing sites move to the aspect of the LV distant to the scar. The RV stimulation site is illustrated by a blue asterisk, the LV sites are illustrated by red asterisks, and the optimal site(s) by the circled red asterisks. From Huntjens et al (Huntjens 2014).

Animal models

Helm et al came to a similar conclusion by inducing LBBB in dog hearts, and then biventricularly pacing them from multiple LV sites. Again they found that pacing over the lateral wall was optimal, and similarly they found a range of sites in which the response was near-optimal (Helm 2007), which were clustered in the left lateral region and covered a ~100° arc, as shown in Figure 25 below.

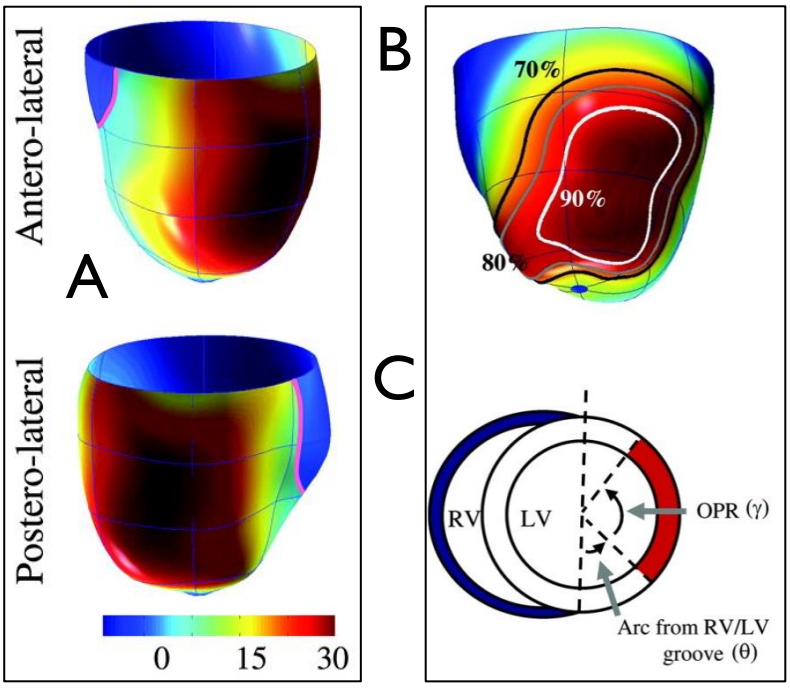


Figure 25 – Optimal BiV pacing sites in dog models of heart failure and LBBB. In section A on the left, the acute percentage change in dP/dt max from baseline LBBB to BiVP at a variety of pacing sites is shown in colour coding, illustrating in two different views that the optimal site is left lateral. Section B, top right, shows anatomical isoregions of response, indicating the size of the lateral 'sweet spot'. At bottom right, section C shows in red the arc of LV in which >70% of maximum potential response was achieved, which covers approximately a 100° arc. From Helm et al (Helm 2007).

They tested multiple haemodynamic parameters, LV dP/dt max, pulse pressure, stroke work, and Tau (the LV relaxation index), finding a similar optimal area with each. Both electrical and mechanical dyssynchrony were improved by CRT. They also found that optimal sites were generally more apical than basal, although they did comment that this finding in particular may not translate well to humans given the smaller size and faster conduction in dog hearts. They did not assess the effect of scar. Finally, their results may be limited by inconsistent methodology in their model production of LBBB, which was a mixture of RV pacing and true LBBB by ablation of the LBB. It has since been shown that, at least in humans, LBBB and RV pacing produce significantly different LV activation patterns (Eschalier 2015), so this inconsistency may have influenced their results.

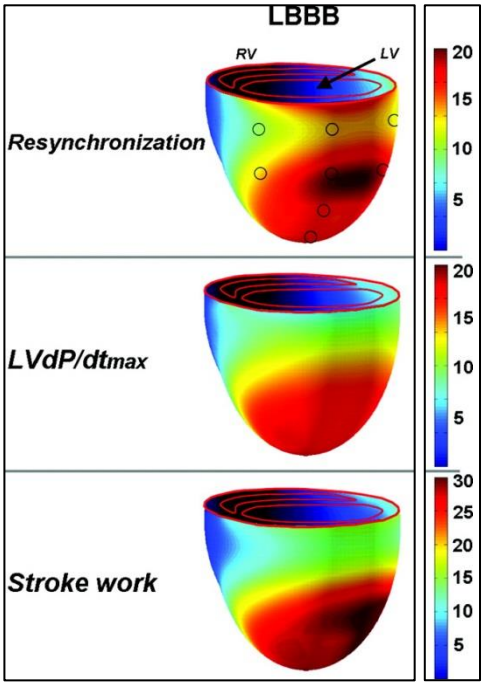


Figure 26 - Results from a study in dogs, displaying the optimal pacing site based on electrical resynchronisation (top), LV dP/dt max (mid), and stroke work (bottom). Colour scale represents the percent increase in the parameter measured. From Rademakers et al (Rademakers 2010).

Similar results were found by Rademakers et al, with LBBB induced by ablation in all dogs (Rademakers 2010). Again the optimal pacing site was in a left lateral position, more apical than basal. Due to the use of dog models, both of these studies were able to assess the AHR at a large number of individual sites, with many repeats of each measure at each site, thus ensuring reproducibility and statistically significant differences. Rademakers et al also found that LV scar changed the optimal pacing site, with the change depending upon the scar site. The authors suggested the need to personalise LV lead site in patients with scar.

Guiding LV lead position by haemodynamic response

The above arguments have stimulated extensive investigation of methods to optimise the LV pacing site. Multiple methods have been used, which I will discuss below.

LV endocardial pacing site selection

The studies of Derval (Derval 2010) and Spragg (Spragg 2010) were discussed in the previous chapter. Both groups paced at a large number of endocardial sites in patients who mostly had LBBB, and found that the optimal site varied between patients, although it tended to be most often in the left lateral region, as shown in Figure 27 below. As previously discussed, the practical limitations of performing these study protocols in human patients affected the number of repetitions that could be made at each site, and thus the ability to differentiate the results from random error, but their results were consistent and similar to those found in the studies discussed above. Neither group made any assessment of LV scar, which is known to significantly influence optimal LV site, as shown in the preclinical models discussed above.

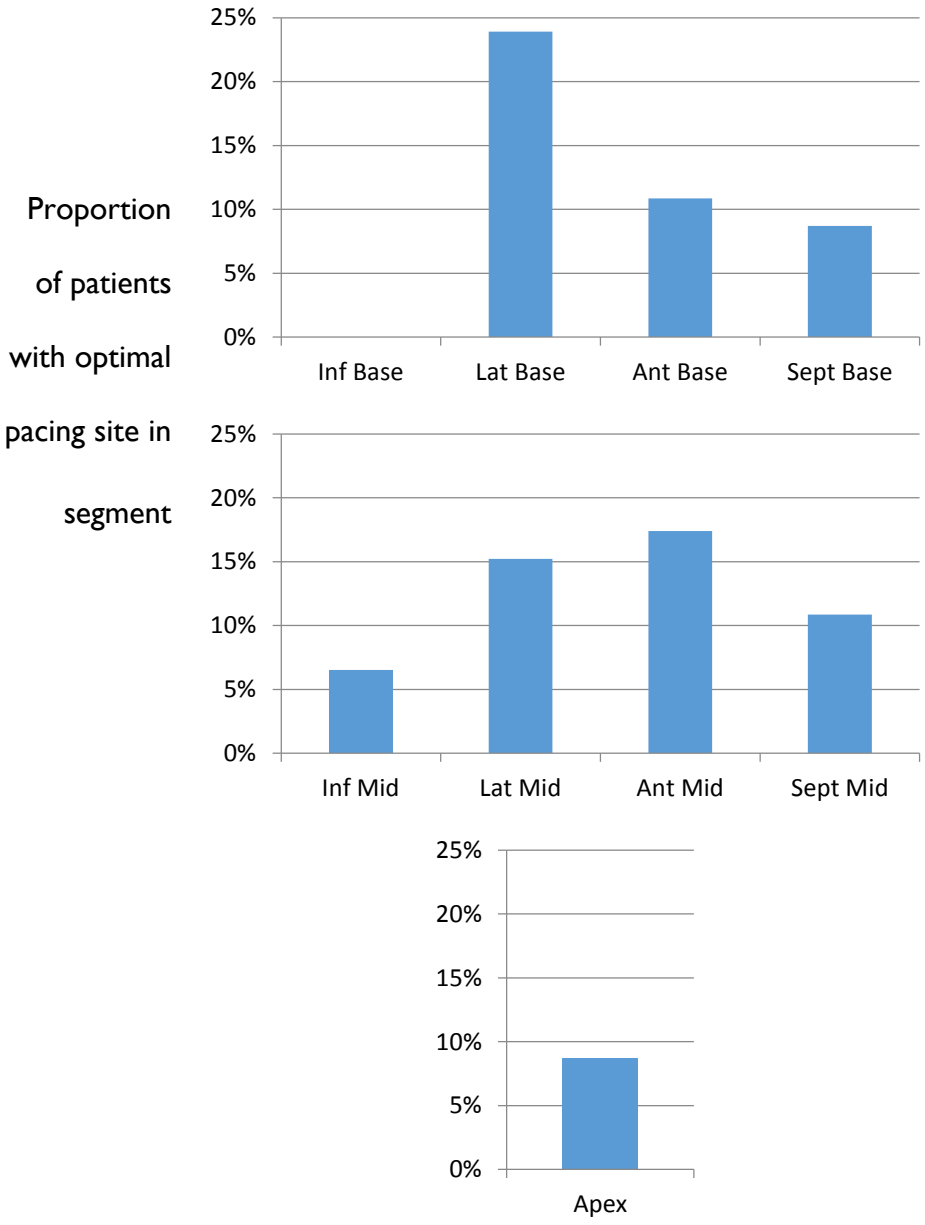


Figure 27 – Optimal endocardial LV pacing sites using combined data from two studies (Derval 2010, Spragg 2010). The bar graphs show the proportion of included patients with an optimal pacing site in each of the 9 investigated segments. Both studies found that the largest number of patients had an optimal site in the lateral region, although there was significant variability between patients, some of which may be due to measurement error as discussed in the text.

Coronary sinus venous branch site selection

The endocardial pacing studies discussed above did have the advantage of being able to assess many different sites without the anatomical restrictions of the coronary sinus anatomy. The CS typically has a limited number of different branches into which a lead could be placed, with one study suggesting a mean of 1.6 ± 0.9 veins in the posterolateral area (Khan 2009).

Several studies have investigated the use of similar haemodynamic monitoring techniques to assess lead site selection within the coronary sinus. A key trial from Prof Rinaldi's group by Duckett et al investigated the use of maximising acute haemodynamic response to guide LV lead placement in 33 patients (Duckett 2011). AHR was assessed using LV dP/dt max measured over at least 10s using a pressure manometer wire. Their patient group all had LBBB with a mean QRSD of 160ms, and a mixture of ischaemic and non-ischaemic cardiomyopathy. They assessed 3.3 ± 1.2 venous sites per patient, and were able to assess two or more sites in 30/33 patients, mostly in lateral or posterolateral veins (29/33). 70% of patients had a >10% AHR to LV only pacing (DDD-LV) relative to AAI/ RV pacing. They found a significant difference between the best and worse venous sites, but did not report the difference between other sites tested. Greater than 10% increase in AHR was found in 94% of 18 patients who were responders to CRT (defined as >15% reduction in ESV on echocardiography at 6 months), and was thus proposed retrospectively as a method to guide venous site selection.

Another group used a thermodilution pulse contour analysis catheter placed in the abdominal aorta to measure LV stroke volume index (SVI) and aortic dP/dt max, and thus AHR to BIVP recorded over 3 minutes at each site (Stockinger 2011). Interestingly, dP/dt max and SVI were concordant in 42 tests and discordant in 21 measurements, but both increased relative to RV pacing at the best available LV site. The best stimulation sites

were in the lateral position in 15/21, and elsewhere in in 6/21 patients. This aortic measurement of dP/dt may not fully reflect the intra-ventricular measurement performed in most other studies. Only 18/33 (56%) of patients had a positive response to CRT as defined using ESV as above, but 94% of these patients had more than a 10% AHR to BIVP. AHR >10% was the most sensitive of several factors tested for the prediction of echocardiographic response to CRT.

This study provides evidence that AHR can predict response, although as all patients had a LV lead guided by maximum AHR and only 56% responded it does not provide convincing evidence that this strategy can increase response rates. One problem may be that the acute response measured was with LV-only pacing, whereas the chronic pacing was with BIVP. It does again illustrate the complexities of measuring response in CRT, as 91% of patients had >1 NYHA class improvement, and 94% of patients had a >10% improvement in their quality-of-life questionnaire score. The latter figures are higher than often found in other trials, whereas the echocardiographic response rate is lower than is typical.

Shetty et al, in a further group of 19 patients, assessed AHR by dP/dt max with a pressure wire, over a minimum of 20s per recording. They assessed 3.5 ± 0.9 veins per patient, as well as the available quadripolar lead configurations within each vein (Shetty 2012). They found a 6.5 ± 5.4% difference in AHR between the best and worst configurations within a vein (i.e. intra-vein variability). This varied between patients, and no pacing vector was consistently associated with the best AHR. However they found a larger 16.9 ± 6.1% increase in AHR between veins and vectors – i.e. between the best vector in the best vein and the worst vector in the worst vein. The best vein site found was lateral in 67% of patients, anterior in 22%, and posterior in 11%. These results have the implication that although an increase in AHR from different pacing sites along a quadripolar lead within a coronary vein is seen, these are small and are less than the potential inter-vein increases.

So there is some scope to make small improvements in AHR by stimulation vector choice of a quadripolar lead, but getting a lead into the best available vein will still increase it more. I will discuss other studies investigating intra-vein site selection at more length below.

Interestingly, the distribution of the optimal pacing site in Shetty et al's results are broadly similar to the optimal region targets suggested by other trials using echocardiographic techniques or myocardial perfusion single photon emission computed tomography to identify the area of latest mechanical activation (Boogers 2011, Khan 2012, Saba 2013). Again, these trials will be discussed in more detail below. Clinical response to CRT in this patient group was not established.

Another group have also shown that AHR measurement can predict chronic response to CRT. de Roest et al performed temporary BIVP using electrophysiology catheters in the right ventricle and a small gauge unipolar pacing wire in branches of the CS (de Roest 2013). They used a conductance catheter to measure LV pressure-volume loops, including LV SV, cardiac output, stroke work, and dP/dt max. They defined both echocardiographic (reduction in ESV ≥ 15%) and clinical response (no hospitalisation for HF and NYHA increase ≥1 class or ≥25% improvement in 6 minute walk distance). After the temporary pacing protocol, the patients had a conventional implantation of a CRT device a few weeks later, with LV lead position guided by the optimal position found at the research assessment. They found an optimal pacing site in the posterolateral region in 85%, and the anterolateral in 15%. Out of the 41 included patients 29 (71%) had an echocardiographic response. Long term responders had a significantly greater AHR by SV, dP/dt max and stroke work than non-responders, but only stroke work was found to effectively predict response, as shown in Figure 28 below.

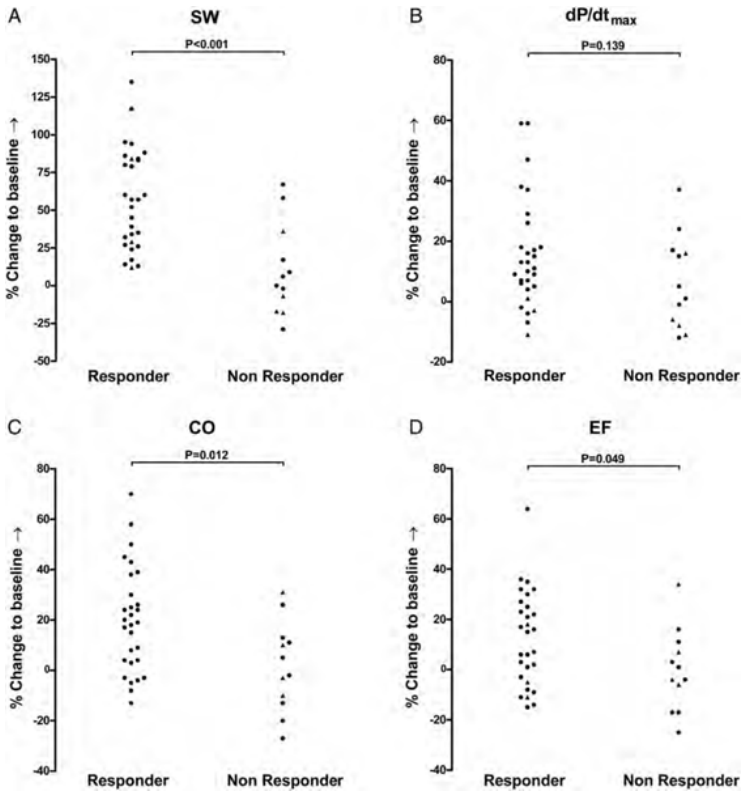


Figure 28 - Acute response to biventricular pacing as assessed by several different parameters. It can be seen that there is significant overlap in the response in all parameters but that stroke work (SW) is the most predictive. This was reflected by the best calculated AUC. From de Roest et al (de Roest 2013).

This paper supports the studies above in suggesting that AHR can predict response to CRT, although they found that dP/dt max was less predictive than other parameters in their population. The authors do acknowledge that the conductance catheter is challenging to use in this population and that, in particular, measures other than stroke work may be recorded less reliably. Again, they reported a high response rate (77% in patients with QRSD>120ms) in their patients, which supports the potential benefit of haemodynamic optimisation to guide LV lead placement.

Similarly to other studies, they suggest that the lateral veins are most often optimal, but that lead placement within the coronary veins should be personalised to the patient in order to derive the most potential benefit. This probably reflects areas of scar and slow

conduction in some patients, where LV pacing will be non-optimal and thus alternative pacing sites are better. This is as predicted from the simulation studies discussed above.

Intra-vein site selection

The studies discussed above investigated the best vein to deliver pacing, i.e. the inter-vein optimum. With the advent of quadripolar pacing leads, it has become clinically feasible to select the intra-vein optimum, as the quadripolar lead allows selection of the pacing site between the poles along it. As mentioned above, when the intra-vein differences were assessed in Shetty et al's study, a 6.5 ± 5.4% difference was found in AHR between the best and worst configurations within a vein. This differential varied between patients, and no particular vector was consistently associated with the best AHR (Shetty 2012).

Asbach et al assessed the change in AHR to CRT between the 10 different pacing vectors available from a quadripolar lead (Asbach 2013). They recorded AHR relative to AAI pacing with LV dP/dt max using a LV pressure wire, using a rigorous protocol with 2 minute assessment periods at each configuration and 2 minute baseline periods of AAI pacing before them. Notably, they found that by tailoring the vector choice to the patient, they could increase the number of patients with >10% AHR to BiV pacing (the threshold for response prediction proposed by Duckett et al as discussed above) from 12 to all 16 patients. They also found that distal configurations were more often optimal than proximal, but no differences in mean AHR across patients at any one configuration or pole.

Valzania et al assessed the effect of four of the available pacing vectors from a quadripolar lead on multiple echocardiographic markers in 21 patients. They found that different echocardiographic parameters were affected by different vectors, but that in particular the D1-P4 vector appeared to improve global longitudinal strain, septal-lateral delay, stroke

volume, and mitral regurgitation, all of which are surrogate end-points that are likely to reflect more effective resynchronisation (Valzania 2013). The small number of tested vectors, and the fact that they only used D1 and P4 as the cathode, limits this study significantly.

I think it is also important to note that optimising CRT attains another level of complexity with quadripolar leads. With multiple available LV lead pacing vectors, plus AV and VV timings, choosing the best option for an individual patient is potentially unworkably complex. Several studies suggest that there are significant haemodynamic differences between pacing vectors (Asbach 2013, Cabrera Bueno 2013, Pappone 2013a, Valzania 2013), with no vectors consistently superior, and so it seems likely that individual-patient optimisation is important. Despite this it remains unknown if optimising quadripolar vector choice can increase either the degree of chronic clinical response in a patient, or the number of patients with a positive response to CRT. Given the challenge in showing that *any* technique of optimising AV and VV timings in CRT results in improved clinical response, obtaining longer term clinical data to inform this is likely to be challenging (International Working Group on Quantitative Optimization: 2013). It is also unclear as to how best to inform this choice, as complex research algorithms using invasive hemodynamic measurements are unlikely to be practical in day to day use, so simpler techniques will be needed if such optimisation is found to be beneficial.

Limitations of the acute haemodynamic response methods for LV pacing site selection

The major limitation of most of the studies discussed above is that AHR is used as a surrogate marker for long-term clinical response. AHR, as measured by dP/dt max and

stroke work, have only been shown to relate to long term outcomes in the two studies discussed above (Duckett 2011, de Roest 2013).

Other studies have found that baseline dP/dt max predicted response, but that the change in dP/dt max with CRT did not do so. Bogaard et al measured LV dP/dt max with a pressure wire in a large cohort of 285 patients (Bogaard 2011). They measured baseline dP/dt before CRT was activated, the dP/dt after CRT activation and the AHR between the two. In a careful multivariate analysis, they found that the AHR was not predictive of response, but the baseline dP/dt was. Suzuki et al found similar results in a much smaller cohort of patients (Suzuki 2010).

It is important to note that these studies were investigating prediction of response, and they did not use the AHR to guide LV lead positioning. They simply correlated baseline dP/dt max and dP/dt max after CRT with outcome. As dP/dt max after CRT represents relatively predictable percentage increase over baseline dP/dt, this is perhaps to be expected, as sicker patients with more damaged ventricles and thus lower baseline haemodynamics are more likely to have adverse outcomes and probably less likely to respond to CRT. Several prior studies have shown that sicker patients derive less benefit from CRT (Bommel 2009, Park 2013, Verbrugge 2013b), and it may be that these studies are simply producing this same result in a different way.

These findings may also reflect different mechanisms acting in short-term and long-term response to CRT (Prinzen 2012). Acute response represents mechanical resynchronisation resulting in improved cardiac output and contractility. The linkage between this and cardiac reverse remodelling is complex, involving a multifactorial mechanism of intracellular changes resulting eventually in remodelling. It is also evident that even in patients who appear to be non-responders to CRT on the basis of a lack of remodelling, there are still haemodynamic benefits of CRT. When Mullens et al turned off

CRT in a cohort of patients with recurrent hospital admissions and limited remodelling they found that multiple haemodynamic parameters worsened significantly (Mullens 2009b). This is also supported by the results of the early crossover trial of CRT, MUSTIC, in which 85% of patients subjectively felt better during the CRT-on period, even though a smaller proportion than this would have been expected to have positive remodelling, and only some remodelling would have been expected after 3 months (Cazeau 2001).

There are also clear practical limitations to this technique due to the need for additional arterial access to place the pressure wire or conductance catheter.

There are also limitations to the statistical approach used in many studies to assess AHR. Most prior studies have simply used the mean of AHR across patients, an approach which is subject to bias. This topic is discussed in more detail in the following methods chapter.

As discussed above, it is known that LV dP/dt max is affected by LV preload (Kass 1987, Mason 1971, Wallace 1963). The left atrial pressure will be affected by changes in both LV emptying and in RV function and thus left atrial filling. This provides a clear mechanism for an order effect in the assessment of LV dP/dt, as each measurement will be influenced by the preceding LV or RV stimulation modality. Not all prior trials have randomised the order of measurements or repeated them serially.

Left ventricular activation patterns and pacing site choice

As discussed in the first background chapter and above, one of the underlying pathologies CRT can treat is dyssynchrony within the LV. The electrical delay exemplified by LBBB results in slow contraction of the free wall of the LV. Thus we would expect to be able to measure the activation in those lateral LV segments as being later than in other LV

segments. Again, this was shown in the simulation and animal model studies discussed above.

It is important to differentiate the two sequential elements to the LV free wall activation. Firstly, slow electrical conduction results in later electrical activation of the free wall. This electrical delay will result in slow mechanical activation of these segments. It can immediately be discerned that the linkage between electrical and mechanical activation may not be straightforward.

Various techniques have been used to identify late-contracting segments. They can be crudely divided into imaging techniques, which are used to identify mechanical activation patterns, and electrical techniques used to identify the electrical patterns. Some groups have also attempted to combine the two.

Mechanical activation patterns

Early studies used echocardiographic techniques, focusing on Doppler imaging (which was then the best available technology for measuring activation times). Ansalone et al used tissue Doppler imaging (TDI) to identify the lateral wall segment with the longest mechanical activation time. They found that patients with an LV lead placed in this site (i.e. concordant with the mechanical activation pattern) had greater response to CRT, as measured with echocardiography and exercise capacity (Ansalone 2002). The TDI technology is however difficult to use, and its reproducibility has been questioned. In particular, various TDI methods were used in the large multicentre PROSPECT study to try and identify predictors of response to CRT, and were found to have very poor reproducibility (Chung 2008). This encouraged the search for other echocardiographic techniques to identify mechanical contraction patterns. The echocardiographic technique that has been frequently used in recent years is speckle-tracking. This is what I have used

in my research, and has been the most studied, so I will review the principles as well as the prior studies below.

Speckle-tracking echocardiography

Principles

This technique uses grey-scale echocardiographic images to follow wall motion and wall strain (Blessberger 2010). The latter parameter of strain is defined as the change in myocardial fibre length at end-systole versus end-diastole, usually expressed as per cent. The first derivative of this by time is the strain rate. Strain measures active contraction only and does not record passive traction of myocardial segments by adjacent segments. Strain can be measured in multiple directions, as shown in Figure 29.

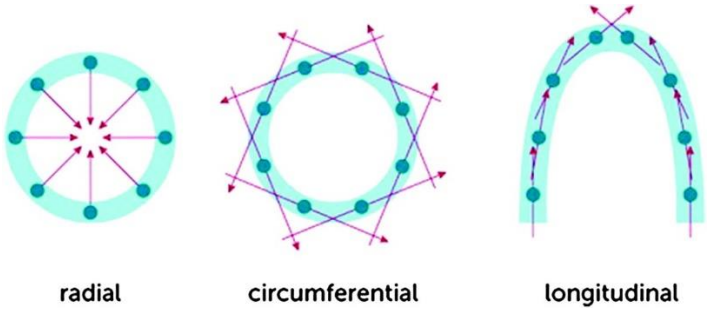


Figure 29 - Different directions of myocardial wall strain. Image from a review (Blessberger 2010).

The strain is measured by speckle-tracking. This algorithm uses speckle artefacts in the echo image, which are generated by reflections and scattering of the echo beam from cardiac microstructures. Some of these markers stay stable and can be tracked through the cardiac cycle to detect myocardial motion and strain (Reisner 2004). The technique has been validated against cardiac MRI as an accurate method to identify regional wall motion abnormalities (Becker 2006).

Use of speckle tracking echocardiography for CRT

An early study by Suffoletto et al using speckle-tracing echocardiography (STE) found that radial strain delay could predict response to CRT (Suffoletto 2006). They also found that they could identify the site of latest mechanical contraction using radial strain, and that patients in whom the LV lead was placed at this site had a greater likelihood of response to CRT. As in many of these studies, these results were from a highly-specialised department. They quote intra-observer reproducibility figures of 6 ± 6% and inter-observer reproducibility of 8 ± 7%. They are presumably referring to peak strain values; they do not clearly quote values for activation times.

Delgado et al investigated all three of radial, circumferential and longitudinal strain (Delgado 2008). Only radial strain values had significant differences between responders and non-responders, and they derived the same cut-off value as Suffoletto et al of 130ms. Ypenburg et al again showed that patients in whom the LV lead position was concordant with the site of latest mechanical activation as derived from radial strain STE were more likely to respond to CRT (Ypenburg 2008). Similar results were shown in the non-randomised STAR study (Tanaka 2010).

These early studies contributed to the development of two randomised controlled trials that compared targeting LV leads to the vein within the site of latest mechanical activation as derived from STE-radial strain. The first trial to be published was the TARGET study (Khan 2012). This trial recruited 207 patients with standard indications for CRT, although they excluded 11% in whom image quality was inadequate for good STE strain analysis. In all patients they used STE radial strain analysis to locate the LV segment with the latest mechanical activation (LMA) within the 8 non-apical and non-septal segments of the standard echocardiographic 17-segment model. They also excluded segments with low

radial strain (<10%) as a prior study by their group had shown that this cut-off accurately identified segments with non-viable scar (Khan 2010).

In the group randomised to LV lead positioning at the site of LMA, the implanters were provided with the STE data. They used a steep left anterior oblique orientation venogram to compare segmental positioning to the short axis echocardiographic images, as illustrated in Figure 30.

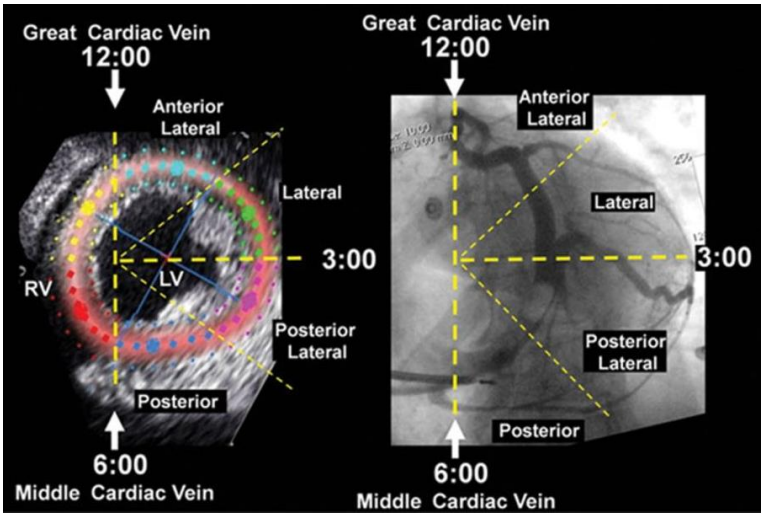


Figure 30 – Co-registration of echocardiographic speckle-tracking radial strain data (on the left) and the venous anatomy on a venogram in a 50-90° left anterior oblique orientation (right). The LV segments are indicated on both images. From Saba et al (Saba 2013).

Where possible, they placed the LV lead into the targeted segment, although due to the limitation by coronary sinus anatomy of lead positioning, they were only able to place the LV lead in the targeted segment chosen in 63% of patients, with another 26% in whom they were able to place the lead in an adjacent segment. In the control group the LV lead was placed in an empirical lateral site as per standard practice, although the LV lead was placed fortuitously in the LMA segment in 47% of the patients in the control group, and adjacent in 29%. The final distribution of LV lead positions by segment was essentially identical between the groups.

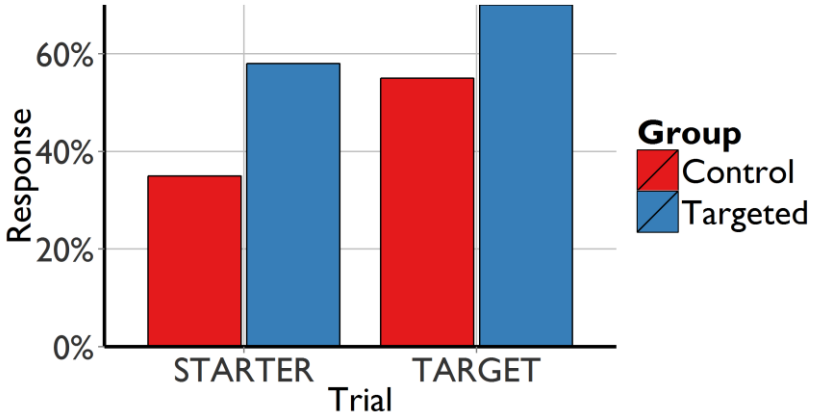


Figure 31 –TARGET and STARTER trial results.

	Controls		**Targeted lead position**		
Study	*n*	*Response*	*n*	*Response*	*P*
TARGET (Khan 2012)	104	55%	103	70%	0.025
STARTER (Saba 2013)	48	35%	73	58%	0.017

Table 7 - Response rates in randomised trials of lead position targeted to the site of latest mechanical activation. In the TARGET trial response was defined as >15% decrease in left ventricular end-systolic volume on echocardiography. The STARTER trial used a combined endpoint of the same echocardiographic marker, with no hospital admission for heart failure or death. I have calculated probabilities for comparisons with the Chi-Square test.

As shown in Table 7 and Figure 31, the targeted LV lead placement group had a greater response rate measured by ESV change on echocardiography. They also had a higher rate of clinical response (≥1 NYHA class improvement in 83% vs 65%, P quoted as 0.003). Finally, they also analysed all patients by whether their LV lead position was in a segment concordant or adjacent to the LMA segment, or whether it was remote from it (i.e. >1 segment away). As shown in Figure 32, there was a very significant difference in outcome in patients with remote LV lead positioning.

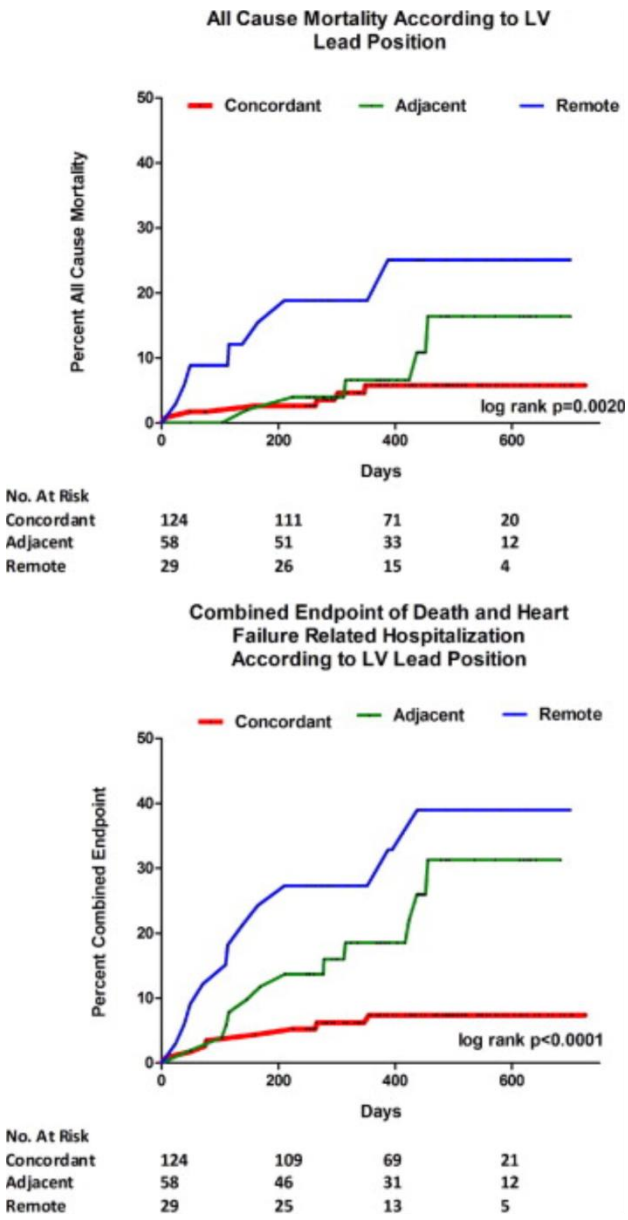
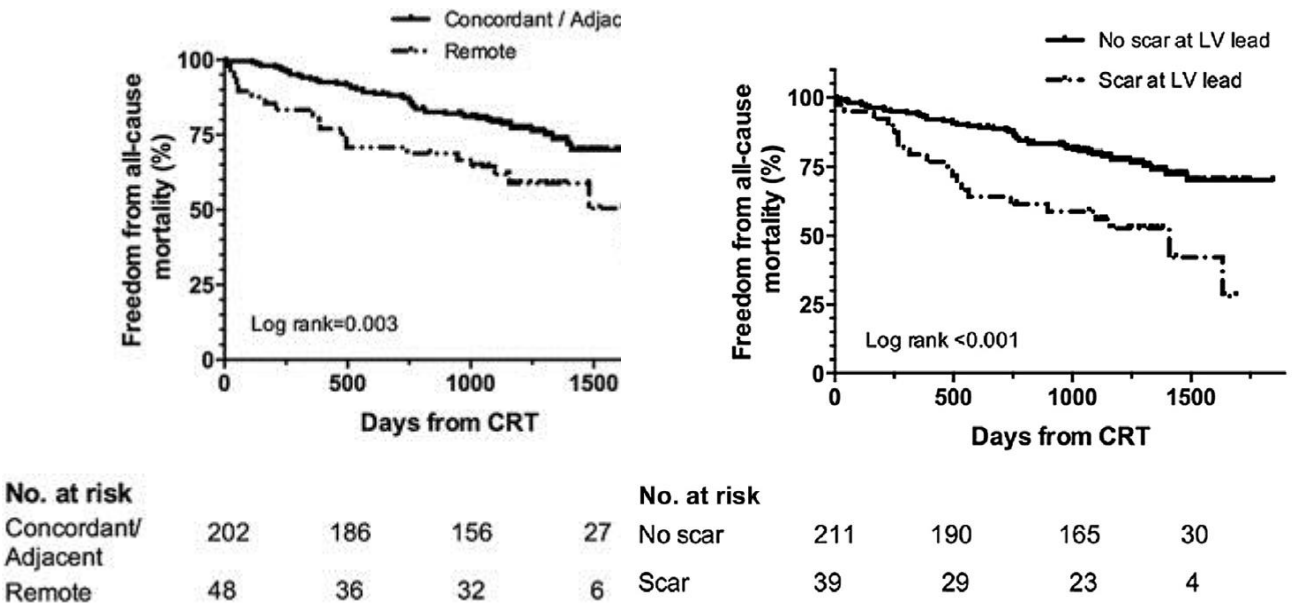


Figure 32 – Outcomes according to LV lead relationship to the LMA segment. From TARGET (Khan 2012)

The STARTER trial was a second very similar RCT, in which patients were randomised to guidance using STE-radial strain or to empirical lead placement (Saba 2013). They did not use a strain amplitude cut-off, but did exclude segments with thin wall and abnormal acoustic reflectance, which is likely to result in a similar outcome. As shown in Table 7 above, targeting the LMA site resulted in increased response rates. Similarly to TARGET, the anatomical distribution of leads between groups was almost identical, although there were more basal leads in the targeted group.

Both groups have followed up their patients over a longer time period and shown persistent prognostic benefits of targeting the LMA (Adelstein 2011, Kydd 2014) (Figure 33 below). The mechanism of benefit in these trials is uncertain, especially as distribution of the final resulting lead positions appears to be identical in the targeted and empirical groups. Several authors have suggested that the benefit of this strategy might be driven predominantly by avoiding segments with scar at the pacing site, and this is supported by the long-term data from both studies (Adelstein 2011, Kydd 2014).



No. at risk				
Concordant/ Adjacent	202	186	156	27
Remote	48	36	32	6

No. at risk				
No scar	211	190	165	30
Scar	39	29	23	4

Figure 33 - Long-term follow up of the TARGET trial. Left: Kaplan-Meier curves of all-cause mortality by whether the LV lead was concordant or adjacent to the LMA site or remote (>1 segment) from it. Right: similar, divided by the presence or absence of scar at the lead site. From Kydd et al (Kydd 2014).

Other studies have similarly shown that scar at the LV pacing site carries an adverse prognosis, using predominantly cardiac MRI to identify scar but also nuclear cardiology methods (Bilchick 2014, Delgado 2011, Leyva 2011, Marsan 2009, Shetty 2013). The consensus of these papers is that pacing at a site of scar carries a significantly worse prognosis than at a segment remote from scar. This could suggest that the benefit of the LMA targeting strategy was mostly driven by the inclusion of protocols to avoid pacing at scarred segments, rather than by the LMA targeting.

Khan et al do not quote reproducibility for their technique used in TARGET. Saba et al quote "intraobserver variability in time to peak strain analysis was 6±6%, and the interobserver variability was 8±7%" for STARTER; neither describe how this impacted upon the choice of site for each loop.

Latest electrical activation and LV lead position

Another developing paradigm is to pace at the site of latest electrical activation. This is logical: CRT is an electrical therapy targeting electrical delay so choosing the site with the longest electrical delay might be expected to maximise benefit.

An early study found a correlation between AHR by dP/dt max and the extent of electrical delay at the LV lead position, as measured by the QLV time (delay from the start of the surface ECG Q wave to the peak of the sensed EGM at the LV pacing site, as shown in Figure 34 below) (Singh 2006). Subsequently a large sub-study of the SMART-AV RCT, including 426 patients, 75% of whom had LBBB, found that patients with QLV less than the median value of 95ms were significantly less likely to respond to CRT (Gold 2011b).

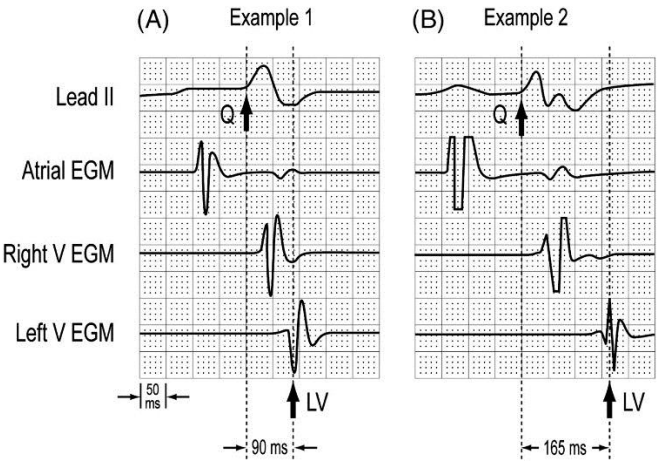


Figure 34 - Measurement of the QLV time. From Gold et al (Gold 2011b).

This finding could simply be another way of measuring whether patients have LBBB or not, as QLV was significantly longer in the LBBB group, although in multivariate analysis they found that QLV was an independent predictor of response and LBBB was not (Gold 2011b). Other clinical studies have found that QLV/LV lead electrical delay appears to be a predictor of response (Kandala 2013a, 2013b).

Several studies have also investigated the relationship between QLV and AHR to BiVP. In 31 patients Gold found a strong correlation with Pearson's R of 0.73 between QLV and AHR to BIVP by dP/dt max, although it is probably not statistically valid to use a Pearson's correlation across patients. In a multivariate analysis they found that the only significant predictor of AHR was QLV, with BBB morphology and QRS length not significant predictors (Gold 2014).

Zanon tested 2.9 veins and 6.4 sites per patient in a group of 32 patients, and found a positive and significant correlation between QLV and AHR by dP/dt max, using the more appropriate method of generalised linear mixed modelling, which allows assessment of the contributions of each patient to an overall model (see Figure 35 below) (Zanon 2014). In 31/32 patients pacing from the latest activated site resulted in the greatest AHR to BiVP. dP/dt max at each site was assessed over 15 seconds only, with no repeated measurements, which would lead to some concern about the reproducibility and accuracy of these measurements.

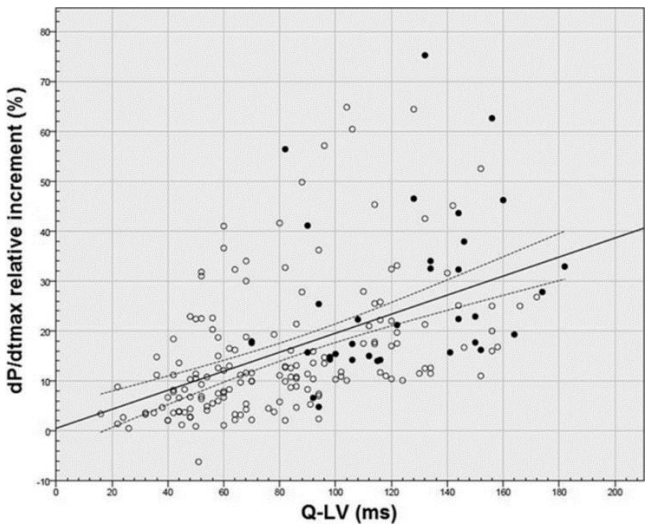


Figure 35 - Relationship of Q-LV measurement and AHR by dP/dt max, from Zanon et al (Zanon 2014). The solid line is a generalised linear multi-level modelling regression line, and the dotted lines are its 95% confidence intervals. The black markers are the sites with the longest QLV in each patient.

Clinical evidence for differential effects of pacing site

In the above section I have reported many small studies investigating various methods to optimise LV lead position. Secondary post-hoc analyses of several of the large studies have also investigated the effect of LV lead site on clinical outcomes. The results of these analyses are shown in Table 8 and Table 9.

Trial	n	Classification of LV transverse axis lead position	Clinical Outcome Differences	Trend
COMPANION (Saxon 2009)	1071	Anterior/ Lateral/ Posterior	Not significant	Posterior worse than others
MADIT-CRT (Singh 2011)	799	Posterolateral (optimal) or anterior/inferior	Not significant	None
PROSPECT (Mortensen 2010)	426	Optimal /not optimal/other	Not significant	Non-optimal worse (anterior and apical)
REVERSE (Thébault 2012)	346	Lateral /not lateral	Not significant	None
RAFT (Wilton 2014)	447	Anterior/ Lateral/ Posterior	Not significant	Anterior worse than others

Table 8 – Clinical results reported in analyses of outcome according to transverse axis lead position, from large trials of CRT.

In summary, from the studies investigating transverse LV lead position in Table 8 there does not seem to be a consistent trend towards worse outcomes in any particular LV lead position in the transverse axis.

Trial	n	Classification of LV longitudinal axis lead position	Clinical Outcome Differences with apical lead position versus other lead positions	
			Death	HF hospitalisation
MADIT-CRT (Singh 2011)	799	Apical / Non-Apical	Increased	Increased
REVERSE (Thébault 2012)	346	Apical / Non-Apical	Not significant	Increased
RAFT (Wilton 2014)	447	Apical / Non-Apical	Not significant	Increased

Table 9 - Clinical results reported in analyses of outcome according to longitudinal axis lead position, from large trials of CRT.

All three studies in Table 9 considering base-apical lead position do however show a consistently negative effect of apical LV lead position. This does strongly suggest that LV lead position can have negative clinical effects that are significant at the level of hard outcomes such as death and heart failure hospitalisation.

The results of the transverse lead position studies are surprising, as the studies discussed above would suggest that there should be a physiologically optimal site that will increase response to CRT. Several explanations are possible for this data. One is that some of these studies used relatively insensitive classifications of LV lead position. In particular, the anterior/lateral/posterior classification will include leads in anterolateral and postero-lateral areas within the non-lateral classifications. These areas are likely to still be beneficial in many patients. This would be compatible with the theory that the area in which LV pacing confers a benefit is large, so that CRT over a wide range of sites will provide clinical benefit, and only extreme non-lateral sites will result in a negative effect, as shown in the results discussed above, where the optimal segment of the LV covered a 100° arc.

Another explanation would be that death and HF hospitalisation are simply too crude as measures of response. If one hypothesises that the benefit from CRT in terms of these outcomes is large, it might be that they are still reduced even by non-optimal CRT. This does not exclude the possibility that greater benefits could have been achieved in an individual patient with more effective CRT, for example resulting in a greater degree of symptomatic benefit.

Finally, on an individual patient basis the optimal site may be variable. This hypothesis would produce clinical results similar to the above, as the optimal site will be scattered between the anatomical area classifications. Again, for an individual patient a greater response might be achievable by a personalised site. This would be supported by the

studies incorporating scar into their models discussed above, which would suggest that different scar positions will change the optimal site, and by the studies investigating AHR at multiple sites.

Multi-site LV stimulation

A further approach to LV site selection is to stimulate at multiple LV sites rather than one in order to capture a larger area of myocardium. Several previous small trials have assessed multi-site LV pacing using more than one LV lead in several coronary sinus branches. Leclercq et al inserted two LV leads and one right ventricular lead in 40 patients with atrial fibrillation and randomised them to either conventional biventricular pacing (BiVP), or to triple site ventricular pacing with two LV leads. They found no difference in clinical end-points, but some improvement in echocardiographic end-points (Leclercq 2008). Another small randomised controlled crossover trial of biventricular versus triple site ventricular pacing in 43 patients found improvements in some clinical and echocardiographic end points (Rogers 2012), although a further trial of 58 patients showed no difference in either clinical or echocardiographic end-points, and just a reduction in ventricular arrhythmias (Ogano 2013). Triple site ventricular pacing has been shown to improve AHR, in particular in patients with scar at the site of one lead (Ginks 2012b). In summary, these trials have not to date shown convincing benefits of triple-site ventricular stimulation over biventricular pacing.

Multi-point LV pacing activates multiple poles of a single multipolar lead, achieving multi-site stimulation within one vein. Currently, only St Jude Medical offer devices with this capability. An increasing volume of studies suggests that this may have benefit over conventional CRT, including an increase in clinical response (Gamble 2014, Pappone 2014,

2015, Rinaldi 2013, Zanon 2015), perhaps in particular in patients with scar in the area of the LV lead (Sohal 2015).

Chapter conclusions

As discussed above, multiple methods to choose an optimal site have been proposed. Animal and computer modelling suggests that an optimal pacing site would be expected. Clinical evidence to support prospective lead targeting is provided by the TARGET and STARTER trials of targeting the LMA using speckle-tracking echocardiography, although the mechanism behind the benefit of this approach remains unclear. In large trials there were not clear signals of an adverse outcome associated with a particular pacing site, apart from a benefit of basal over apical pacing. Multiple studies have used haemodynamic response to investigate pacing site selection, although there is limited evidence that this approach can improve clinical outcomes. There is very little evidence as to how these approaches might be linked together, and whether a hybrid strategy would be beneficial.

Chapter Five – **Methods**

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Introduction and aims

In the background sections and meta-analysis, I discussed the research literature to date around left ventricular (LV) endocardial pacing for CRT. There is some evidence to suggest that the technique may have significant benefits over conventional CRT, and certainly that it provides a valid alternative to CRT in those in whom conventional implantation via the coronary sinus is not possible and surgical epicardial lead placement is unsafe or unwanted. Concerns remain about the thrombotic risks in particular and the techniques for passing a lead across the inter-atrial septum are complex and difficult.

Endocardial pacing across the interventricular septum

These limitations stimulated Dr Betts (Consultant Cardiologist and Electrophysiologist at the Oxford Heart Centre, and the co-supervisor of this thesis) to consider alternative options for reaching the LV endocardium from the right heart.

His concept of a ventricular septal puncture to place a lead offers several potential advantages. With this approach there is no lead in the low pressure left atrium, where lead thrombi are more likely to form (Supple 2011), no atrial septal puncture , and a shorter left-sided lead length. These features may make lead thrombosis or paradoxical emboli less likely than with the atrial transseptal route. The LV is a larger cavity than the left atrium and has thicker muscle walls, reducing the chance of inadvertent perforation. The structure of the septal muscle seems to facilitate rapid tissue contraction around a defect. Another group have described ventricular septal puncture to access the left ventricle for endocardial ablation in one patient, in whom a cardiac MRI on the subsequent day confirmed complete closure of the interventricular septal puncture (Vaseghi 2013). Animal studies show that even large defects caused by the passage of an 18Fr sheath through the septum close spontaneously (Halabi 2013). This approach avoids lead interaction with the mitral valve, potentially preventing worsening of mitral regurgitation.

A small number of patients had already had LV leads placed by Dr Betts via this technique, in situations where there were no other good options, when I started my research. We then designed a formal study to assess clinical outcomes and safety of LV endocardial pacing using this new technique, LV CONSEPT: **L**eft **v**entricular endo**c**ardial pacing thr**o**ugh the ve**n**tricular **sept**um.

LV lead site targeting

As part of this study we also assessed where on the LV endocardium would be the optimal site for lead placement. As I have established in prior chapters, this is an area of

intense research and there are few clear answers, in particular as to how the techniques of choosing the site of latest mechanical activation and of latest electrical activation correlate with the acute haemodynamic response (AHR). Hence our secondary aim was to investigate optimal endocardial lead positioning.

Following on from this study, I wanted to further assess the interaction of these different techniques of LV lead targeting. In order to do this, I designed a study to try and ask the same questions in patients having conventional LV lead placement via the coronary sinus. Again, the main question was how the sites of latest mechanical activation and latest electrical activation correlate with AHR to LV pacing. This study was IDEAL-CRT: **I**ntra-cardiac haemo-**d**ynamics and **e**chocardiographic assessment to optimise **l**ead placement for **CRT.**

Longer-term follow-up of both LVCONSEPT and IDEAL-CRT will allow investigation of the effects of AHR on chronic outcomes, although even with the combination of these cohorts I do not expect that the number of patients will be adequate to provide any major contribution to this question.

Accuracy of haemodynamic measurements and the potential of non-invasive cardiac output monitoring

As discussed above, my experiments involve the assessment of AHR to biventricular pacing (BiVP) in various situations. The main parameter that I had planned to use to assess AHR was dP/dt max, which is well established as a method of assessment, as discussed previously. There is no established 'gold standard' in this area, although dP/dt max is by some way the most used parameter. However, its measurement by LV catheterisation and pressure wire placement is invasive, and not without some risks to the patient. These limitations, coupled with the lack of hard evidence of benefit from haemodynamically-guided lead placement, have restricted its use to research. A non-invasive technique to

achieve the same result would be of benefit to patients, and might potentially permit wider use of haemodynamic monitoring to guide CRT. There is also evidence that stroke volume and related parameters may provide different information about CRT acute response and might contribute to the prediction of chronic response.

Furthermore, knowledge of the level of precision obtainable in dP/dt max and related measures will allow me to assess the accuracy of my other experiments. Accordingly, throughout both studies I planned to assess cardiac output with a non-invasive method and assess the accuracy of this and its correlation with results recorded from dP/dt max.

General study methods

Clinical assessment

The aim of clinical assessment of patients after CRT is to objectively record patient outcomes. This is assessed with a mixture of symptomatic and functional assessment and imaging, predominantly echocardiography. The latter is more objective but does not necessarily correlate closely with symptomatic benefit for the patient (Fornwalt 2010).

Basic techniques used included:

- New York Heart Association (NYHA) class assessment. In order to attempt to make this more granular, I utilised the common sub classifications of classes. Class 2a was defined as dyspnoea after unusual exercise such as running or climbing ≥ 2 flights of stairs, and 2b as dyspnoea after brisk walking or climbing 2 flights of stairs (Spoladore 2010). Class 3a was defined as symptoms due to walking on level ground ~500 feet or 1 flight of stairs, and 3b as walking on level ground less than that (Thibodeau 2012). When calculating NYHA class results for the populations I represented these classes as 2, 2.5, 3 and 3.5.

- ECG: I performed a standard 12-lead ECG in all available ventricular pacing modes at each visit.

6 minute walk test

This is a standard test of cardiorespiratory function, aiming to assess the ability of the patient to function at a level close to normal daily life. I used a 20 metre corridor, the longest available (but shorter than the recommended 30m) but this was otherwise performed as per guidelines (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories 2002).

BNP levels

BNP (brain naturietic peptide) release is stimulated by cardiac stretch, and thus it is a relatively sensitive marker of cardiac function and status. It is recommended in guidelines for the diagnosis of HF, and some evidence supports its use in guiding HF therapy (Cowie 2010, Januzzi Jr. 2012, Roberts 2015). Levels are also influenced by inflammation, acute illness and multiple other factors (Januzzi Jr. 2012). In CRT follow-up, BNP has been shown to be decreased by CRT, and to be related to the extent of response to CRT (Fruhwald 2007, Januzzi Jr. 2012). Thus BNP provides an objective measure of CRT response.

Quality of life questionnaire

I aimed to record the potential benefit of CRT to patients in terms of improving symptoms, which although a subjective measure could provide insight into changes in outcome important to the patient's quality of life.

Studies of CRT have used several questionnaires, although the most commonly used tool is the Minnesota Living with HF Questionnaire. We would have liked to have used this, but at the time of starting the study we did not have funding for it, and so elected to use a

different measure. The EQ-5D-5L tool is a general health status questionnaire with extensive validation that has been used in other CRT studies (Herdman 2011). It is a simple questionnaire that asks patients to rate their quality of life, over five levels between no symptoms and severe symptoms, in five domains: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each level can be scored to produce an overall score for this section. Finally, they are asked to rate their current symptoms from 0 to 100 on a visual analogue scale.

The EQ-5D-5L has been shown to have moderate accuracy in assessing changes in HF status, although it is not as discriminatory of changing HF status as the 6-minute walk test and HF-specific questionnaires (Spertus 2005).

Clinical composite score

As a summary assessment of the patients change in HF status I chose to use the clinical composite score (CCS), as summarised in Figure 36 below, which has been suggested as the most valid outcome measure for CRT trials (Fornwalt 2010, Packer 2001).

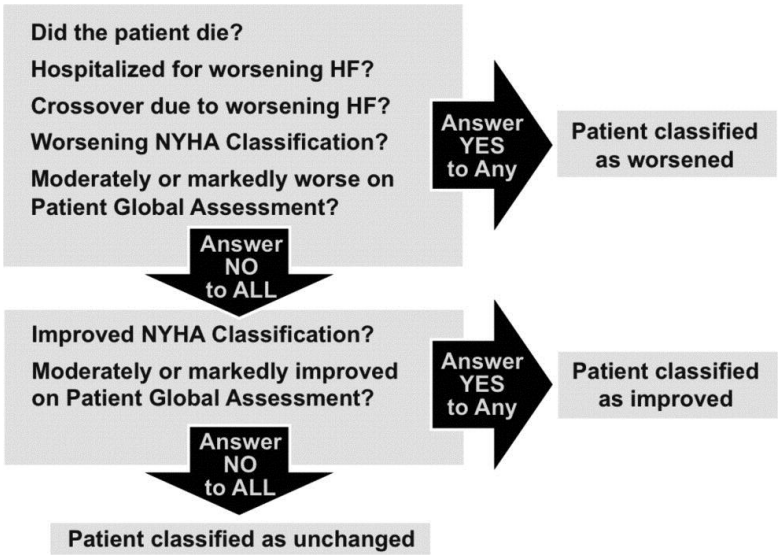


Figure 36- Packer Clinical Composite Score derivation. Diagram from Martin et al (Martin 2012).

Echocardiography

Echocardiography studies were performed on a Philips iE33 system by the author, who has British Society of Echocardiography transthoracic accreditation. Standard echocardiography good practice was followed, using a dedicated couch and ECG triggered recordings.

Assessment of LV chamber volumes was performed using 2-dimensional echocardiography according to the BSE guidelines (Wharton 2012), and used to derive a biplane model ejection fraction.

3D echocardiography was also performed to obtain pyramidal datasets of the LV from the apical view. 4-beat triggered loops were obtained to retain adequate temporal resolution of the 3D loop for speckle-tracking analysis. This requires a consistent heart rate, and thus these were not available in most patients with atrial fibrillation. As part of the analysis 3D LV EDV, ESV and EF measures were obtained.

2D echo analysis was performed in Philips Xcelera software.

Speckle tracking assessment

The principles of speckle-tracking echocardiography were discussed in the background chapters. I attempted to replicate the methods of the TARGET and STARTER trials as described in their papers (Khan 2012, Saba 2012).

I acquired multiple 2D loops of the left ventricle in the parasternal short axis view, at the basal and mid-ventricular level. The apical LV was not imaged as per prior studies, and as considerable evidence suggests this is not a valid target for LV leads. The field of view was adjusted in order to maximise frame rate at 60-80Hz.

Images were analysed using TomTec 2D cardiac performance analysis software version 1.2. I traced around the LV endocardial border in end-systole, and adjusted the automatically generated epicardial border to match the anatomy. The software then automatically tracks endocardial movement. The tracking was visually inspected and adjusted if segments were not adequately tracked.

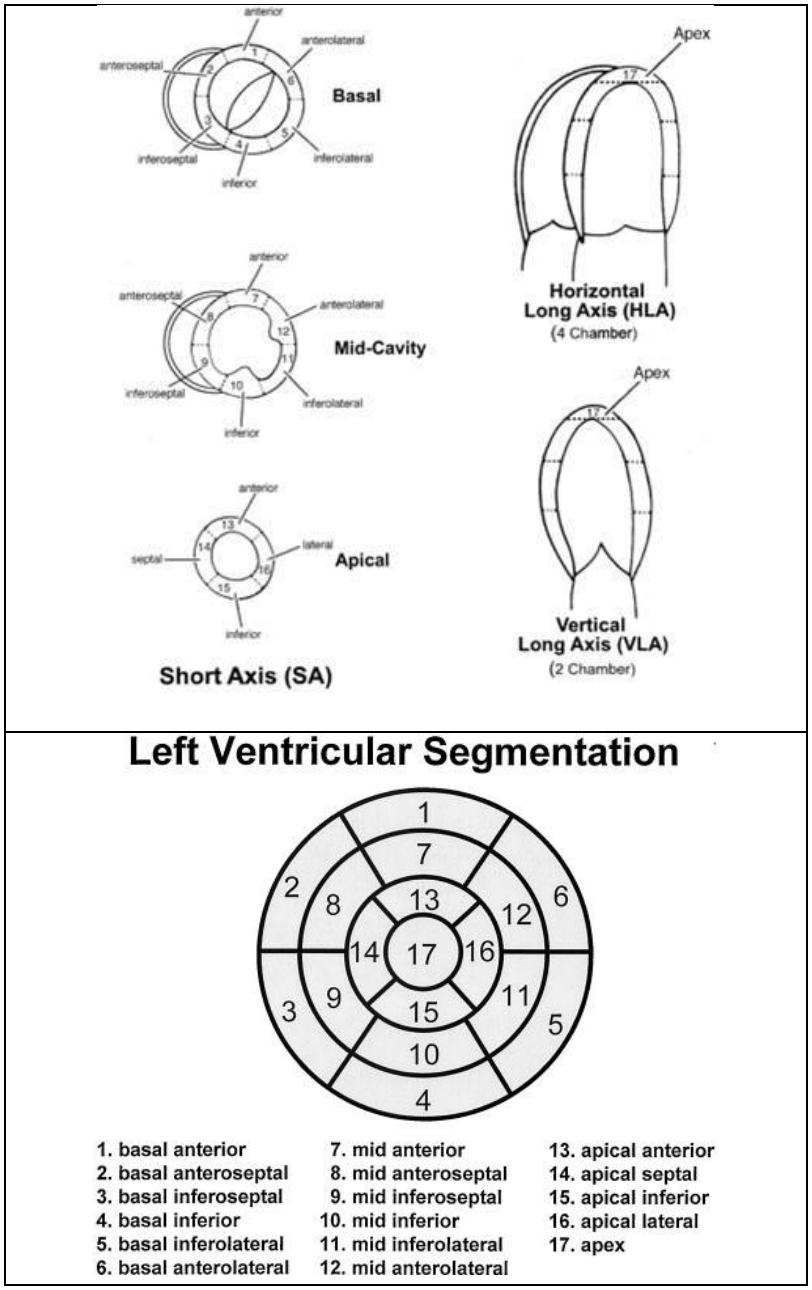


Figure 37 - LV segmentation, AHA 17-segment model. At the top echocardiographic views are shown, with the segment numbering and standard nomenclature below. Below a "bullseye" model is shown. From Cerquiera et al (Cerqueira 2002).

The software then generates radial strain curves for each of the 6 LV segments at the current level, which were mapped to the standard AHA 17-segment model of LV segmentation (Cerqueira 2002) (as shown in Figure 37 above). Time to peak radial strain is produced for each segment, along with the peak strain amplitude. Radial strain was chosen as this is the measure utilised in all other studies. As per the TARGET trial, segments with peak radial strain <10% were considered to be non-viable and excluded from consideration as a pacing site (Khan 2010, 2012). I also excluded segments with poor image quality such that the LV endocardium could not be tracked by the software or clearly seen for the majority of the cardiac cycle.

This process was repeated at the basal and mid-ventricular levels. The segment with the longest time to peak strain from all 12 segments assessed was then identified as the site of latest mechanical activation. A representative image is shown in Figure 38 below.

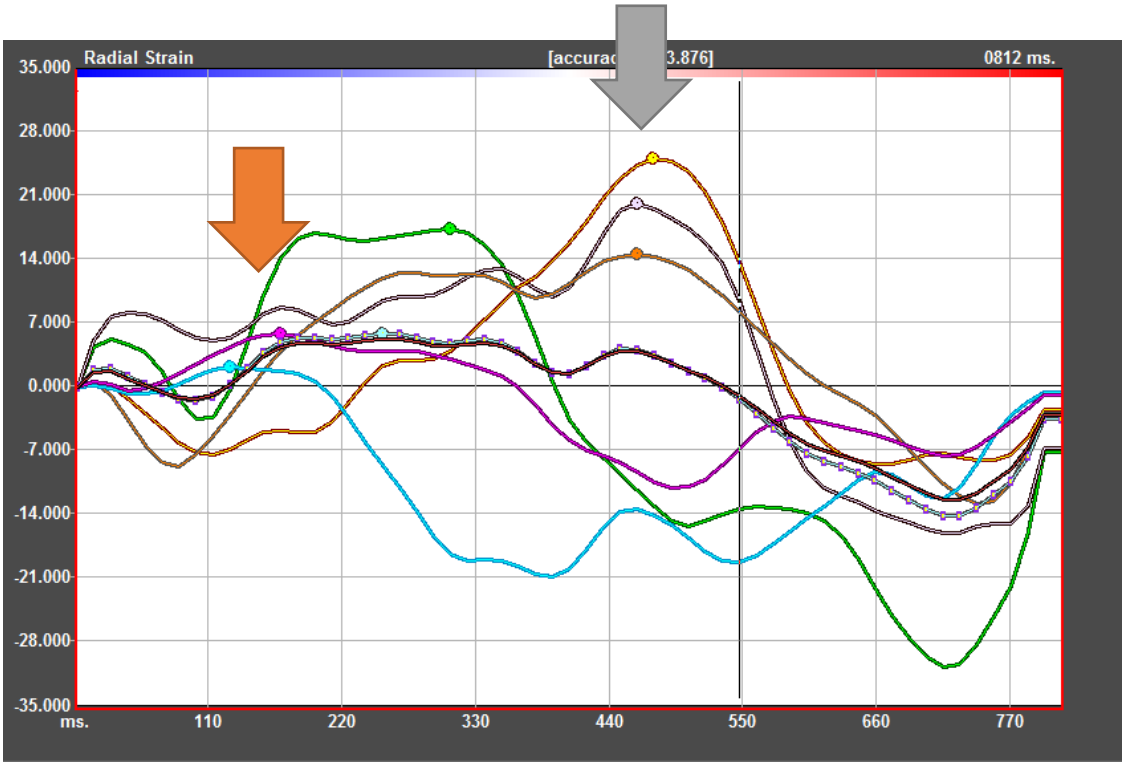


Figure 38 – LV 2D radial strain analysis example showing significant intra-ventricular dyssynchrony before CRT in a patient in the IDEAL-CRT study. The strain-time curves for each segment are shown. Peak strain in the posterolateral segments (green arrow) is much later than in the septal

segments (red arrow) which are also of low peak amplitude suggesting septal scar. The anterolateral segment in green is in between the two extremes. The point of the RV free wall insertion into the RV was labelled on the 2D images to allow the software to orient itself to the LV segmentation.

TomTec 4D LV analysis software version 3.2 was used to analyse the 3D dataset. The user selects landmarks within the LV, and the software then automatically tracks the ventricular endocardial contour. This can be corrected as needed, and the software then tracks the contours through the cardiac cycle. The final result is strain and time to peak strain analysis over all LV segments. There is not an established strain cut-off value to determine scar from 3D strain analysis, so there was not an obvious way to exclude scarred segments using this methodology. 3D strain analysis was not used in the RCTs, and so although I did perform it in addition this was used for secondary analysis.

The identified site of latest mechanical activation and any segments identified as likely scar were then mapped onto the 17-segment model, to be shown to the implanting physician.

Assessment of acute haemodynamic response to CRT

My primary method of assessing AHR to biventricular pacing was with pressure wire assessment of LV dP/dt max, as discussed in the background chapters. This was inserted via 6F radial or femoral arterial access, as appropriate for the clinical circumstances of the patient. A 6F MPA2 catheter was passed across the aortic valve and used to deliver a St Jude Medical (SJM) Certus pressure manometer wire. The MPA2 was then withdrawn into the ascending aorta, and the pressure wire was positioned in the left ventricular outflow tract. Patients who were not anticoagulated were given a 2500 unit bolus of intravenous heparin at the time of pressure wire insertion to minimise thrombotic risk.

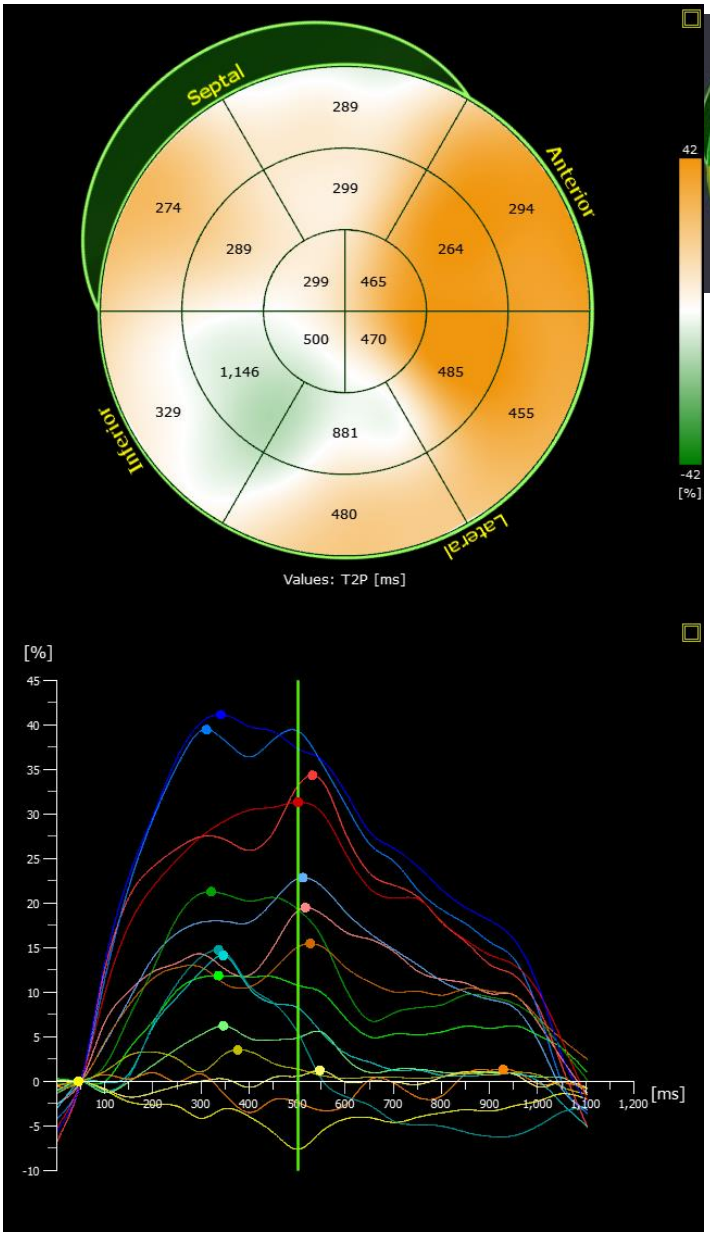




Figure 39 – 3D radial strain analysis example, again from a patient in the IDEAL-CRT study before CRT implant. At the top a map of time to peak strain is shown. At the bottom are the strain-time curves for each segment, which are coloured as per the map to the right. Again the lateral segments are late, with earlier septal contraction, and very low strain amplitudes in some of the inferior segments, suggesting scar.

The precise protocol of recordings varied between studies and so is discussed within the sections relating to the individual studies below. In all studies assessments were made of the AHR to BiVP relative to baseline measurements. These baselines were stable pacing at a heart rate of 80bpm (or faster when occasionally required to exceed sinus rhythm) in dual-chamber mode DDD A-RV pacing, or when patients were in atrial fibrillation RV-only VVI mode pacing. For tests the pacing mode was changed to biventricular pacing, and I waited 20-30 seconds to allow haemodynamic adjustment before making recordings during biventricular pacing.

The SJM Certus wire is a 00.036 cm/0.014 inch angioplasty wire, with a high-fidelity pressure manometer sensor 3 cm from the tip. The pressure wire is plugged into an analyser module (Radi-analyser express), which is connected to a laptop running the Physiomon software (St Jude Medical; version 2.01). LV systolic pressure is recorded at 200Hz, and used to derive LV dP/dt and thus dP/dt max and dP/dt min for each beat. The value of LVSP and LV dP/dt are plotted continuously, and time periods can be recorded by the user.

In the Physiomon software recordings can be reviewed and used to exclude beats. In all studies, ectopic beats were identified by their abnormal timing patterns, and the ectopic as well as the beats before and after it were excluded.

The results of each recording are stored in structured text files. I produced a Microsoft Excel (version 2010, Microsoft) sheet and associated macros which extracted the haemodynamic results from each beat and imported them into the main results spreadsheet for each patient. These results were then combined to produce a large dataset including each beat of analysis from all patients in the study.

AHR results were calculated as both *absolute* change and *percentage* change of dP/dt in the test state from dP/dt in the baseline state.

$$Absolute\ AHR = \frac{dP}{dt}max^{[baseline]} - \frac{dP}{dt}max^{[test]}$$

$$Percentage\ AHR = \frac{Absolute\ AHR}{\frac{dP}{dt}max^{[baseline]}}$$

Non-invasive cardiac output monitoring

As discussed above, I wished to investigate the possibility of assessing AHR to BiVP with a non-invasive cardiac output monitor. The system used was the Cheetah Reliant

bioreactance NICOM™, which uses two pairs of electrode stickers placed on the patient's chest to measure thoracic impedance and derive cardiac output. I will discuss this technique in more detail in the next chapter.

CRT response

As previously discussed, definitions of CRT response used have been extremely variable. Most authors have attempted to dichotomise response, and so I attempted to use the most commonly used cut-off limits from the literature, with particular reference to a prior systematic review of measures of CRT response (Fornwalt 2010).

Variable	Response Criteria
NYHA score	≥1 class decrease
LV EF	>5% absolute increase in EF
LV ESV	>15% relative decrease in volume
6 minute walk test	>10% relative increase in distance
EQ-5D-5L	>1 point decrease in score

Table 10 – Response Criteria used

LV CONSEPT study

LV CONSEPT: **L**eft **v**entricular endo**c**ardial pacing thr**o**ugh the ve**n**tricular **sept**um.

Two groups of patients were included in the study: firstly, patients with conventional indications for CRT (UK NICE 2007) who are not able to have lead implantation via the normal coronary sinus route due to adverse anatomy revealed during failed prior attempt(s); and secondly, patients with a successful conventional CRT lead placement who have not responded to the therapy, and in whom we felt that poor placement of the LV lead was likely to be a major determinant of non-response. For the latter group, we considered poor LV lead placement as positioning outside of the basal or mid anterolateral, lateral or posterolateral segments.

Objectives and end-points

Primary Objective

- To investigate if left ventricular transseptal endocardial pacing is safe and feasible in patients in whom conventional CRT implantation has failed and in non-responders to conventional CRT.

Secondary Objectives

- To assess the clinical response to left ventricular transseptal endocardial pacing for CRT in these patients
- To investigate the ability of this procedure with LV assessment techniques to choose the optimal position for the left ventricular lead, and to target the lead to this position.

Primary end point

- Freedom from adverse effects as defined below at 6 months post procedure
    - Acute: coronary artery damage; tamponade or effusion; acute lead displacement; peri-procedural systemic thromboembolism; arrhythmia; bleeding
    - Chronic: systemic thromboembolism; lead displacement, dysfunction or fracture; system infection; bleeding; arrhythmia

Secondary end points

- Procedural success rate
- AHR at the site of latest electrical activation and latest mechanical activation
- Change in NYHA class, quality of life assessed by EQ-5D-5L, 6-minute walk distance, BNP levels
- Change in LV EF and LV ESV
- Longer term safety and clinical outcomes over 2 years after the procedure.

Power calculations

As LVCONSEPT was designed as a pilot observational study intended primarily to identify safety issues and determine feasibility, the number of participants was intended to be sufficient to meet this aim. Accordingly, we decided to recruit 20 participants. No power calculations were done, as appropriate for a pilot study design.

Study participants

Inclusion Criteria	Exclusion Criteria
• Aged 18 years or above • Receiving optimal pharmacological therapy • Satisfy current NICE guidelines for CRT • Have failed CRT as defined by a failed attempt at placing a left ventricular epicardial lead via the conventional coronary sinus route **Or** • Non-responder to conventional CRT (non-response defined as no improvement in NYHA status, without clear evidence of echocardiographic response), with non-classical LV lead position and without other evident reasons for non-response	• Patients in whom, in the opinion of the investigators, an alternative route for LV lead placement would be safer or more effective for the patient • Contraindications to oral anticoagulation (e.g. HAS-BLED score of 4 or more, history of severe bleeding) or inability to safely take oral anticoagulation

All patients were recruited in Oxford, although we received referrals into Oxford for this procedure from both around the region and nationally.

Funding

This study was funded by

1. A competitive "Novel and Emerging Technology" research grant from the charity Heart Research UK.
2. Initial 'seed' funding from the Oxford Biomedical Research Centre

3. Donation of pressure wires and 3D electro-anatomic mapping pads from St Jude Medical Ltd.

Initial assessment

Patients were seen before the procedure, and the following items were recorded:

a) Consent and study recruitment
b) History and aetiology of heart disease
c) Current medications
d) ECG parameters (rhythm and QRS duration)
e) NYHA class
f) Symptom score – EQ-5D-5L questionnaire
g) 6 minute walk test
h) Blood tests for BNP
i) Echocardiogram, including LV chamber dimensions and speckle-tracking assessment of site of latest mechanical activation and scar distribution as discussed above

Procedural methods

All procedures were performed on therapeutic anticoagulation with warfarin at an INR of 2-3. The operations were performed under general anaesthesia for almost all patients, and conscious sedation for a few in whom this was felt to be safer. It was likely that a significant proportion of patients eligible for this study would already be on warfarin due to prior AF or other indications, given the known high frequency of other indications for warfarin in patients with severe HF. Non-warfarin oral anticoagulants (dabigatran, rivaroxaban, apixaban) have not yet been used in this indication, and there is some concern about their use in cardiac contexts outside atrial fibrillation stroke prevention (Boehringer Ingelheim Limited 2013), and so these were not used in this study. Use of warfarin during CRT implantation has previously been shown to be safe, with low rates of problematic bleeding in a large randomised controlled trial (Bernard 2012, Birnie 2013).

Ventricular septal puncture

The technique of trans-ventricular septal puncture was developed by Dr Betts over the first few cases using this approach. These cases preceded the formal LV CONSEPT study. The patients were individuals in whom conventional LV lead placement was not possible and surgical lead placement was too high risk or not wanted by the patients. In the first case trans-atrial septum LV lead placement had previously been attempted unsuccessfully.

I will describe the final study technique used, with some discussion of the evolution of the technique. A 6F sheath was placed in the femoral artery for arterial pressure monitoring and angiography. An incision was made over the existing generator and an extrathoracic subclavian vein puncture using a standard Seldinger technique was used to gain venous access. A 91cm deflectable 8.5F inner lumen catheter sheath with a tapered dilator (Agilis©; St Jude Medical Inc, Minnesota, USA) was passed over a guidewire into the right ventricle. Left ventriculography was performed in right anterior oblique and left anterior oblique views to identify the LV borders. In earlier patients an angiogram of the left coronary arteries was performed to ensure the puncture site was not adjacent to a major septal perforator vessel, but as we gained confidence and consistently found a lack of perforators in the puncture area, we decided this was no longer needed.

During the development of the technique, in the first 3 cases, a rigid Brockenbrough needle and radiofrequency needle were used to puncture, but it was consistently found that the use of the rigid needle straightened out the curve of the deflectable sheath and dilator, advancing the puncture site apically. In the first 2 patients, contrast injections following the initial puncture showed subendocardial staining of the lateral apical LW wall and it was not possible to advance the guidewire. In both a second puncture attempt was required to allow easy passage of the wire and then sheath and dilator into the LV cavity. Use of a guidewire allowed for a greater degree of sheath and dilator flexion to get to a

more mid-basal puncture site as passage of the wire to the dilator tip did not alter the shape and position. Withdrawing the dilator to a position proximal to the curve in the sheath allowed an even more acute angle and basal puncture site. Use of the guidewire and diathermy pen radiofrequency energy technique resulted in the quickest positioning, puncture and advancement of the sheath and dilator assembly.

The sheath and dilator were deflected and rotated to position the tip on the mid-septum, with reference to the ventriculogram in LAO and RAO fluoroscopic views (see Figure 40 below.) In order to allow a tighter bend of the sheath and thus attain a basal puncture site, the dilator was partially withdrawn. The septum was punctured using the stiff, straight proximal end of a 0.032 inch guidewire, which was passed through the sheath to rest against the septum. A diathermy pen was then used to deliver 30W of energy in short intervals to the proximal end of the wire, whilst carefully probing through the septum. When the wire was felt to give and move into the LV cavity, the dilator and sheath were advanced. The guidewire was withdrawn to confirm flow of pulsatile, oxygenated blood, and then reversed and moved further into the LV cavity, in order to safely advance the sheath fully across the septum.

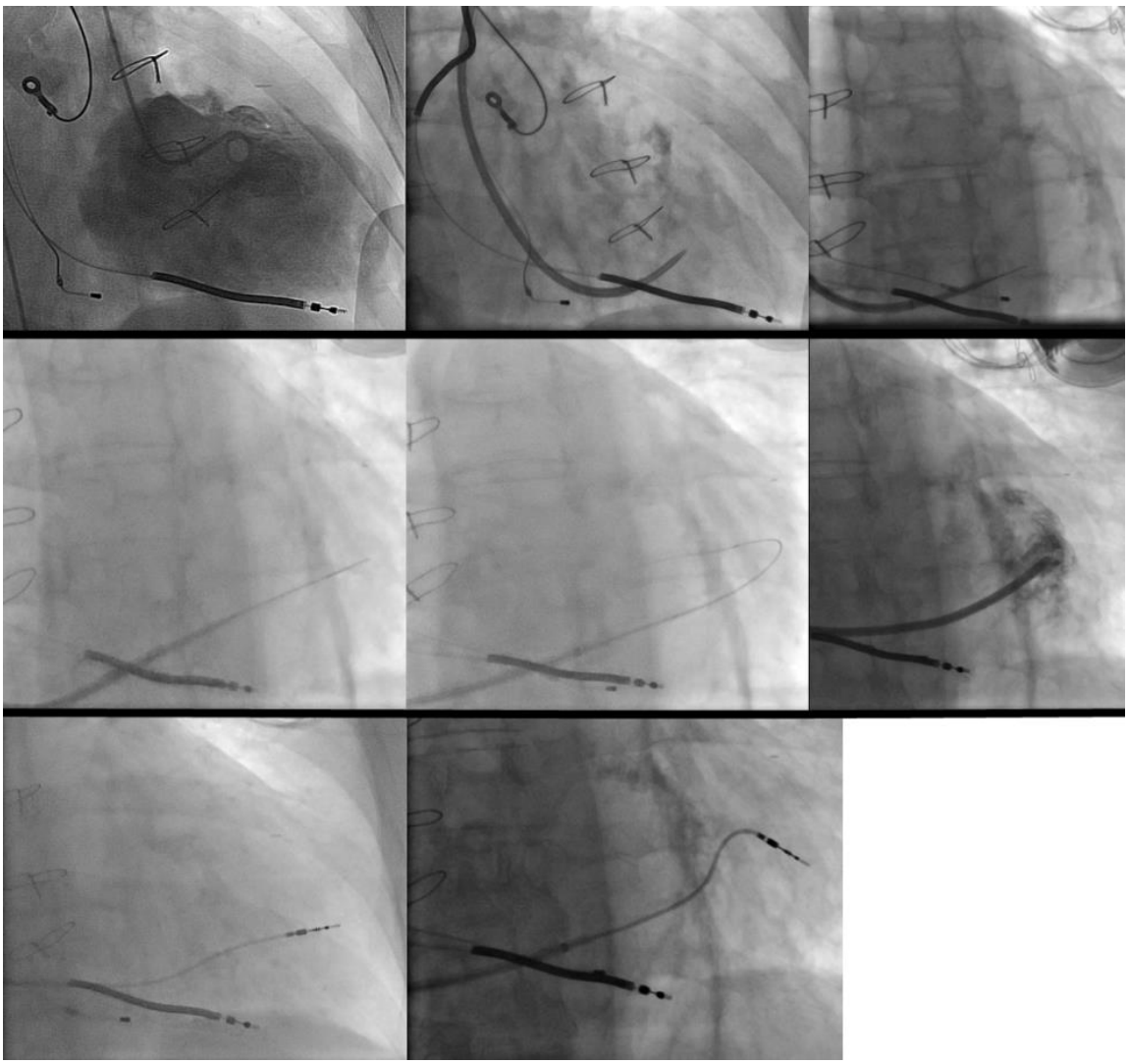


Figure 40 - Images of procedure. From top left, all in right anterior oblique view: Left ventriculogram; flexible sheath with tip perpendicular to the interventricular septum; wire is moved forward onto septum;

Middle left in RAO view: straight end wire is pushed across the septum into the LV; wire reversed and curved in LV; sheath passed into LV, contrast injection shows LV endocardium.

Bottom left: final lead position, RAO view; final lead position in the anteroposterior view.

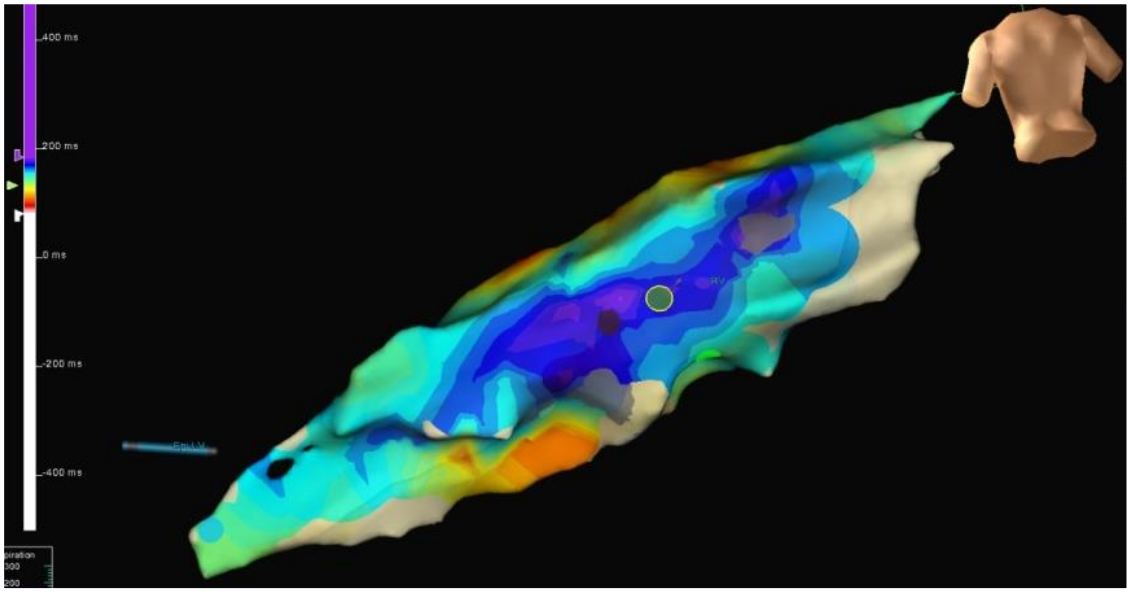
Electro-anatomic mapping

Once LV access had been attained, we mapped the LV activation pattern using the St Jude Medical 'NavX' electro-anatomic mapping (EAM) system. This uses 6 sensors on the patient to generate a 3-dimensional electrical field, which is sensed via the catheter tips and used by proprietary software to locate the tip in 3D space. This allows a 3-dimensional map to be built up with both the endocardial voltage sensed at the catheter tip and the associated cardiac morphology.

A decapolar electrophysiology catheter was placed into the LV via the Agilis steerable sheath and used to map LV endocardial activation, initially during pacing from the RV lead, which was connected into the electrophysiology lab system so that it could be used to pace and also visualised on the 3D EAM map. The map allowed identification of the site of latest electrical activation, which we defined as the latest area of activation without scar (identifiable by low voltage signals on the EAM map).

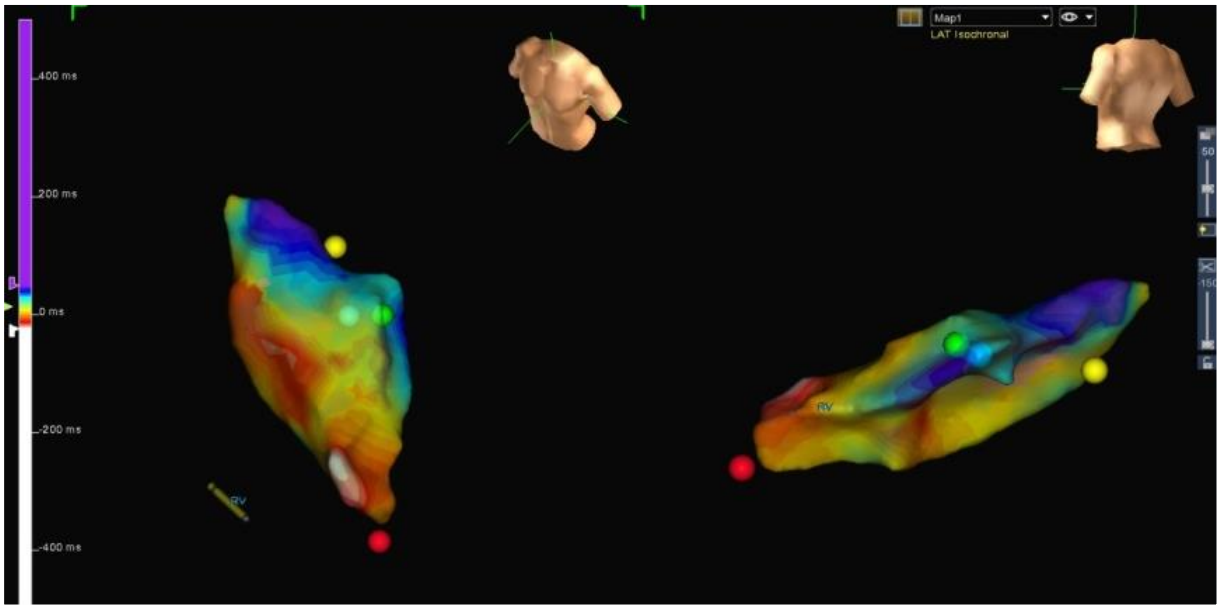
The LEA site was then mapped onto a segment of the 17-segment LV model used for echocardiography, using the RV lead, interventricular septum and aortic outflow as reference points to assist accurate location of the segments. Example maps are shown below in Figure 41. During the mapping and pacing protocol, heparinised saline was infused through the sheath to prevent thrombosis.

Figure 41 – Two examples of electro-anatomic mapping.



TOP: a view of the left ventricle from the postero-lateral aspect. The colour codes the extent of electrical delay, showing a clear area of delayed activation in blue-purple in the basal-lateral area of the LV. The green dot in the centre of it denotes a pacing site.

BOTTOM: two views of the LV in a second patient, again showing a baso-lateral area of late activation, extending down the lateral wall. The red dot is an apical pacing site, the green and blue dots lateral sites, and the yellow dot is a pacing site in the basal area showing latest electrical activation. The RV apical lead is included in the map and shown at the bottom left.



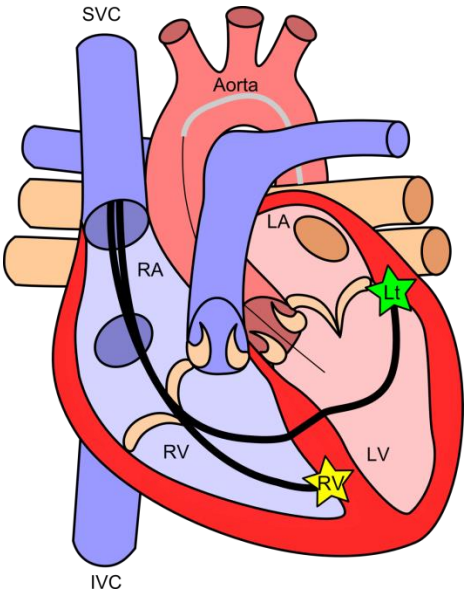


Figure 42 – Diagrammatic representation of catheter and pacing lead positions in LVCONSEPT. A standard RV lead was already present. The LV was accessed via interventricular septal puncture, with a lateral pacing site shown. The pressure wire was placed in the LV outflow tract. If an RA lead was present, it was not used during the pacing protocol.

Pacing protocol

We then assessed AHR at several sites within the LV, aiming to investigate the optimal pacing site for the patient. We targeted sites with likely benefit based on existing evidence, so paced at the below sites. The sequence of sites was computer-randomised on a per-patient basis to minimize order-effect bias.

1. The segment of latest mechanical activation (LMA), as determined on the pre-procedure echocardiogram.
2. The site of latest electrical activation (LEA) during RV pacing, as determined on the intra-procedural LV EA map.
3. Empirically on the baso-lateral wall, as this is the site most often recommended as the optimal empirical pacing site for LV pacing via the coronary sinus.
4. At the LV apex, as a 'control' LV pacing site that would be expected to be inferior to the other sites.
5. When patients had a pre-existing coronary sinus lead, the LV endocardial site that was as close as possible to the lead. This was assisted by connecting the LV lead into the EAM system so that it could be visualised as part of the map.

In the first patient we performed this pacing procedure using the final pacing lead, but this was hard to manipulate within the LV cavity, and so thereafter we switched to using the same EP catheter used for the EA map to pace the LV. The EP system only allowed pacing at two simultaneous sites, so we could not perform sequential DDD-BiVP pacing in this study. Instead all protocols were performed using RV-LV BiV pacing in VVI mode. The majority of patients in the LVCONSEPT study were in atrial fibrillation and without atrial activity, so DDD pacing would not have be an option for most patients.

At each site, once the LV catheter had been navigated to the site and any ectopic beats had settled, we recorded the baseline state in RV pacing at 80bpm over 30 seconds, with concurrent recording of invasive haemodynamics and NICOM cardiac output. Then simultaneous RV-LV BiVP was commenced and the AHR was calculated as the difference between baseline mean dP/dt max and during BiVP, as illustrated in Figure 43 below.

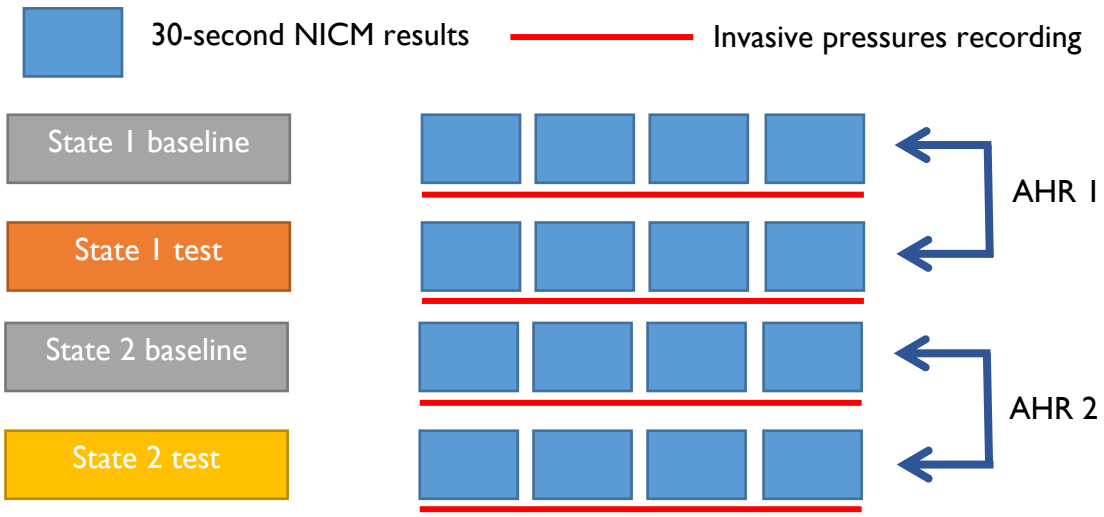


Figure 43 - AHR assessment protocol for LVCONSEPT study.

In order to assess reproducibility, we repeated one randomly chosen measurement in each patient.

At each site I recorded the QLV time during RV stimulation, which as discussed above was the time from the start of the surface ECG Q wave until the peak EGM activation at the pacing site. The width of the surface QRS was also recorded, using a 12-lead ECG during each pacing intervention (including baseline RV pacing recordings).

In summary, at each site I recorded:

a) Segment (17-segment model)
b) QLV time
c) QRS width
d) AHR to BiVP

Lead placement

Once the pacing protocol was complete, AHR results for each site were calculated. The target LV pacing site was the site with greatest AHR. The Agilis deflectable sheath was exchanged for a slit-able, deflectable lead delivery catheter and dilator (Medtronic Attain© or Select Secure©; Medtronic, Minneapolis, USA), which was steered towards the lateral LV wall target site. An active fixation bipolar pacing lead was delivered through the sheath and connected to the EAM system, allowing visualisation of the lead tip with the system to assist in steering it to the identified target site. Lead parameters were assessed after fixation at the site, and high output pacing was performed to assess for phrenic nerve stimulation. The delivery catheter was slit and withdrawn before the lead was secured and attached to the generator.

For the initial procedures we used a standard Medtronic CapSureFix 5076 7.2 French active fixation pacing lead. Later the Medtronic SelectSecure lead became available to us, which is a 4.1 French lumenless pacing lead. The lead itself is rotated in order to screw the active fixation tip into the endocardium. We felt that the small diameter and resulting

reduced surface area of this lead might potentially reduce the risk of thromboembolism from the lead, and so switched to using this lead.

After lead fixation the leads were connected to a standard CRT device. We re-used the patient's existing device if it was appropriate and if they had adequate battery life remaining.

After the lead had been attached to the generator, we reassessed AHR to BiVP at the final pacing site.

Post procedure

The CRT device was programmed in the standard manner. We used a ventriculo-ventricular delay of 0 as long as this produced a prominent R wave in V1, with LV pre-excitation programmed if this was not the case. AV intervals were set empirically at a short interval of 120-130ms as per our normal practice. We did not perform routine CRT optimisation.

The patients were kept in hospital overnight and monitored. On the subsequent day they had a chest x-ray to confirm no movement of the pacing leads, and a device check to confirm normal function. If these were satisfactory they were discharged, on therapeutic anticoagulation with warfarin.

For the first few procedures done outside the trial, and the initial trial cases we aimed for an INR target of 2-3. There is no consensus on the ideal INR target for patients with endocardial leads, with a variety of protocols used in the literature. We subsequently had one patient who had a stroke, as will be discussed in more detail in the LVCONSEPT results chapter. Accordingly we modified our protocols to aim for a target INR of 2.5-3.5. All patients were contacted at this stage (8 months after the entry of the first patient into the trial) and asked to increase their INR target.

Follow up

My aim with follow up was to achieve relatively close follow up over the first 6 months to track patient response to CRT, and then to continue long term follow up, looking mainly for complications, as prior trials have shown that the benefit of CRT is normally evident over the first 6 months (Cleland 2013).

	Pre-assessment	*6 week follow-up*	*3 month follow-up*	*6 month follow-up*
Current symptoms and status	✓	✓	✓	✓
Consent to study	✓			
Symptom questionnaire	✓	✓	✓	✓
Examination	✓	✓	✓	✓
ECG	✓	✓	✓	✓
Echocardiogram	✓		✓	✓
BNP level	✓		✓	✓
6 minute walk test	✓	✓	✓	✓
Device check		✓	✓	✓
Chest X-ray			✓	

Table 11 – summary of events at each visit.

Several of our study recruits lived at a considerable distance from Oxford, and so I combined the 6-week and 3-month visits in some of these patients to reduce the burden on them.

At follow-up transthoracic echocardiography, in the same manner as pre-procedure, was performed to assess LV volumes and systolic function and to assess for evidence of flow across the septal puncture site. Device checks were performed to monitor lead pacing parameter stability, and in addition a chest x-ray was done at 3 months post procedure to confirm lead stability.

IDEAL-CRT study

IDEAL-CRT: **I**ntra-cardiac haemo-**d**ynamics and **e**chocardiographic assessment to optimise **l**ead placement for **CRT**

Objectives and end-points

	Objectives	**Outcome Measures**
Primary	To assess whether pacing at the site of latest mechanical activation produces the maximal acute haemodynamic response to biventricular pacing, when compared to pacing at a conventional empirical LV pacing site.	AHR to pacing at each site
Secondary	To assess if further increases in acute haemodynamic response at the site of latest mechanical activation can be achieved with different pacing configurations	AHR with different pacing configurations
	To assess how electrical activation patterns, measured as QLV times within the coronary veins, correlate with AHR and mechanical activation	AHR relationship to QLV

Power calculation

With a sample size of 22 patients, I calculated that the probability of detecting an 8% absolute difference in AHR between sites, by making a T-test comparison of the average AHR at each site, was 88% (i.e. the power). Previous studies investigating AHR at different pacing site have detected changes of at least this magnitude and used this methodology (Duckett 2011). As discussed in more detail below, the approach of using T-tests to make

the comparison in this manner may lack validity, but this was the method I used at the time when I was planning the study, after discussion with a statistician.

Study participants

I wished to recruit a standard CRT population, so inclusion criteria were broad, and I only excluded patients if pressure wire haemodynamic assessment would be unsafe.

Key Inclusion Criteria	**Key Exclusion Criteria**
• Patients with a standard indication for cardiac resynchronisation therapy undergoing this procedure in Oxford.	• LV EF >35% • Severe peripheral vascular disease (that would make arterial access more risky) • Haemodynamic instability (such that a longer procedure is inadvisable)

Initial assessment

This was essentially identical to LVCONSEPT:

- Focused medical history, indications for CRT assessed
- Current symptom status
- 6-minute walk test
- EQ-5D-5L quality of life questionnaire
- ECG
- Echocardiogram:
    - Standard images for chamber volumes and ejection fraction
    - Dys-synchrony assessment
    - 2D and 3D images for speckle-tracking analysis to locate the site of latest mechanical activation
    - From this I derived a segmental map of the left ventricle, with a target segment of latest mechanical activation to guide the lead implant procedure.

Procedure

As discussed above, the aim of the study was to assess the acute haemodynamic effects of pacing at the site of latest mechanical activation versus the empirical lateral site that would normally be chosen. Thus I aimed to assess two veins per patient, a vein in the LMA segment and the vein the operator would otherwise have chosen.

We obtained arterial access, preferentially via the radial artery. The right ventricular and right atrial leads were placed as normal at the start of the procedure. A coronary sinus venogram was performed (as is routine for most operators) to identify venous branches that were potential targets for a LV lead. A 30-40° left anterior oblique view of the CS was acquired in order to correlate with the echo images as per the methods used in the TARGET and STARTER trials, as shown in Figure 44 below.

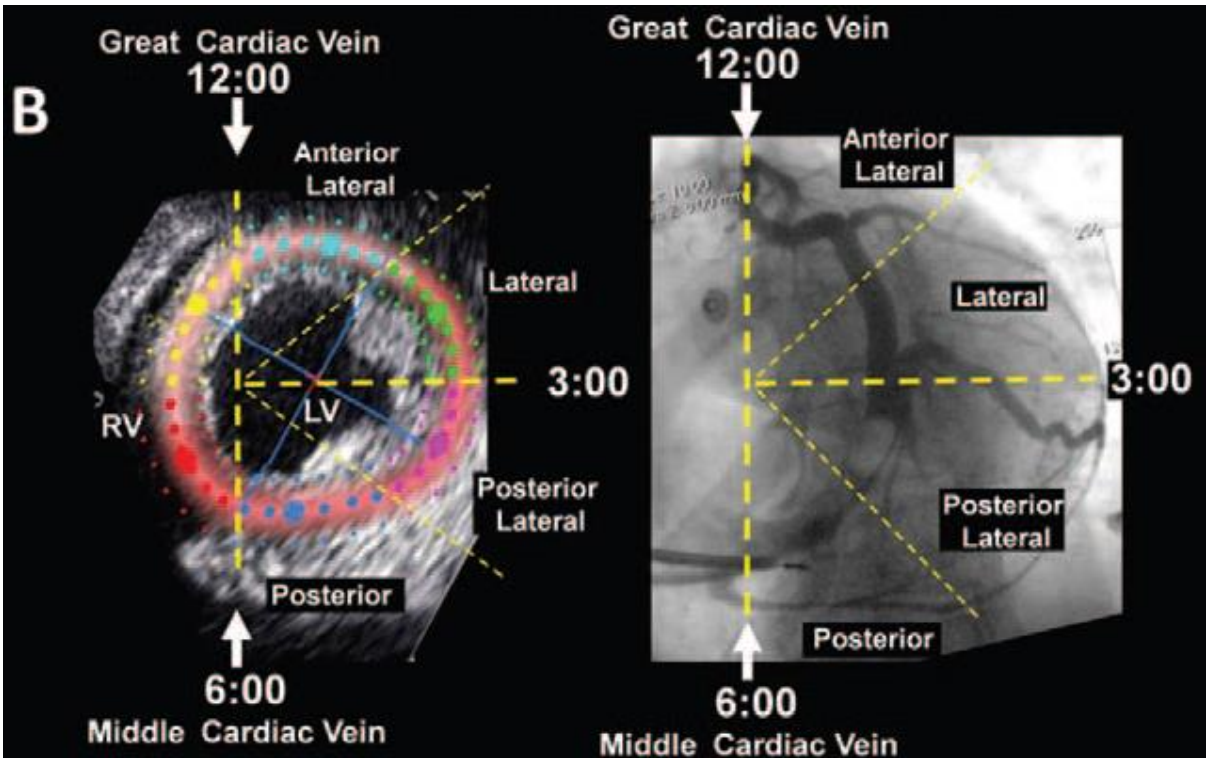


Figure 44 – Mapping of echocardiographic segments to the left ventricular anatomy, from the STARTER trial publication (Saba 2012). On the left is the parasternal short axis mid-ventricular view, with segmentation of the non-

septal segments superimposed. On the right is the LAO 40° projection of the coronary venous system showing the same segmentation.

After the venogram, but before the results of the speckle tracking were revealed, the operator was asked to nominate (in order) their preferred target veins. I then revealed the LMA segment and we identified a target vein within that segment, or in an adjacent segment if there was no suitable vein within the LMA segment. If the operator had already chosen that vein as their first choice, we used their second choice vein as the comparator vein, such that the comparison was always made between the LMA vein and a suitable empirically chosen vein.

The protocol was written to not specify the choice of LV lead used; operators were free to choose bipolar or quadripolar leads of any manufacturer as required. In practice, our centre uses a large volume of St Jude Medical quadripolar LV leads, and these were actually used in all patients.

The LV lead was initially placed in the comparator vein (i.e. the vein not within the LMA segment) and AHR to BiVP in this vein was assessed. Subsequently the lead was moved into the target LMA vein, and the AHR re-assessed. Ideally I would have liked to have randomised the order of vein choice, but this would have excessively prolonged the procedure, as if the non-target segment was the second vein to be assessed we would have then had to move the lead back to the first vein. It took several minutes to move the lead, so this allowed a period of haemodynamic normalisation, such that I would not expect significant order effect.

The anatomical location of each assessed vein was located on the 17-segment map, and each vein was classified as to whether it was in the lateral segments or not.

AHR assessment

I modified the AHR assessment protocol from the LVCONSEPT protocol. In that protocol we were assessing 4-5 sites, with only one pacing configuration per site, and it was practically slow and difficult to move between sites. This limited the number of repeats that could be performed, but I compensated for this by recording long 2-minute periods of haemodynamics at each site and baseline.

For this protocol, I wished to assess the differential between the responses at each pole of a quadripolar lead as well as between veins. The pacing configuration could be quickly and easily changed and repeated multiple times in order to ensure an accurate assessment. Accordingly I changed the protocol to involve multiple 30-second recordings, with a baseline 30-second recording before and after each pair of test BiVP configurations. The order of the tests within the vein was randomised per-patient. The AHR was calculated relative to the mean of the baseline values before and after each pair of tests.

This protocol is based on that recommended by Thibault et al, who carefully investigated reproducibility of dP/dt max recordings in a similar experiment (Thibault 2014). They assessed a baseline after each test, and repeated each test multiple times. Based on their data and the data I had already acquired from the first LVCONSEPT patients, it was evident that short-term error between baselines was small, and so I decided to repeat a baseline after each pair of measurements rather than after every one. This also reduced the time taken to undertake the protocol.

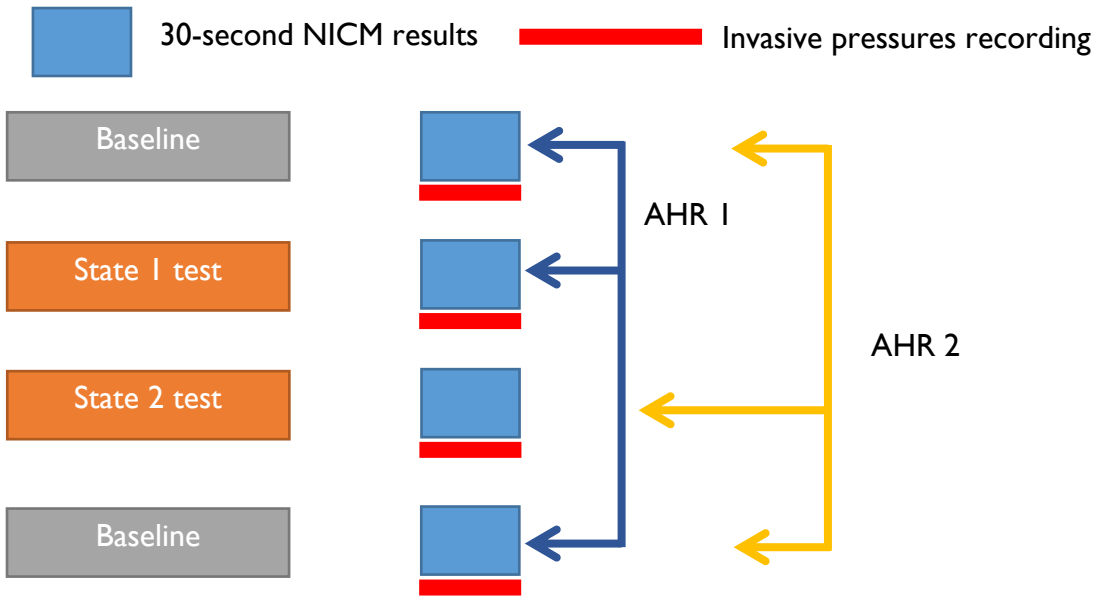


Figure 45 – AHR assessment methodology used in IDEAL-CRT. Each BiVP test was compared against the mean of the baseline recordings before and after it.

The other modification from the LVCONSEPT protocol was that pacing was performed using a St Jude Medical Pacing System Analyser, which allows 3-channel Atrial-RV-LV biventricular pacing. Thus all pacing was performed using AV sequential DDD pacing at 80 bpm, or 5 bpm above the patient's intrinsic atrial rate if faster, with a fixed AV interval of 110ms in order to ensure reliable ventricular capture. VVI pacing was used for patients in atrial fibrillation. Baselines were DDD RV pacing, and tests were DDD RV-LV biventricular pacing with no interventricular delay.

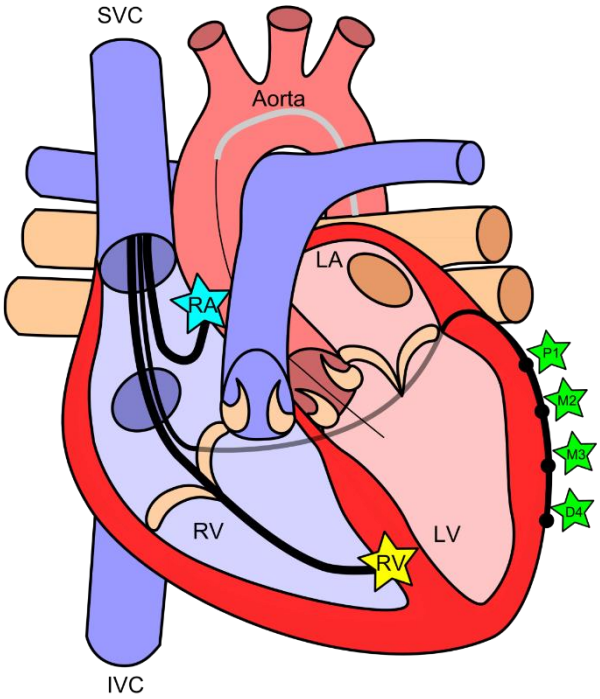


Figure 46 – Diagrammatic representation of pacing in IDEAL-CRT, showing A-V sequential biventricular pacing at four poles of a quadripolar lead placed via the coronary sinus, as well as a pressure wire placed via the aorta.

Biventricular pacing was assessed using each of the four poles (D1, M2, M3, P4) of the quadripolar lead as the cathode and a metal plate instrument in the device pocket wound as the anode for unipolar pacing. This allowed the effective isolation of the effect of pacing at each pole, rather than using a local anode and potentially complicating the effects with anodal interactions. On the first occasion that each pole was used in a vein, I checked that reliable capture was occurring without phrenic nerve stimulation. All pacing was performed at 5V output. Accordingly, in each vein 12 test measurements were made (4 poles, 3 times each) with 7 baseline measurements.

I did not attempt to localise each pole to a left ventricular segment, as we did not feel that this was practical. All poles were considered as being in the same segment for analytical purposes.

As in LVCONSEPT, the NICOM machine was used to non-invasively measure haemodynamics, with multiple single 30-second recordings rather than four sequential recordings as in LVCONSEPT.

After the pacing protocol had been completed in the comparator vein, the lead was moved to the LMA target vein. At this stage the operator continued the procedure and secured the lead and removed the sheath used to implant the lead. Whilst the operator continued the procedure, AHR in this vein was assessed using the same technique, with pacing performed via the device itself rather than the PSA but with all other settings identical.

The pressure wire and sheath were removed after all measurements are complete.

In both veins, QLV measurements were made during RV pacing from each pole of the quadripolar lead during RV pacing, in the same manner as previously described.

Follow up

Patients were seen at 6 months post procedure to assess response to CRT. The same tests were performed as pre-procedure, and used to derive the Packer Clinical Composite Score as for LVCONSEPT.

DOUBLE-CRT study

DoUbLE-CRT: Dual Site Left Endocardial Pacing for Cardiac Resynchronisation Therapy

This trial is still incomplete, and final results will not be included in the thesis, but some data from it will be used in the subsequent chapter, and so I will discuss the study design.

The primary objective of this study is to assess if dual-site left ventricular endocardial pacing produces a larger acute haemodynamic response than biventricular pacing from the left and right heart. This will be measured similarly to IDEAL-CRT based on AHR.

In order to access multiple ventricular sites we needed patients having procedures with access to the left side of the heart. Accordingly, the patient group chosen were patients undergoing VT or AF ablation procedures in Oxford, in which the left heart is routinely accessed for ablation. In order to select a group comparable to CRT candidates we chose patients with abnormal LV function. We did not mandate conduction abnormalities, as LBBB would be induced by RV pacing during the procedure.

Procedure

All data was collected during the procedure. All patients were in a steady state under general anaesthesia. We achieved arterial access, and placed a left ventricular pressure wire as in the above protocols.

The left ventricle was accessed with two catheters, with a combination of retrograde aortic access and puncture of the inter-atrial septum, as used routinely for electrophysiology procedures. Left ventricular activation maps were acquired similarly to LVCONSEPT during RV pacing.

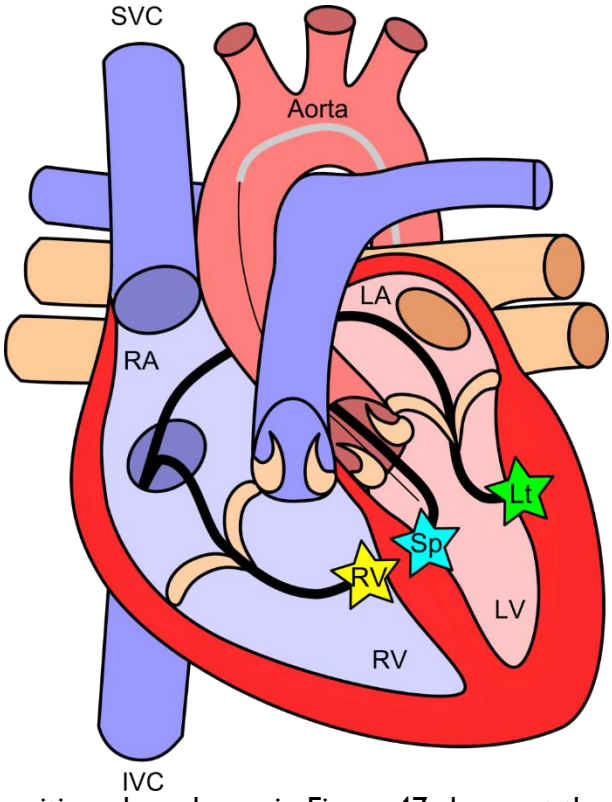


Figure 47 - Diagrammatic representation of catheter positions for the DOUBLE-CRT study. RV – right ventricular pacing site, Sp – LV septal site, Lt – LV lateral site (at the site of latest electrical activation).

Electrophysiology catheters were positioned, as shown in Figure 47 above, at the right ventricular mid septum, and at the:

1. Left ventricular septum, as close as possible to the endocardial aspect of the RV catheter
2. Left ventricular lateral wall, at the site of latest electrical activation identified from the activation map

This provided two single-site LV pacing configurations, which could be combined to produce dual-site configurations:

3. RV and LV septal
4. RV and LV lateral
5. LV septal and LV lateral

As in LVCONSEPT, pacing was delivered via the EP system, which was limited to two-channel pacing. Accordingly, all pacing was done in VVI mode at 80 bpm (although similarly, a majority of the patients were in AF).

Pacing protocols were performed similarly to IDEAL-CRT, with a baseline of 30 seconds of RV pacing followed by two 30 second test configurations, and then a further baseline. The five pacing configurations listed above were tested, in a randomised order, 3 times each. QRS duration was measured in each configuration.

There was no follow up for patients in this study.

Statistical analysis

Most prior studies using similar methodology have used quite simple analyses to compare results across and between pacing sites or modalities. Almost all authors have simply taken the mean of each group, for example the results at each vein in IDEAL-CRT, and compared the means using T-testing. Given the literature, this was the approach I originally intended to take, and indeed the power calculations for IDEAL-CRT and DOUBLE-CRT were based on this methodology, after initial discussions with a statistician.

After further thought, and additional discussion with the statistician it became clear that this approach is limited. My data will include multiple levels of clustering, with results influenced by patient-level and repeated-measures effects. There would be expected to be an influence of individual patient-related factors on AHR in a given configuration, and so simply performing tests on the results of pacing in a particular configuration over all patients is not valid. The average of all results would be unduly influenced by outlier results in one or a small number of patients. One of the key assumptions underlying T-testing is independence of data points within the average from each other (Field 2013), which is not the case in this situation.

Furthermore, tests results were repeated multiple times during an experiment to ensure reproducibility, but this will also introduce further data clustering from the repeated measures and further violate the assumption of independence. Although other authors have suggested using repeated measures designs like this in order to ensure that the effects of pacing interventions are separated from random noise (Thibault 2014), they have not allowed for this in the analysis (Thibault 2013) so this approach is susceptible to undue bias from the influence of patient and test-retest variability.

Some authors have taken account of this using ANOVA (analysis of variance) (Zanon 2014), which allows for patient-level variability, but can be problematic with multiple levels of patient and repeated-measures variability. In particular, the number of repeats will vary from patient to patient depending upon the number of available pacing sites or configurations, producing data referred to by statisticians as 'unbalanced' (i.e. different numbers of samples per patient), which breaks one of the key assumptions of ANOVA (Field 2013).

The other problem with analysis of AHR by invasive haemodynamics is that the procedures are always complex, and accordingly the numbers of patients recruited have universally been small, as in my studies. This limits the power of analysis. One potential method to improve the discrimination of the data would be to increase the data sample size by analysing every beat rather than averages. This is complex multi-level data, and after detailed discussion with a statistician I was advised that this approach would be best assessed using multi-level modelling with random effects. Other authors have used this for analysis of similar data (Zanon 2014).

Mixed-effects multilevel modelling

The generalised linear mixed model (GLMM) has "become widely recognised as one of the major [statistical] methodological developments of the second half of the twentieth century" (Berridge 2011). Essentially GLMMs are a more complex example of analysis of variance (ANOVA) and linear models, and can be used for analysis of multi-level correlated or clustered data.

Crucially, GLMMs do not assume normal distribution of the dependent variables, and can accommodate a mixture of dependent variable types (for example normal and binomial "yes/no" data). GLMM analysis accounts for multi-level data such as mine by allowing random factors to vary alongside the parameters under assessment, which in the case of my data are the errors attributable to the patient and the recording repeat. The GLMM analysis then assesses the variation not attributable to these random errors. The patients and recordings are assumed to be random samples from the population of all possible patients and recordings within that patient.

Analysis was performed using R (version 3.2 (R Core Team 2015)), which is an open source programming language designed primarily for statistical analysis. Multiple additional packages implementing statistical methods are available. Almost all analysis was performed using R, with a few simple analyses performed in Microsoft Excel. The package *lme4* (version 1.1-7) was used for mixed effects modelling (Bates 2010) and *ggplot* (version 1.01) was used for graphs (Wickham 2009). The *lmerTest* R package (version 2.0) was used to derive P-values for GLMM models, using the Satterswaite method to produce P values for comparisons (Bates 2010).

Study ethical approval and registration

All three studies had prospective ethical approval and were registered on clinical-trials.gov.

Study	Ethics registration number	Clinical-Trials.Gov reference
LV CONSEPT	13/SC/0186	NCT01818765
IDEAL-CRT	14/SC/0148	NCT02061241
DoUbLE-CRT	14/SC/1286	NCT02211456

Chapter Six – Reproducibility of assessment methods

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Introduction

In this chapter I will attempt to assess the reproducibility and accuracy of the methods I use in this thesis. In particular, I will assess the use of invasive dP/dt max and a non-invasive cardiac output monitor to measure acute haemodynamic response to biventricular pacing for CRT.

In addition, I will assess the reproducibility of the speckle-tracking echocardiography methods of selecting a site of late mechanical activation.

Assessment of acute haemodynamic response

Non-invasive cardiac output monitoring

Non-invasive cardiac output monitoring (NICM) devices have been actively studied over recent years, with the primary aim of using them to guide the management of patients with haemodynamic disturbances. The aim in these situations appears largely to have been to measure the *trend* of changes in haemodynamics.

Several methods have used thoracic impedance to attempt to derive CO parameters. The human thorax can be considered as a circuit with a resistor and a capacitor, which produce the thoracic impedance. As the blood is ejected from the heart, both the resistance and the capacitance change, which alters the amplitude and direction of the impedance.

Bioreactance NICOM

The Cheetah Reliant bioreactance NICOM™ system uses two pairs of electrode stickers placed on the patient's chest to inject a high-frequency sine wave into the body and monitor change in thoracic impedance.

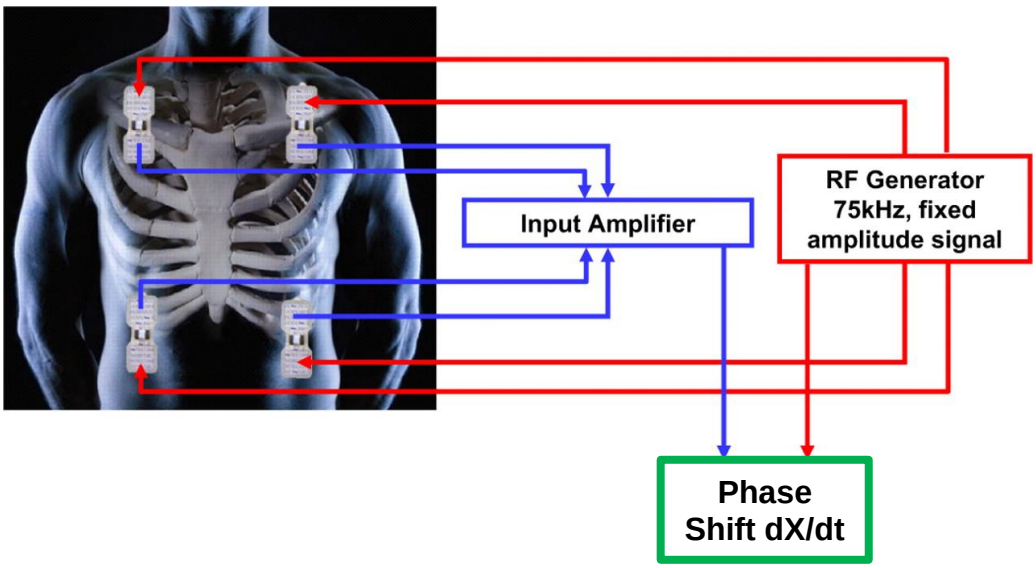


Figure 48 - Schematic of NICOM bioreactance assessment, from Keren et al (Keren 2007). The measurement signal 'X' is the phase shift between the input and output signals, used to derive the peak rate of change of the signal dX/dt max. This is proportional to the peak aortic outflow during each beat, and is not dependent upon the distance between electrodes.

Stroke volume (SV) is calculated by the NICOM system from ventricular ejection time (VET; the time between the two crossings of the zero line of the signal) as $SV = constant \times VET \times \frac{dX}{dt}max$ (Marik 2013). It is not entirely clear from the literature how the constant is derived, although it seems to be from patient demographics and size and has been reported to have been "optimised in prior studies" (Raval 2008).

Cardiac output (CO) can then be calculated from heart rate (HR) as $CO = SV \times HR$, and indexed to body surface area to produce Cardiac Index and SV index. The machine records these parameters continuously and outputs the average of the previous 30 seconds.

Clinical Validation

NICOM™ has been shown to correlate with invasively measured CO by several studies. Keren et al showed a correlation with CO measured by thermodilution in 27 patients (Keren 2007). Their analysis consisted of simple correlation only, with no assessment of

per-patient factors, which limits its validity (Bland 1995), but it produced a Pearson's R correlation of 0.9. It is worth noting that they include a graph indicating considerable short-term variability of NICOM results, which I would at about 10%.

Squara compared thermodilution and NICOM in a single-centre study of 110 patients in intensive care (Squara 2007). They assessed only periods of stable CO, and found a correlation coefficient of 0.64. Again they do not appear to have accounted for the effects of different patients in their analysis and did not report short-term reproducibility of results.

In a multi-centre study of 111 patients, NICOM-derived parameters were reported to track those recorded invasively. They report a coefficient of variation as 0.3 L/minute around a mean of approximately 7.5 L/min (thus a relative variation of 4%) (Raval 2008). Another group correlated NICOM with invasive CO, finding a correlation factor of 0.77, but a relative error of 17% from invasive CO, and a precision for NICOM of 8 ± 3% (Marque 2009).

NICOM has been used in post-procedural CRT optimisation by the Cambridge group (Khan 2011). Khan et al report on 216 patients, comparing 158 patients who had optimisation aiming for the highest CO using NICOM, with 58 historic controls who had no CRT optimisation. Measurements at each setting were made over at least 3 minutes. They report that when the protocol was repeated in 20 patients, the same-day variability was 8%. The maximum improvement in CO achieved was 14 ±18%. They reported that NYHA class was better in the optimisation group, and LVEF was higher, although the validity of this in a non-randomised design is limited. No validation of the NICOM machine against another technique of CRT optimisation was reported.

Aims of experiments

The potential to use NICOM as a way to assess acute haemodynamic response to CRT is clearly exciting. If NICOM could be shown to be useful in this setting, it would also provide potential for its use in CRT optimisation, where the requirement for an accurate non-invasive way of detecting changes in haemodynamics is also urgent (International Working Group on Quantitative Optimization: 2013). There is no validation of NICOM in the setting of patients with implanted cardiac devices, and so I wished to assess its accuracy in this setting. I aimed to assess the extent to which NICOM results agree with dP/dt max, which was used as a comparator, appreciating that there may also be error in the results of dP/dt max and that there is no agreed 'Gold Standard' measurement.

Accordingly I aimed to assess:

- Do NICOM-derived parameters increase with AHR to BIVP?
- Do the results of assessment of AHR by NICOM agree with those produced by dP/dt max?
- Are measurements by NICOM of SV and derived parameters, and AHR produced from these, reliable and reproducible?
- Are measurements of dP/dt max and LV systolic pressure, and AHR produced from these, reliable and reproducible?
- What magnitude of change in AHR can reliably be detected by each method?

Methods

NICOM measurements were taken on patients in the IDEAL-CRT, LVCONSEPT and DOUBLE-CRT studies. The four electrode pads were applied to the patient's back as suggested by the company, and CO, CI, SV, SVI, and dX/dt max were recorded throughout the haemodynamic testing, every 30 seconds. At the same time as the NICOM

measurements, left ventricular systolic pressure (LVSP) was recorded from a pressure wire in the left ventricle over 30 seconds, as previously described, and used to derive LV dP/dt max and LV dP/dt min. It should be noted that the primary aim of these studies was not to investigate NICOM results, and so we were limited in terms of the time that could be dedicated to NICOM assessment.

Two main techniques of NICOM assessment were used in the studies, as discussed in the methods section and illustrated in Figure 49 and Figure 50 below. In LVCONSEPT the average of four NICOM measurements was taken over 2 minutes. In the other studies multiple separate 30-second recordings were used.

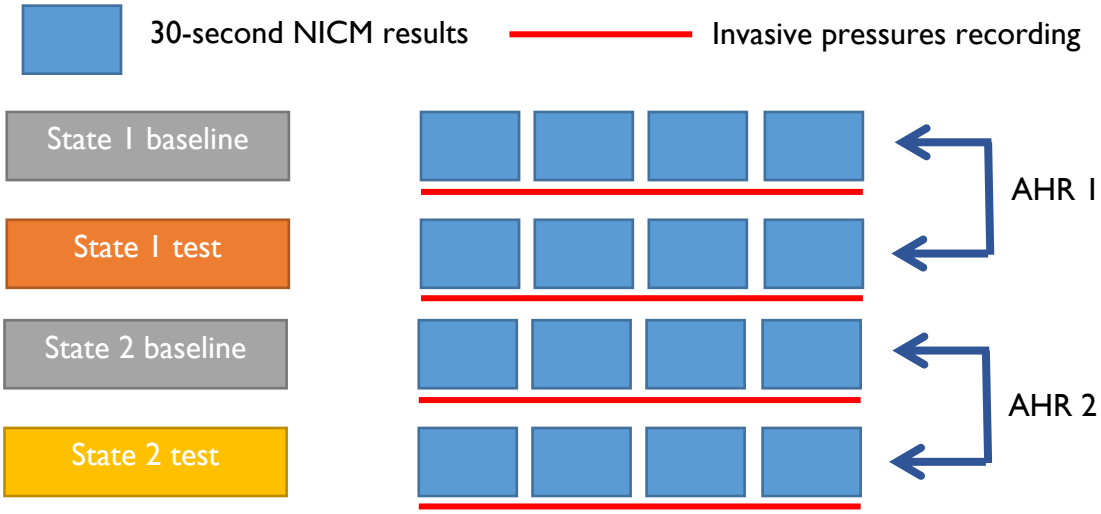


Figure 49 - Single long (2-minute) recording methodology, as used in LVCONSEPT. Four NICOM measurements and continuous dP/dt max at each setting were averaged over 2 minutes, and compared to a 2 minute baseline immediately before. A small number of tests per patient were performed using the same methodology in patients in the IDEAL-CRT and DOUBLE-CRT studies. The four NICOM measurements at each setting were averaged over the 2 minute period. Similarly, the dP/dt max recording over the 2 minutes was averaged. The AHR was the difference between the average of the baseline values and the average of the test values.

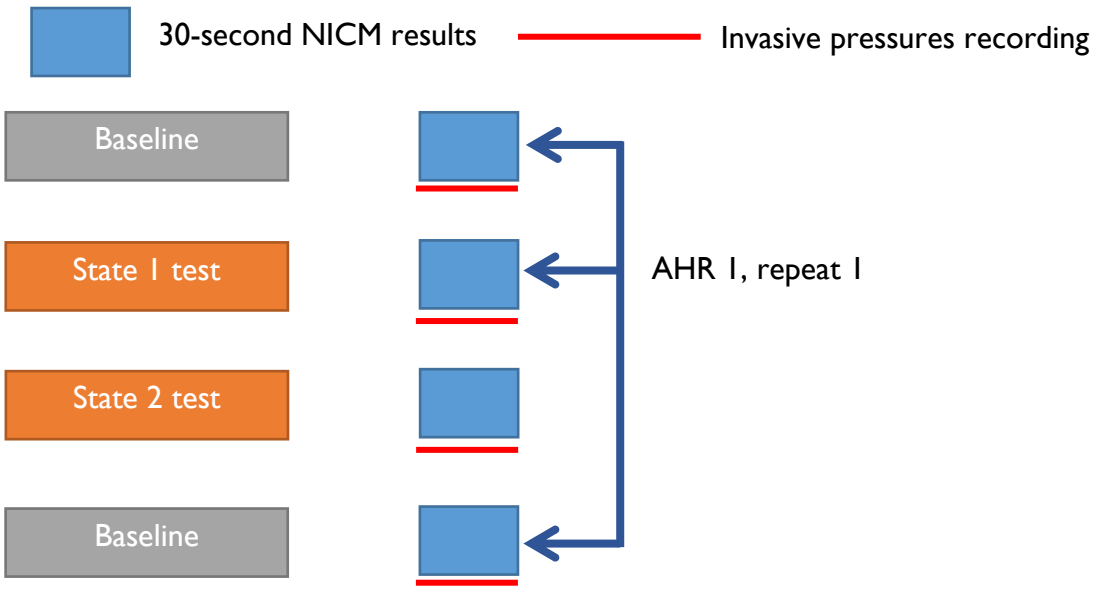


Figure 50 - Multiple repeated 30 second recordings methodology, as used in the main part of the IDEAL-CRT and DOUBLE-CRT studies. 30 second dP/dt max recordings of each pacing configuration were taken, in a random order, 3 times for each configuration. The AHR was the difference between the test value and the average of the baselines before and after each test.

Finally, given that the results of the two measurement techniques would be expected to be similar, the combination of the results from all studies was used. Analysis was primarily by generalised linear multi-level modelling (GLMM) as described before, but multiple tests have been performed, and so for clarity I will describe the statistical methods used alongside the results below.

Results

Patients included

33 patients across the three studies had NICOM values available. The patient characteristics are shown in Table 12.

Parameter	Result
N	33
Age	67 ±14
Male	76%
QRS Duration	151 ±24
Ischaemic aetiology	66%
EF	28±7%

Table 12- Overall patient population included, mean ± SD reported for continuous variables.

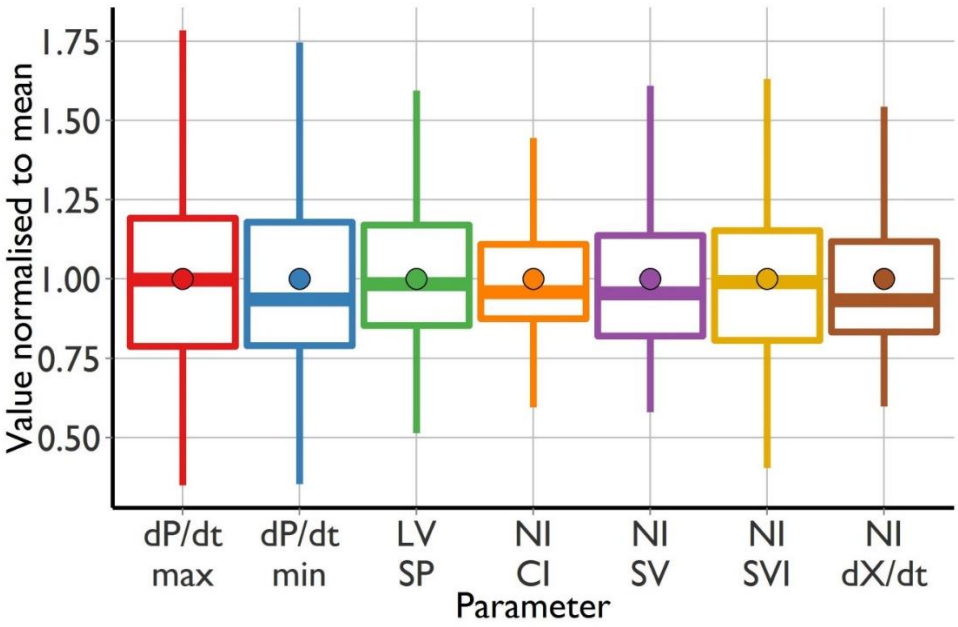
Values of Haemodynamic parameters

AHR was assessed multiple times with each method, as shown in Table 13 below.

Technique	Patients	Samples	Samples per patient	AHR samples	AHR samples per patient
All Recordings	39	971	24.9	580	14.9
2 minute recordings	30	229	7.6	118	3.9
30 second recordings	26	742	28.5	462	17.8

Table 13 - Numbers of samples available.

Mean values for each parameter were variable, as would be expected for several different patients with differing haemodynamic changes. The relative variation of each parameter around its mean was similar, as shown in the normalised graph in Figure 51 below.



Technique	dP/dt max	dP/dt min	LV SP	NI-CI	NI-SV	NI-SVI	NI dX/dt
Mean value	914	-979	111	2.3	57.0	29.0	74.1
SD	267	309	24	0.4	13.2	7.8	18.5

Figure 51 – Box-whisker plots of values of parameters recorded, normalised to the mean of each parameter for comparison. The horizontal lines are the parameter median with a box at the interquartile range. Whiskers extend to the furthest result that is within 1.5 times the IQR. The mean is represented by the filled circle. The table shows means and standard deviations (SD).

Acute haemodynamic response measured with different parameters were largely between -20 and +40%, as shown in Figure 52 below.

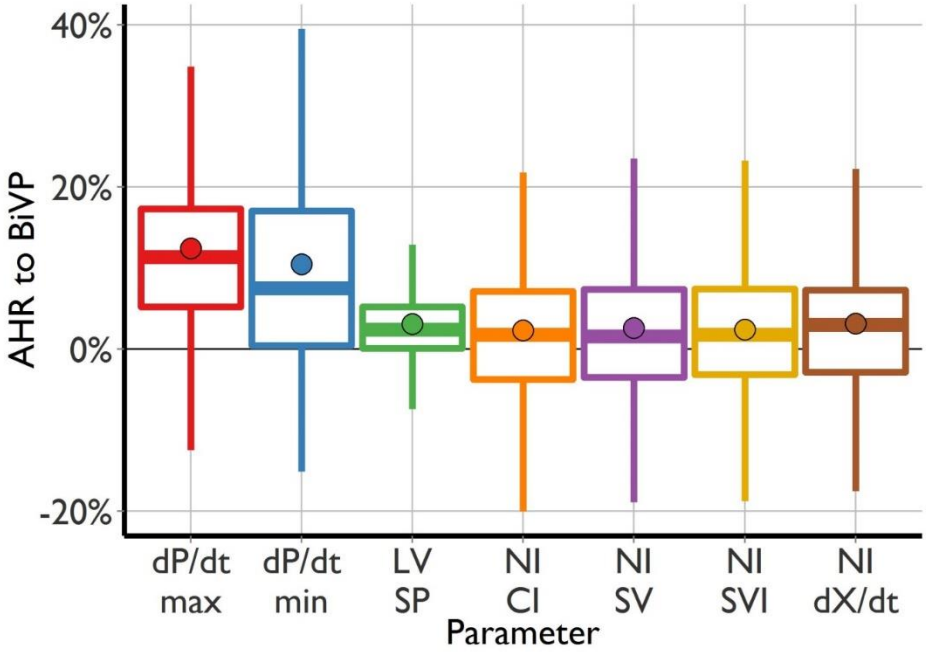


Figure 52- Box-whisker plots as above, of mean AHR to biventricular pacing as assessed with the different parameters. The amplitude of AHR measured using LV SP and the NI parameters was lower than that measured by dP/dt.

This smaller mean AHR was however largely due to much greater variability of AHR by the NI-SV and its derived parameters. 90% of dP/dt max AHR responses were positive, but only 57-63% of the NICOM derived AHRs were positive, as shown in Table 14 below and suggested by the box distribution in Figure 52 above.

Technique	dP/dt max	dP/dt min	LV SP	NI-CI	NI-SV	NI-SVI	NI dX/dt
Mean AHR %	12.5	10.3	3.1	2.4	2.6	2.3	3.2
AHR SD %	12.5	21.1	6.1	11.5	11.6	12.1	12.1
AHR positive	90%	76%	75%	57%	59%	59%	63%
Mean absolute AHR%	13.5	12.6	4.2	7.5	8.0	7.9	7.6

Table 14 - Mean values of AHR, with SDs. The proportion of positive AHRs are shown, and subsequently the mean the of absolute AHR (i.e. positive *or* negative). The absolute AHR values of the NICOM parameters were

significantly higher than the mean values, due to a greater preponderance of negative values.

Do values of NICOM parameters correlate with invasive haemodynamics?

To assess the overall relationship between these different parameters, I used multilevel modelling, as described previously, to allow for variable error between patients. For each parameter I assessed the relationship between dP/dt max and the parameter, using a variable-slope, variable intercept GLM model, with patient as a random factor. With this model both the slope and the intercept of the relationship between the parameter and dP/dt max are allowed to vary between patients, and an overall estimate is made.

All parameters had a significant correlation with dP/dt max values, apart from stroke volume index and dX/dt, which both had a strong trend towards a correlation. The values for the combination of both methods are shown in Table 15 below, although very similar results were obtained for each method individually (not shown).

Technique	dP/dt min	LV SP	NI-CI	NI-SV	NI-SVI	NI dX/dt
Estimate for regression coefficient (95% C.I.)	-0.7 (-0.9--0.6)	9.0 (7.4-10.7)	48.4 (7.3-85.7)	1.7 (0.0-3.4)	2.9 (-0.5-6.2)	2.2 (-0.2-4.7)
P	<0.001	<0.001	0.018	0.048	NS (0.09)	NS (0.07)

Table 15 – GLMM regression estimates of values of parameters against dP/dt max, with P values of significant correlation, using a combination of both assessment methods. 95% Confidence Intervals are given.

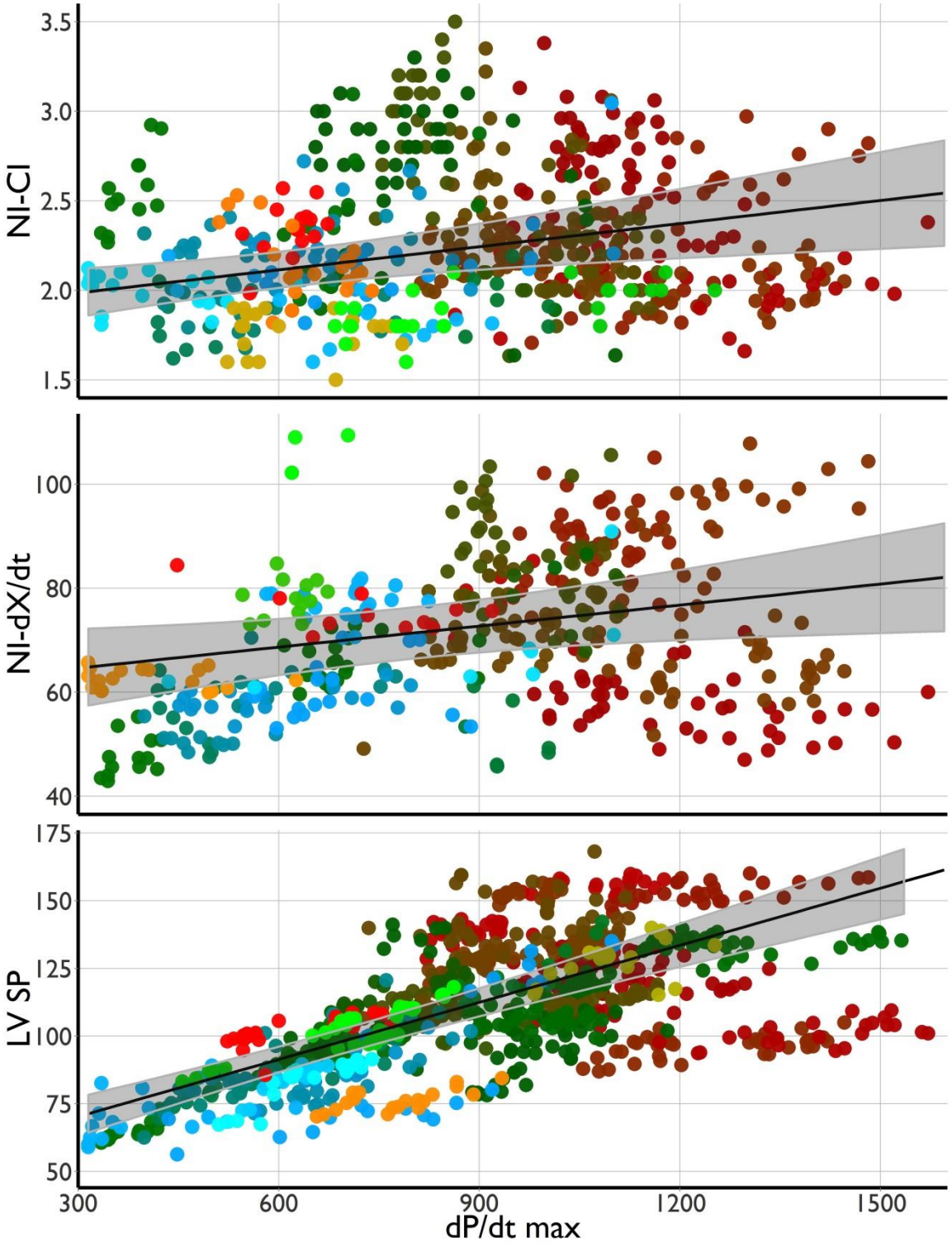


Figure 53 - Values of dP/dt max plotted against simultaneous values of NI-CI, NI-dXdt, and LV SP, using the combined data set. Colours represent individual patients; the GLMM regression lines are shown, with their 95% C.I.s in grey.

Does AHR as assessed by invasive haemodynamics correlate with AHR detected by the NICOM parameters?

I assessed correlation between dP/dt max and the other parameters, which would be expected to vary between patients. Accordingly Pearson's correlation coefficients were calculated for each patient, as shown in Table 16 below.

Technique	dP/dt min	LV SP	NI-CI	NI-SV	NI-SVI	NI dX/dt
Mean within-patient Pearson's R with dP/dt max (range)	-0.64 (-0.07--0.98)	0.59 (-0.14-0.99)	0.35 (-0.76-0.83)	0.32 (-0.80-0.72)	0.32 (-0.80-0.71)	0.36 (-0.78-0.79)
Proportion of positive correlations	0%	89%	61%	57%	54%	29%
Concordance	22%	79%	57%	59%	58%	62%

Table 16 – Top row; mean of the absolute value of the Pearson's within-patient correlation factor between dP/dt max and other parameters. Secondly the proportion of correlations that were positive is shown, and thirdly the simple concordance in positive or negative change – i.e. the proportion of times that AHR by dP/dt max had the same sign as AHR by the other factor.

The within-patient correlations were very variable, with a wide range including some high positive and negative correlations, but with a low mean correlation for the NI parameters. Correlation was negative in up to half of the patients, suggesting that the NI-derived parameters decreased as dP/dt max increased.

To assess the overall relationship of the AHR as assessed by these different parameters, I used multilevel modelling as described previously to allow for variable error between patients. For each parameter I assessed the relationship between AHR by dP/dt max and AHR by the parameter, with a multilevel GLM analysis as described above. The results are shown in Table 17 below and illustrated for NI-CI and LVSP in Figure 54 below.

Technique	dP/dt min	LV SP	NI-CI	NI-SV	NI-SVI	NI dX/dt
Estimate for AHR regression coefficient, (95% C.I.)	0.49 (0.38-0.61)	0.99 (0.73-1.25)	0.09 (-0.04-0.20)	0.07 (-0.05-0.17)	0.06 (-0.07-0.17)	0.01 (-0.23-0.21)
P	<0.001	<0.001	NS (0.14)	NS (0.22)	NS (0.32)	NS (0.88)

Table 17 - GLM regression of AHR by invasive and non-invasive parameters against AHR by dP/dt max, with P values of significant correlation, using the combination of both assessment methods.

As would be expected, the other invasive parameters measured from the same wire as dP/dt max detected AHR similarly. The AHR detected by LV SP was smaller (coefficient of 0.99), and the dP/dt min was much smaller. The AHR detected by the NI parameters was not significantly related, with much smaller regression coefficients of around 0.09. There was a trend towards a relationship for NI-CI and NI-SV. These results suggest that NI-CI may be able to detect AHR but the AHR detected will be ten times smaller than that by dP/dt max.

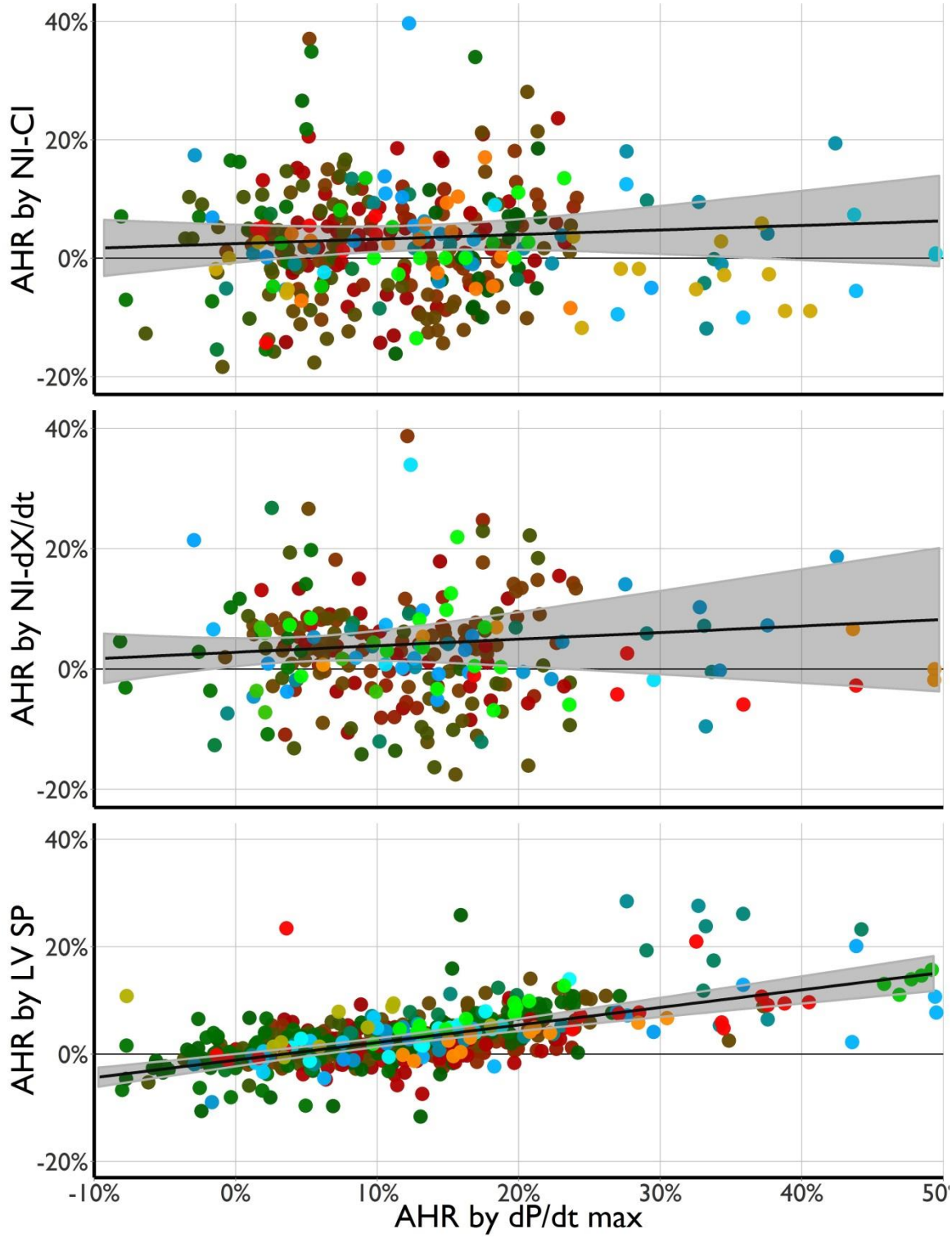


Figure 54 - AHR by dP/dt max versus AHR by NI-CI (top), NI-dX/dt (middle), and LV SP (bottom), utilising the combined data set. Colours represent individual patients; the GLMM regression lines are shown, with their 95% C.I.s in grey.

When the analysis was sub-divided into the two data collection methods, rather than considered alone, again none of the NI-derived parameters had a significant correlation with AHR by dP/dt max, although the trends were similar, and similar significant correlations were found for LVSP and dP/dt min.

Assessment of reproducibility

I suspected that the reason for the lack of correlation of AHR by NI parameters might be due to measurement error, so I went on to analyse reproducibility and repeatability of the measurements.

There were two levels at which I could assess reproducibility.

- Firstly, using the '2 minute' data, in which 4 consecutive recordings were taken over a 2 minute period. This will assess short-term variability, and if anything should be a simpler test to pass, as the situation is a steady-state.
- Secondly, I could assess reproducibility across repeated measurements at the same settings. In both the IDEAL-CRT and DOUBLE-CRT datasets, multiple measurements were taken with identical pacing settings, without moving the lead or catheter, over a short time period (~10min). The patient was in a steady state, and so although more variation would be expected over a longer time period, I would expect reproducible results for an accurate measurement. This will allow the assessment of both variability of absolute values at the steady state, and of AHR to a repeated identical pacing setting. These methods are illustrated in Figure 55 below.

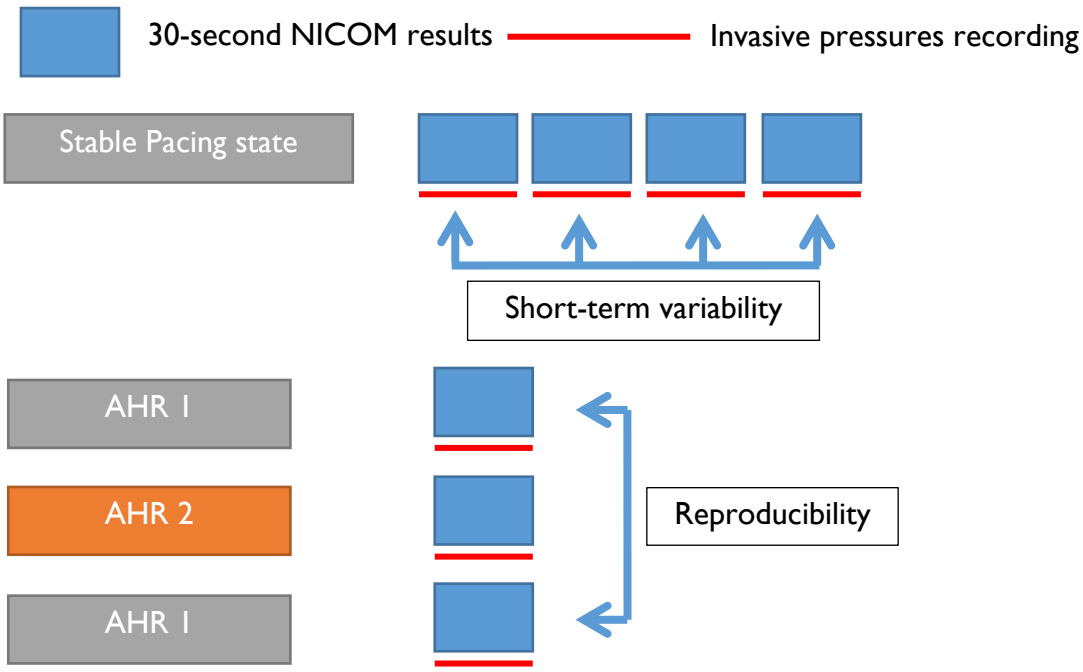


Figure 55 - Illustration of tests of variability and reproducibility.

The assessment of variability and reproducibility in pacing and CRT haemodynamic measurements has been a topic of significant research of late, mainly aiming to find a reproducible method for the optimisation of atrio-ventricular intervals after CRT. Professor Francis and his group in London have investigated the mathematical basis of this, and derived equations in order to calculate the number of repeated measures needed to separate random variability from a genuine haemodynamic change induced by a new pacing setting (Francis 2013). In order to separate the genuine response from random error, the ratio of the response to different settings (for example, an increase in AHR) to the measurement scatter must be high enough. Scatter is defined as the pooled standard deviation of repeated measurements at the same setting. This can also be thought of as a signal-to-noise ratio. The signal is the change we are trying to detect, and the noise or scatter is the random background change due to measurement error, change in the patient's state, or irrelevant physiological fluctuations.

The number of replicates needed to correctly identify the best site between more than one site, 95% of the time, can be estimated as $Replicates = \left(\frac{1.64 \times \sqrt{2} \times Scatter}{1.5 \times Effect\ size}\right)^2$, where *Scatter* is the pooled SD of repeated measurements at the same setting, divided in time, and *Effect size* is the size of change to identify, in the same units as *Scatter*. *Effect Size*/*Scatter* is equivalent to a signal-noise ratio (Francis 2013, International Working Group on Quantitative Optimization: 2013).

For the calculations, I have used an effect size of half of the mean absolute AHR, on the basis that it is likely that I would need to identify changes of at least this magnitude to have any chance of usefully comparing between pacing site using the parameter.

Reproducibility Results

Technique	dP/dt max	dP/dt min	LV SP	NI-CI	NI-SV	NI-SVI	NI dX/dt
Absolute values of parameters							
Mean Value	971	-1022	113	2.32	57.8	29.4	76.3
Short-term variability (SD at same settings)	11.4	19.6	1.65	0.15	3.79	1.92	3.94
Variability as a percentage of mean	1.2%	1.9%	1.5%	6.3%	6.5%	6.5%	5.2%
N samples for above	218	218	218	209	209	208	195
Reproducibility scatter (SD of replicates)	37.6	96.8	4.72	0.19	4.85	2.85	5.58
Reproducibility scatter as a percentage of mean	3.9%	9.5%	4.2%	8.2%	8.4%	9.7%	7.3%
N samples for above	225	225	225	135	136	135	90
AHR							
Mean Absolute AHR	13.49	12.63	4.17	7.53	7.99	7.93	7.64
Reproducibility (SD of replicates)	3.76	17.56	2.50	8.02	8.80	9.42	7.81
N samples for above	169	169	169	96	97	96	60

Table 18 – The top section shows the reproducibility of absolute values of parameters at the same settings, including both the short-term variability over 2 minutes at the same settings, and the reproducibility at the same settings. The bottom section shows reproducibility for AHR measurements.

Technique	dP/dt max	dP/dt min	LV SP	NI-CI	NI-SV	NI-SVI	NI dX/dt
Signal to noise ratio	1.9	0.4	1.0	0.5	0.5	0.5	0.6
Replicates needed to detect mean AHR	1	13	3	8	9	11	8

Table 19 – Signal-to-noise ratio and corresponding number of replicates needed to detect the mean AHR.

As shown in Table 18 above, the reproducibility scatter and the short-term variability of the NI-derived parameters were high. Most significantly, the noise or measurement scatter of the NI-derived parameters was of a magnitude greater than the interquartile range of effect size. The signal-to-noise ratios and resulting number of replicates required to detect the mean AHR are shown in Table 19 above.

Speckle-tracking echocardiography to select a site of late mechanical activation

I have detailed the techniques used in the Methods section. I will assess reproducibility of the techniques in a similar fashion to above. Again, I will assess how consistent results are between repetitions.

To do this, in each patient I recorded consecutive echo loops at the basal and mid-ventricular levels. Imaging was optimised before the first loop, and then probe position and settings were not changed between loops. The patient was asked to hold their breath to minimise motion artefact. Both loops were analysed as described in the Methods chapter. All loops were assessed before analysis, and if image quality was inadequate they were excluded.

In addition, in a sample of 25% of patients I analysed the same loops twice, to assess the reproducibility of analysis of exactly the same data.

The target segment was chosen in each repeat as the segment with the longest delay and strain >10%, as previously described.

Results

450 segments were assessed over 35 patients. Of these, 368 segments were assessed more than once in two viable loops. Strain was 20.4 ± 13.1% in the first assessment, and 20.0 ± 13.8% in the second (P=0.68 for comparison), and delay was 416 ± 185ms and 439 ± 178ms respectively (P=0.07).

Target segments were chosen in each repeat. The target segment chosen was the same in 9/32 (28%) of patients. The segments chosen were generally nearby, with a difference of 1.5 ± 1.3 segments. In 10/32 (39%) of patients the segments chosen were 1 segment apart, such that overall in 59% of patients they were one segment apart or matching. Reproducibility in the delay at the two target segments was 78 ± 61ms or 13.3 ± 9.9%. Scatter in delay as defined above was 55ms.

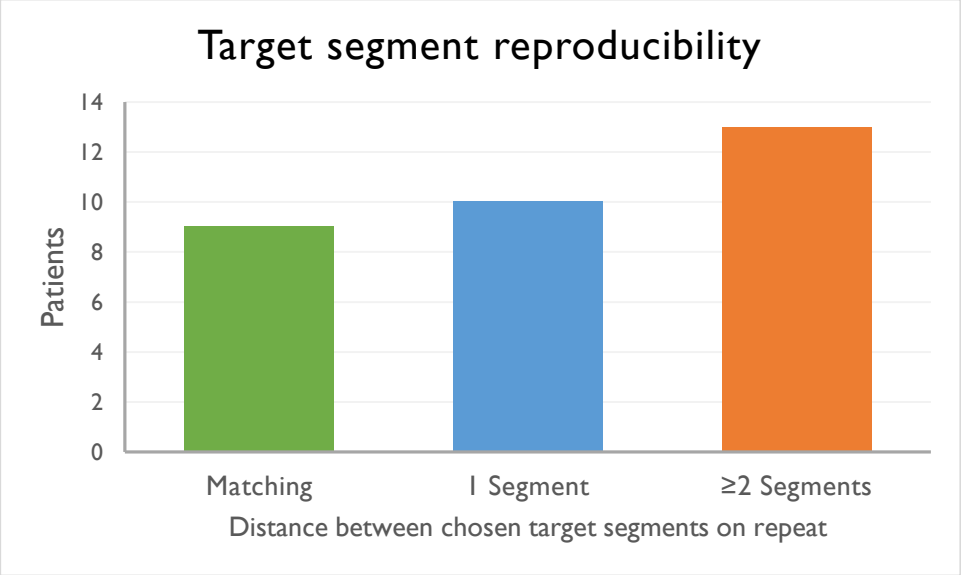


Figure 56 – Illustration of reproducibility of target segment between consecutive echo loops.

Assessing reproducibility on re-analysing the same echo loops, the difference between target segments was 1.1 ± 1.1 segments. 50% of segments matched, and 75% were matching or within 1 segment. Reproducibility in the delay at the two target segments was 15.7 ± 14.0%.

Discussion

Relationship of SV and derived parameters to dP/dt max

This is a large dataset of simultaneous measurements of invasive blood pressure and derived parameters and non-invasive measurements of stroke volume and derived parameters. As would probably be expected, almost all of the absolute values of the parameters correlate with each other. They are all measuring features of cardiac function, and so in general it would be expected that they would be linked. The linkage between SV and dP/dt max would not be expected to be straightforward, as they are clearly measuring different elements of cardiac function. dP/dt max is known to be influenced by cardiac pre-load, but is well established as a measure of cardiac contractility (Mason 1971). Stroke volume in CRT will be influenced by a variety of factors, not only contractility but also mitral valve timings and flow, which may be changed by biventricular pacing. Atrio-ventricular timings would not be expected to change significantly, as in all patients the same AV interval was used throughout. Similarly, it would be expected that SV and cardiac output and thus cardiac index would have a very straightforward link, as heart rate was held constant throughout.

To a large extent however, this is a moot point as the intent of these experiments was to investigate the use of NICOM as a method to assess AHR to BiVP. I found a very variable response of the NICOM parameters to BiVP, with a positive AHR in only about 60% of BiVP recordings. This response was frequently not concordant with the response by dP/dt. Again, it might be expected that the AHR by SV and related parameters would not be the same as that by dP/dt max, although it is surprising to find an apparent decrease in AHR as assessed by NICOM-SV in as many as 50% of cases with a positive AHR by dP/dt max.

Other groups using conductance catheters to assess SV have also not found a consistent increase in SV with BiVP or a straightforward relationship with dP/dt max. Stockinger et al assessed SVI with a conductance catheter and found that SVI did tend to increase with BiVP, but not as consistently as dP/dt max (Stockinger 2011). dP/dt max and SVI were concordant in 42 tests and discordant in 21 measurements, giving 66% concordance which is broadly comparable to my results. de Roest et al assessed AHR in 41 patients, and found that in the 29 long-term responders the mean AHR by SV was 19 ± 20%, suggesting (from the SD provided and a normal distribution) that about 65% of them increased SV with AHR to BiVP, whereas in the 12 non-responders it was 1 ± 19%, suggesting that SV decreased in almost half. Corresponding figures for dP/dt max were 15 ± 18 and 6 ± 15%, which are not widely different from my results (de Roest 2013). In fact, de Roest went on to show that Stroke Work as derived from SV and blood pressures was a better predictor of long-term outcomes than dP/dt max.

Pappone's group found similar correlation results between the AHR by dP/dt max and AHR by SV measured with a conductance catheter (Pappone 2013b), with significant positive correlation in 25% (coefficient > 0.3), significant negative correlation (coefficient <-0.3) in 27%, and insignificant correlation in the remainder, similar results to mine. These data are interesting, and suggest the possibility that SV measures a different physiological response to BiVP, which may be clinically meaningful.

Reproducibility of NICOM

Unfortunately, my reproducibility testing shows that the performance of the NI-derived parameters was poor. The absolute values of AHR were slightly lower than those obtained from dP/dt max, but the short-term error and reproducibility were both much worse. As shown in Table 18 there was ~6% error in the NI parameters when recorded over 2 minutes at a steady state, which should be the situation with the smallest error,

and is less applicable to genuine reproducibility. The error between repeated measurements at the same settings was higher at ~8%, compared to ~4% for dP/dt max. Predictably, these errors in baseline measurements produced even more error in the AHR values recorded, such that the error in AHR for the NI-derived parameters was approximately the same as the absolute value of the AHR, as illustrated in Figure 57 below.

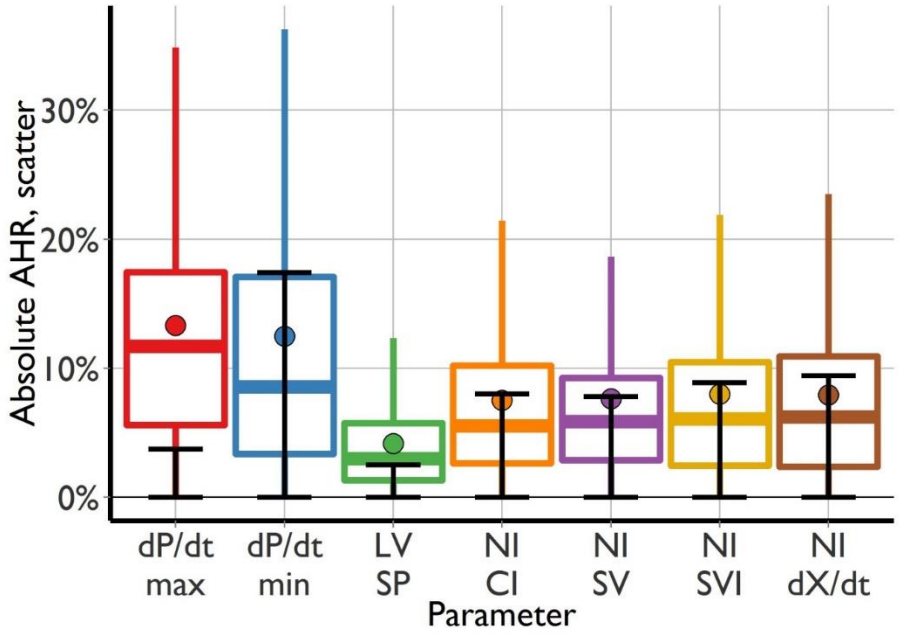


Figure 57 – A box plot of the absolute AHR to each parameter, with the reproducibility 'scatter' of each parameter illustrated by the black error bars. It can be seen that for dP/dt max, the lower quartile of the AHR is greater than the noise, suggesting that most changes will be successfully identified. For the NI-derived parameters and dP/dt min, the measurement noise is greater than the IQR of the AHR, and any signal will be overwhelmed by the noise.

This meant that it is hard to identify genuine change from the noise. The best-performing NI-parameter was NI-dX/dt, but this still required 8 repeats to reliably identify half of the mean AHR. It is clear that performing this number of 30 second replicates in order to assess one pacing setting is unlikely to be feasible in most circumstances. This is also taking half of the mean AHR; it is likely that in many practical circumstances we would want to identify a smaller AHR than this.

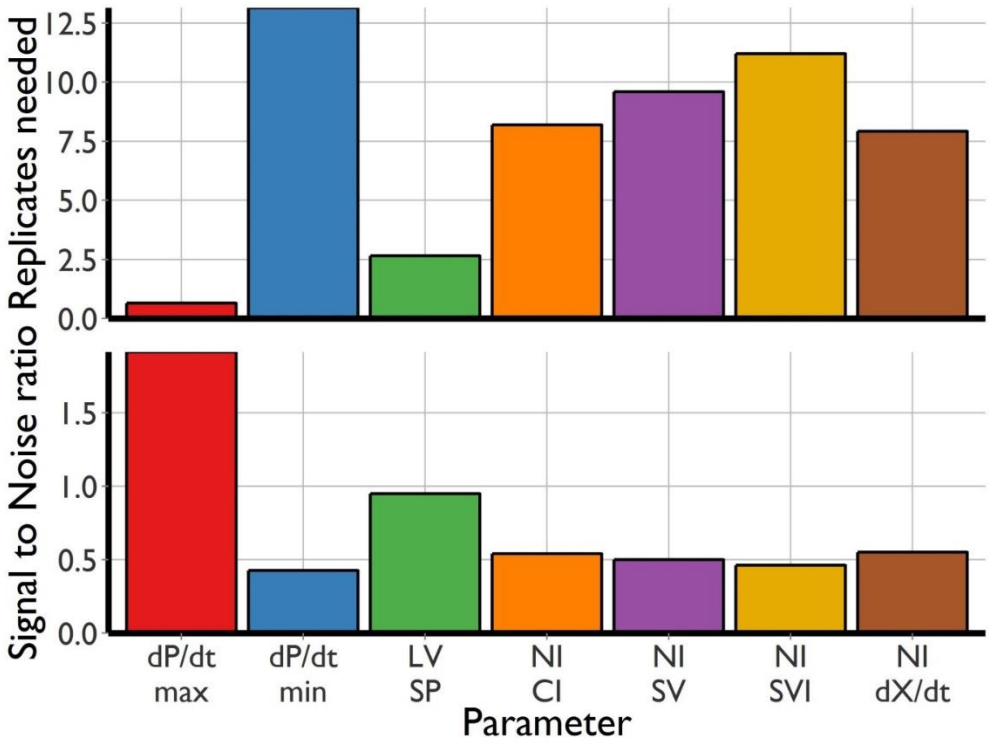


Figure 58 – Signal-to-Noise ratio (to detect half of the mean absolute AHR; bottom) and corresponding number of replicates required (top).

In effect this leaves the NICOM parameters with limited utility for CRT, as its accuracy is not within the range required for CRT assessment. The studies used to validate NICOM, as discussed above, were all measuring longer-term haemodynamic response over a prolonged time period. In fact, where NICOM measurement repeatability was assessed, the figures quoted were in the 4-8% mark, which are very comparable to my results.

The above results in terms of AHR by SV are therefore of very limited utility, and I do not intend to further analyse them, as it seems unlikely that any useful or valid results would be obtained. Accordingly, I will not use the NICOM results further in the thesis.

The utility of dP/dt max and LV SP

As shown in Figure 57 and Figure 58, LV systolic pressure was shown to be a reasonably accurate method to assess AHR. It correlates closely with dP/dt max, as would be expected. The extent of noise in the signal was however greater. This is presumably due

to other factors influencing pressure, in particular variations in cardiac afterload and preload. Other groups have also shown that LV SP and blood pressure can be used to assess CRT.

Professor Francis' group assessed dP/dt max, LV SP, and LV pulse pressure as methods for CRT AV optimisation. Using a similar technique of repeated comparisons of invasively measured dP/dt max in 25 patients they found that the scatter in dP/dt max was 49mmHg/s (Finegold 2013). They expressed this as the absolute value of the change rather than a percentage. The same value calculated from my data would give a similar scatter of 34mmHg for dP/dt max. They used 20 beats per sample, so my longer 30s samples at 80bpm (mean beats/sample 39) would be expected to give a smaller scatter.

Thibault et al carefully investigated the reproducibility of dP/dt max recordings in a similar cohort (Thibault 2014). They found that the median discrepancy between multiple recordings of the same BiVP protocol was 3.9%. They also investigated the sources of variation in dP/dt max, finding a sinusoidal variation in levels attributed to respiration with a period of 5.4 cardiac cycles, as well as baseline drift. Given that my recordings were all made over a minimum of 30 seconds, several respiratory cycles would be expected and this should largely be averaged out.

For LV SP, my scatter value expressed as an absolute change in LVSP was 2.75mmHg, very similar to theirs at 2.54mmHg. Their mean AHR to BiVP was 60mmHg/s, significantly lower than my figure of 99mHg/s. Their mean AHR to BIVP for LVSP was 2.7mmHg, similar to my figure of 3.7mmHg. They went on to conclude that dP/dt max was less useful for optimisation of CRT than LVSP as the signal-to-noise ratio was lower. This finding may be limited to CRT AV optimisation, as they found that the relative *further* increase in HR to optimal AV settings was greater for LV SP than for dP/dt max. Their optimisations were

performed1-3 days after CRT implant, when there may already be a degree of haemodynamic adjustment, which would influence the extent of change in dP/dt max.

My data suggest that in the context of acute implantation and identifying/optimising AHR to BiVP, dP/dt max has better characteristics than LV SP. Having said this, I have shown that LVSP is valid for use with suitable numbers of repeats. Work from other groups has also shown that the extent of change in LVSP might be greater immediately after the transition to CRT, which could potentially improve the signal from LV SP. Measurement of this transition period was not made in my protocols (Manisty 2012). Furthermore, this data provides support to the potential use of peripheral blood pressure to assess CRT, which can be measured non-invasively. This is the subject of the BRAVO trial, again led by Professor Francis' group, which is investigating the utility of a non-invasive high-fidelity blood pressure monitor to assess CRT AV optimisation; it remains unpublished (Whinnett 2014).

The utility of dP/dt min

The results of assessment of AHR using dP/dt min clearly differ from the other invasive haemodynamics. dP/dt min correlated well with dP/dt max, but reproducibility was poor. It may well be that there are other factors influencing the LV diastolic physiology (as measured by dP/dt min) that change in a different way during a procedure to dP/dt max. Other authors have found a significant decrease in LV dP/dt min with biventricular pacing, which I also found (Kato 2014, Pappone 2013c).

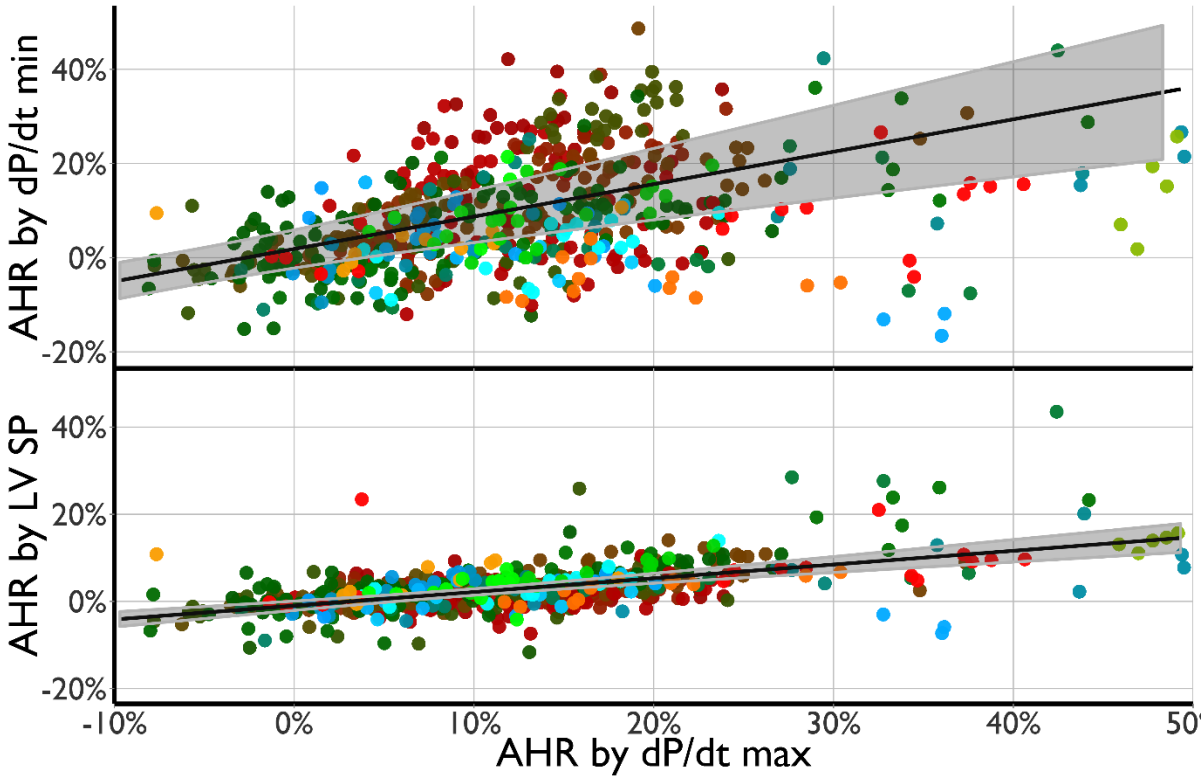


Figure 59 - AHR by dP/dt min (top) and AHR by LV SP (bottom) versus AHR by dP/dt max, with GLMM lines and confidence intervals as before. The significantly greater variability in AHR by dP/dt min is easy to appreciate.

There are some data to suggest that improvements in left ventricular diastolic physiology may be a useful predictor of long-term response to CRT. In a small pilot study, AHR by dP/dt min was a better predictor of response than dP/dt max, although Tau (the time constant of left ventricular relaxation) was an even better predictor (Kato 2014). I have not to date assessed Tau from my data (some software produces this automatically; the software I used does not). This would be interesting information but the practicalities of extracting and calculating this data for analysis are extremely challenging. Other authors have shown that improvement in echo-derived parameters of LV diastolic function are also predictors of response (Doltra 2014).

Unfortunately, similarly to the NI-derived parameters, the poor reproducibility of dP/dt min would limit the utility of further investigation of this parameter, as the very high error

between repeated assessments will mean that results obtained using it would be extremely inaccurate.

Assessment of AHR using every-beat analysis

As discussed above, the limiting factor in analysis of AHR to BiVP is sampling error, requiring significant numbers of repeated measures to accurately assess the extent of response. I have reported the number of replicates needed to identify half of the mean AHR, but in practice I might want to identify smaller differences between, for example, two poles of a quadripolar lead. If, for example, I wanted to identify a 2% difference in AHR by dP/dt max, I can calculate using the data and methods reported above that 8 repeats of dP/dt measurements would be needed. Thus far I have reported results of analysis using averaged periods of beats, but another possibility would be to analyse each beat. It would be expected that this would increase scatter, but there would be the benefit of massively increasing the sample size. A further issue is that I would then need to account for another level of random error, from the between-samples error as well as between-patient. This can be done relatively easily using the multilevel model methodology by accounting for the recording as well as the patient.

I re-analysed the invasive haemodynamic data using this methodology. Each beat of BiVP was considered separately, and AHR calculated against the baseline average.

Results of each-beat analysis – reproducibility scatter

Using the same methodology as above, the AHR as derived from each beat was assessed to derive scatter values.

Technique	Patients	Beats	Samples per patient	AHR samples	AHR samples per patient
All Recordings	39	62011	1597	35075	899

Table 20 – Number of beats available for analysis

Technique	dP/dt max (mmHg/s)	dP/dt min (mmHg/s)	LV SP (mmHg)
Absolute values			
Mean Value	971	-1022	113
Reproducibility scatter for individual beat analysis (SD of replicates)	55.6	98.5	6.9
Reproducibility scatter as a percentage of mean	5.7%	9.6%	6.1%
AHR			
Reproducibility scatter for individual beat analysis (SD of replicates) %	6.34	13.89	5.67

Table 21 – Reproducibility of multiple beats. Scatter values are higher than for averaged recordings, as expected, although only by ~1.5% of the mean for dP/dt max.

Using the above figures, I can derive the number of replicates required to detect small changes in AHR. For dP/dt max, 2 beats would be required to detect half of the mean AHR, but in order to detect a 2% change 24 beats would be required. Accordingly, if I acquire and analyse more than one 30 second (~40 beat) sample, there should be an excellent ability of this methodology to detect even small changes in AHR. Reversing the formula, I can calculate that 30 beats would be able to detect a 1.7% change in AHR.

The increase in scatter for LV SP using this methodology is proportionately greater, so detecting an equivalent small change (proportional to a 2% change in AHR) would require 175 beats. This suggests that the beat-to-beat variability in LV SP is greater, and

accordingly that it is less useful for this method of analysis. Similarly, the high error in dP/dt min, despite the larger effect size, means that 106 beats would be required to detect a proportional small change.

Reproducibility of speckle-tracking echocardiography measurements

The reproducibility of my speckle-tracking measurements was relatively poor. When the same loops were analysed multiple times, in most cases the segment chosen was the same or adjacent. When two different echo loops taken in the same patient without changing anything else were analysed, results were worse, with the same segment or adjacent segments only selected in 66% of patients.

Prior data on reproducibility of strain imaging were reported in an early paper as 6-8% (Suffoletto 2006). Another paper found that specifically for radial strain, as used in my studies and in all the prior CRT studies, the error was 12-14% (Saito 2009). This is similar to the reproducibility figures I have found. No study has reported the accuracy of estimation of a target segment using these techniques, although unpublished analysis from the Cambridge group has also found an error of 1-2 segments (personal communication, Dr Anna Kydd, Papworth Hospital, Cambridge).

A paper written by colleagues in Oxford (Augustine, Leeson et al) is under consideration for publication. This shows poor inter-observer correlation for radial strain in particular, and also poor agreement between different vendors' software. This latter point is also relevant. The Cambridge group behind the TARGET trial, and also the STARTER trial group, used GE software. I did not have this available to me, and instead used TomTec software as detailed above. It does appear that results of strain analysis from different

vendors are not directly comparable and it is conceivable that the TomTec software may not produce results that are as reliable as GE software.

I have not assessed inter-observer variability, focusing instead on repeated measures and intra-observer. This was mainly a practical limitation, as the technique was not being undertaken by anyone else in Oxford for most of the time I was analysing these studies. This means there is not any suitable person to reanalyse my data without significant training (and thus probable worse results). My results in terms of intra-observer variability of strain appear to correlate with prior findings of reproducibility.

Another component of the problem is variable image quality. Although as described in the methods, I excluded loops or segments of particularly poor quality, it was still subjectively clear that tracking was better as image quality improved.

The low reproducibility of this technique will limit the conclusions that can be drawn from results based on it.

Chapter Summary

- The NICOM technique estimates stroke volume from thoracic impedance.
- I showed that values of stroke volume and cardiac index derived in this manner do correlate with values of dP/dt max recorded invasively.
- Despite this, AHR as assessed by NICOM parameters including stroke volume does not correlate with AHR by dP/dt max, although this could be due to differential physiological response to BiVP between these parameters.
- Poor reproducibility in NICOM measurements severely limits their reproducibility, and means that the above conclusions are of limited validity.
- LV systolic blood pressure had better reproducibility and could be used for CRT assessment, although more repeats would be needed that dP/dt max.
- LV dP/dt max had good reproducibility and would reliably identify small changes.
- The use of every beat analysis of dP/dt max is viable and will identify even small change in AHR.
- Speckle-tracking identification of a site of late mechanical activation was accurate to 1-2 segments only

Chapter Seven – Left ventricular endocardial pacing across the interventricular septum: clinical results

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Introduction

The novel method of LV endocardial pacing across the interventricular septum was detailed in the Methods chapter, as were its theoretical benefits. We aimed to assess the following:

- Safety of the technique
- Adverse events over long-term follow-up
- Response to CRT after lead placement via this technique

We hoped to show response results that were at least as good as conventional CRT, with acceptable safety. In addition, we attempted to assess the optimal site for LV lead placement. This was effectively a nested secondary study, and I will discuss these results in the subsequent chapter.

Methods

The LVCONSEPT study was undertaken as described in the preceding Methods chapter, recruiting patients with either indications for CRT and a failed conventional coronary sinus LV lead implant, or non-responders to CRT with a poor LV lead position.

Patients were followed-up in person at 3 months and 6 months, although not all patients attended the 3 month visit, generally because they lived a long way from Oxford. Thereafter they were followed-up telephonically. In addition, patients who had NHS care in Oxford had the results of routine clinical reviews after 6 months available.

All comparisons were made between the baseline and 6-month assessments, using the Wilcoxon signed-rank test for non-parametric variables such as NYHA class and EQ-5D-5L scores, and paired T-tests for the other continuous variables.

In addition to those patients included within the LVCONSEPT study, a small number of other patients had endocardial LV leads placed across the interventricular septum in Oxford, as mentioned in the Methods section. These cases were largely performed before the LVCONSEPT study commenced, but also included two cases who were not suitable for the study (as a minimally complex procedure without the research elements was desired). Follow-up on these patients was less systematic, but simple clinical parameters were available. The majority of patients were seen in Oxford, and so pacing follow-up was available, as well as intermittent clinical reviews. In the case of those patients seen elsewhere, I contacted the physicians to get more details where possible.

Follow-up was censored for this report as of 21 March 2016.

Results

Patients

The 20 patients planned have been recruited, between June 2013 and March 2016.

Parameter	Result
N	20
Age	67 ± 12
Male	80%
QRS duration	157 ± 14
Ischaemic aetiology	45%
NYHA class	2.9 ± 0.4
EF	28 ± 7%

Table 22 – LVCONSEPT patient details.

In terms of the indication for an endocardial LV lead, 15/20 (75%) patients had had a prior attempt or attempts at CRT and had not had a successful LV lead placement. One of these patients already had an LV lead, but it had failed due to lead fracture, and no other appropriate veins were available at attempted re-implant.

5/20 (25%) patients already had functioning LV leads and were recruited as non-responders in whom it was felt that LV lead placement was non-optimal. Of these patients, four had coronary sinus LV leads and one had a surgical epicardial lead.

16/20 (80%) patients were already taking warfarin before consideration of study entry; the others were started on warfarin pre-procedure. 12/20 (60%) of patients had persistent AF, and 4/20 (20%) had paroxysmal AF, leaving only 4 (20%) patients without AF.

The patients recruited were at a high risk of adverse outcomes at baseline. The CHA_2DS_2-VASc score was a mean of 3.7, median 4, with an interquartile range of 2. Use of published data to calculate personalised risk via the online SPARC tool website (Olesen 2011, Sprague 2003) gave a mean annual risk of stroke or embolism of 2.4 ±1.2% on standard warfarin therapy. The VALID-CRT risk score provides an estimate of likely mortality in a CRT population (Gasparini 2015). Mean estimated 2-year mortality using this tool in this study population was 22.2 ± 8.3%.

Patients screened for inclusion

Multiple patients with apparent non-response to CRT were screened for possible inclusion, but many were excluded due to evident comorbidities that were likely to be preventing response, or because they had a LV lead position that was already optimal or near-optimal. Patients with failed LV lead placement via the coronary sinus were more likely to be recruitable.

12 patients were assessed in detail and not recruited, for a variety of reasons. In one patient we were able to place an LV lead via the conventional CS route, and in a second programming changes allowed LV lead capture. 3 patients were felt to have too extensive co-morbidities to be likely to benefit. 2 patients with prior low LV were found to have improved LV function at re-assessment. 1 patient with LV thrombus at the time of

assessment was felt to be currently too high risk for this approach. 4 patients were offered the option of LV endocardial leads but after discussion decided they would rather have a surgical epicardial lead. 1 patient died before having decided if she wanted to participate.

Registry patients

9 patients are included in the registry, having procedures performed between October 2011 and September 2014.

Parameter	Result
N	9
Age	65 ± 12
Male	88%
Ischaemic aetiology	55%

Table 23 – Registry patient details.

Of the registry patients, 3 patients had had a prior attempt or attempts at CRT and had not had a successful LV lead placement. 6 patients had failed or extracted LV leads and no other valid CS targets.

Procedural results

All study procedures were performed by Dr Tim Betts, with my assistance. General anaesthesia was used in all cases. Procedure time decreased steadily as experience was gained, as shown in Figure 60 below. This does not include time to place the LV lead, as in the registry patients this was done immediately after gaining LV endocardial access, but in the LVCONSEPT patients we went on to perform the mapping and haemodynamic protocols. Mean time in the LVCONSEPT patients from successful venous access to passing the first catheter inside LV was 25 ± 19 minutes. The overall LVCONSEPT

procedural times were long, with the time from the patient arriving on the table to wound closure being 3-4 hours.

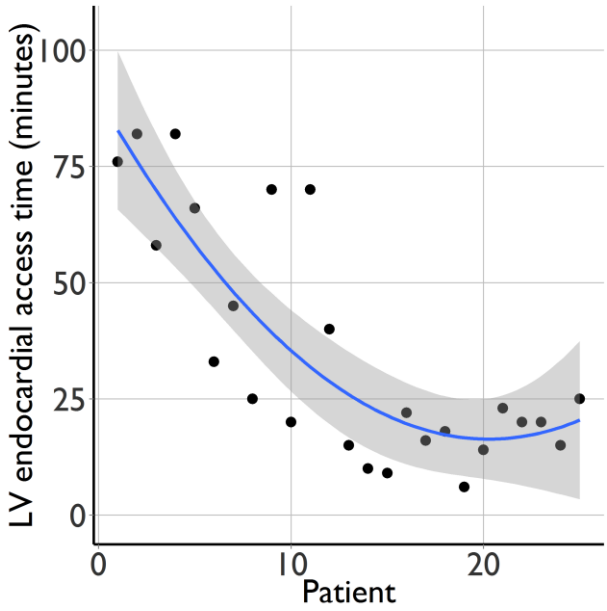


Figure 60 – Time to LV endocardial access (from venous access to first catheter inside LV) for both the registry and LVCONSEPT cohorts. The line and shaded area show the rolling mean and 95% confidence interval.

Procedural Complications

We were able to place a LV endocardial lead in all cases where this was attempted.

In the registry group, a pericardial effusion requiring drainage occurred in the second patient. This was felt to be due to the use of the rigid Brockenbrough needle, and this complication was not seen after the switch to use of a guidewire.

In one registry patient the use of RF energy resulted in the induction of sustained monomorphic ventricular tachycardia that was treated with a 200J synchronized external shock.

In LVCONSEPT, haemodynamic assessments were not able to be made in two patients, as one became unstable due to anaphylaxis to a component of the anaesthetic agents, and in another the procedure was prolonged due to difficulty in extracting old leads to gain

vascular access. In another patient initial failure to achieve a septal puncture was caused by a guidewire micro-fracture.

Two patients developed significant wound haematomas, both of which required re-operation. In one patient, who also had extraction of a right atrial lead during the procedure, a pre-existing right ventricular lead became displaced after the procedure and required revision. Accordingly, 17/20 (85%) patients were free of an acute procedural complication.

There were no incidences of pneumothorax or wound infection. No LV leads acutely displaced. No patient suffered a peri-procedural stroke, TIA or systemic embolism.

Primary end-point: freedom from adverse events

18/20 patients have been assessed at 6 months; the final 2 patients were recruited in early 2016 and have not reached their 6 month follow-up. Two patients were unwilling to return for research follow-up, and only telephone assessment of NYHA class and vital status could be made.

In the first 6 months, one patient suffered a stroke, and one suffered a TIA. No arrhythmias occurred in the first 6 months. No patients suffered lead dysfunction. Two patients died, not for reasons related to the procedure. Thus the rate of freedom from procedure-related serious adverse events at 6 months was 16/18 (89%). The complications which occurred are listed in more detail below.

Stroke and TIA

- Patient 8 suffered a lacunar ischaemic stroke after 5 months with partial neurological recovery, which was associated with labile INRs.

- Patient 10, who had a history of previous TIA and known severe carotid artery disease, had a probable TIA (based on history, although he was not seen by a doctor for several days) about 6 weeks after the procedure. No change in medication was made; he has not had further events.

Death

- Patient 4 died of pneumonia after 3 months. This was based on information from the treating doctors; she did not have a post-mortem. There was no apparent link to the procedure and she appeared to have been improving when seen about 2 weeks previously.
- Patient 12, a non-responder to CRT with severe heart failure, was included on the basis of an apical anterior LV lead position, persistent broad QRS during optimised BiVP and persistent severe symptoms. He did not improve, and died 5 months after the procedure of progressive heart failure.

Clinical follow-up

Clinical response at 6 months was variable dependent upon the method of assessment. The primary response outcome defined was Packer clinical composite score, which improved at 6 months in 12/18 (67%) and worsened in 6/18 (33%). As shown in Figure 61, Figure 62, and Table 24 below, there were significant improvements in NYHA class, 6-minute walk test distance and quality of life as measured by the EQ 5D-5L. Clinical response was similar between patients recruited on the basis of failed lead placement (9/13; 69%) and in prior non-responders (3/5; 60%; P=NS).

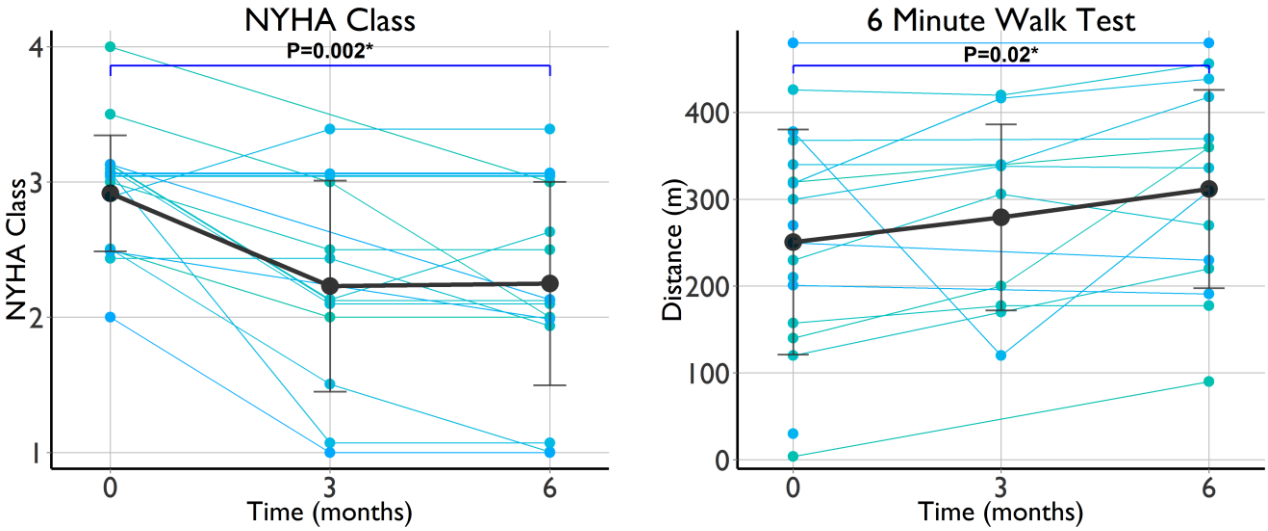


Figure 61 – Clinical response as measured by NYHA Class and 6-minute walk test

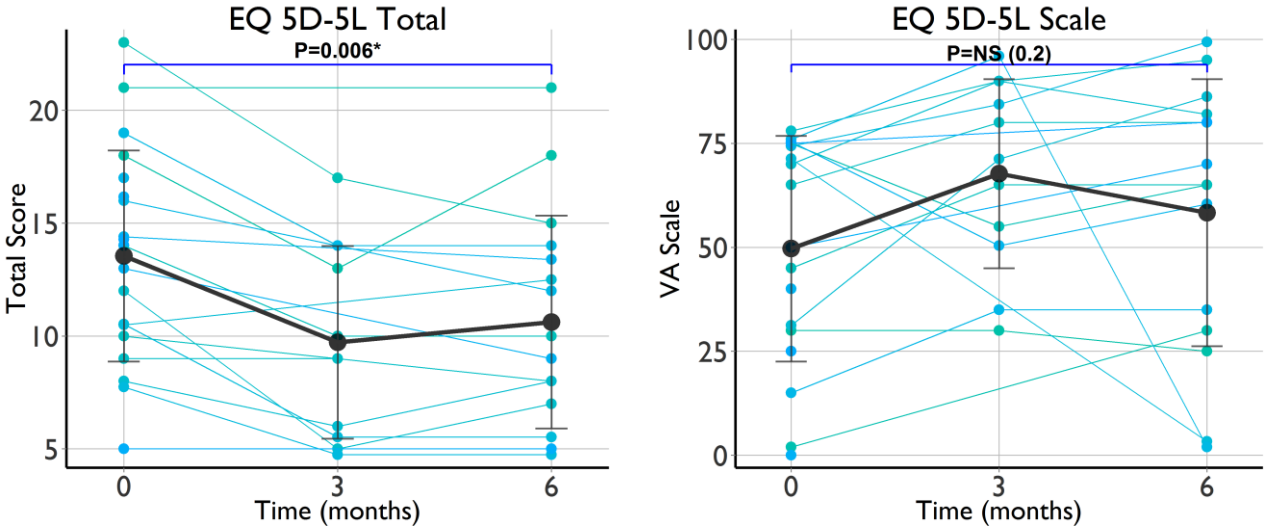


Figure 62 – Clinical response as measured by EQ 5D-5L total score and visual analogue scale

	Baseline	6m	Mean Change	Responders	P	Criterion	Test
NYHA Class	2.9 ± 0.4	2.3 ± 0.8	-0.7	8/18 (44%)	0.002*	≥1 class decrease	W
6 MWT (m)	267 ± 129	312 ± 114	45	9/15 (60%)	0.02*	≥10% increase	T
EQ 5D-5L Total	13 ± 5	11 ± 5	-3	9/16 (56%)	0.006*	>1 decrease	W
EQ 5D-5L VAS %	55 ± 25	58 ± 32	3	9/15 (60%)	NS (0.2)	>5 increase	W
BNP (pg/mL)	77 ± 99	81 ± 123	10	6/12 (50%)	NS (0.8)	≥10% decrease	T

Table 24 – Clinical response results in more detail. Statistical test performed: W – Wilcoxon signed rank test. T – T-Test.

Echocardiographic response rates were higher than clinical response, as shown in Figure 63 and Table 25, and were non-significantly higher in failed implants (10/11; 86% on the basis of LV EF) than in prior non-responders (3/5; 60%; P=0.14 by Fisher's exact test).

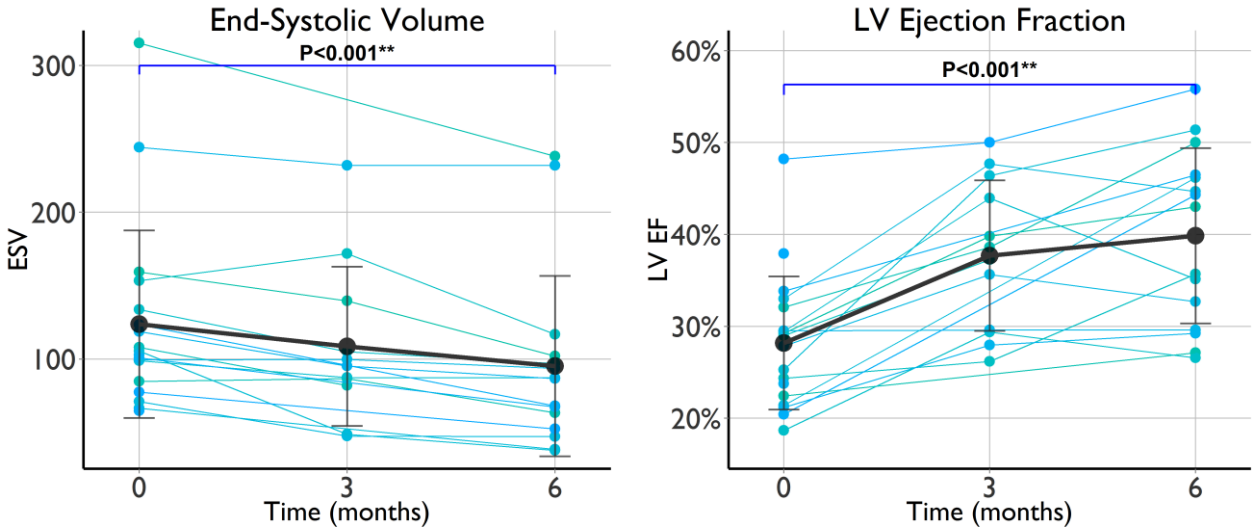


Figure 63 – Echocardiographic Response as measured by ESV and EF

	Baseline	6m	Mean Change	Responders	P	Criterion
ESV (mL)	129 ± 66	94 ± 60	-34mL	13/16 (81%)	P<0.001*	≥15% decrease
EF %	28 ± 7%	40 ± 9%	11.8%	13/16 (81%)	P<0.001*	≥5% increase

Table 25 – Echocardiographic response rates. Paired T-tests used for both comparisons.

Extended follow-up

Patients were followed up with telephone calls for two years, as per the protocol. At the time of writing 9/20 patients have exited the study, after 2 years' follow-up or death. Total follow-up for the LVCONSEPT patients is to date 1.5 ± 0.8 years, a total of 27.3 patient-years.

Additional adverse events which occurred are detailed below.

Stroke and TIA

- No additional events occurred after those in the first 6 months detailed above.

Death

- As discussed above, two patients died at 3 and 5 months post-procedure.
- Patient 3 died 13 months post procedure of pneumonia. He was recruited on the basis of non-response to CRT; he had no improvement symptomatically after endocardial pacing but did improve in terms of EF and LV volumes. He had a history of prior slow ventricular tachycardia which recurred 9 months post procedure but was controlled medically. He continued to slowly decline before developing a fatal pneumonia.

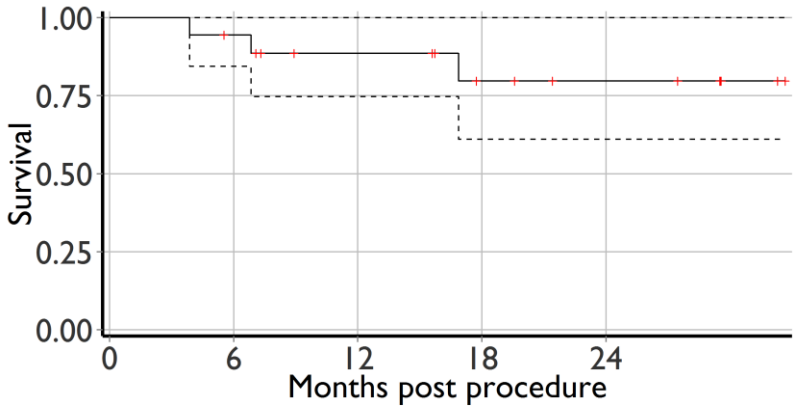


Figure 64 - Kaplan-Meier survival curve for the LVCONSEPT patient group. The dotted lines represent the 95% CI.

Arrhythmia and lead dysfunction

As discussed above, one patient with prior VT had further VT. No additional events occurred. No patients suffered lead dysfunction.

Electrical parameters

Lead capture thresholds were stable in all patients over 6 months, with expected falls between implant and first follow-up. In a subset of patients who were followed up in Oxford, long term electrical results were available.

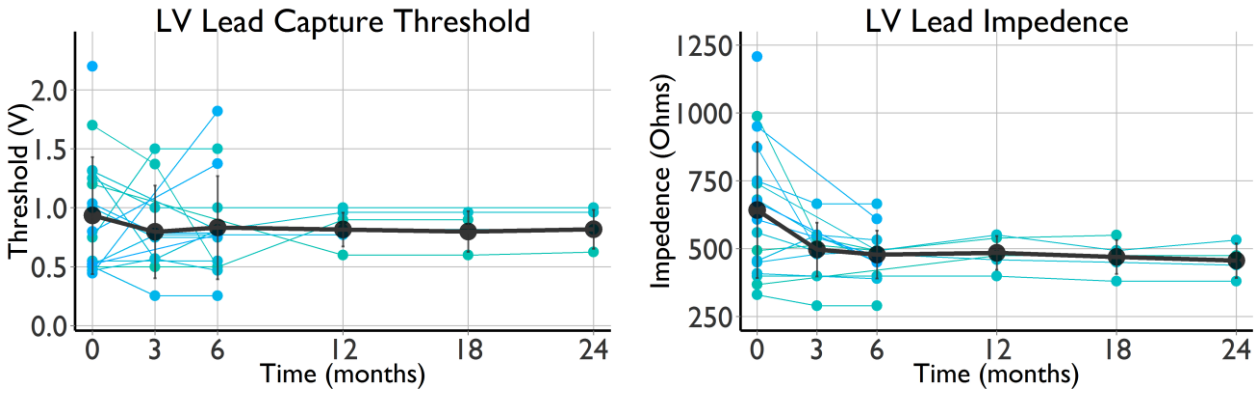


Figure 65 – Long-term electrical parameters. Left; lead capture threshold in Volts. Right: Lead impedance in Ohms. Note limited numbers of patients in whom long-term results are available.

Summary of Adverse Events over Extended Follow-up

Adverse events are summarised in Table 26 below. The number of events is very small, and so whilst it is possible to calculate confidence intervals for this data based on the Poisson distribution, they are not very informative. For all of the results the 95% CIs are extremely broad.

Event	Number	Rate per 100 patient-years	95% Confidence Interval
TIA	1	3.67	0.1-20.4
Stroke	1	3.67	0.1-20.4
Lead failure	0	0	
VT/VF	1	3.67	0.1-20.4
Transplant	0	0	
Death	3	11.00	2.3-32.1

Table 26 - Summary of adverse events during LV CONSEPT follow-up, over 27.3 patient-years. Poisson Confidence Intervals are shown.

Registry follow-up

The nine registry patients have been followed-up for 24 ± 19 months, a total of 17.6 patient-years. Two patients have been lost to follow-up, one has had a cardiac transplant, and three have died.

Clinical follow-up for response was of limited quality and was not systematic, but 7/9 patients were felt by the treating physicians to have improved clinically.

Stroke and TIA

- One patient had an ischaemic extension of an old stroke one year after the procedure, reportedly with the INR >2 at the first measurement after the event.

Arrhythmia and Lead Dysfunction

- One LV lead ceased to capture apart from at very high output (>5 volts) 3 months after implant. Chest radiography was unchanged suggesting micro-displacement or lead tip exit block. He died 3 years later.
- One patient continued to experience frequent VT storms despite symptomatic improvement to NYHA class II, although without clear echocardiographic response. After unsuccessful attempts at catheter ablation he underwent emergency cardiac transplantation.

Death

- One patient died from severe sepsis arising from septic arthritis in his knee, 3 weeks after the implant procedure. No evidence of endocarditis or lead infection was seen on acute echocardiography. A post mortem examination was not performed.
- Two patients died of progressive heart failure, after 2 and 3 years follow-up respectively.

Combined follow-up

Using data from both the registry and LVCONSEPT study patients allows an overall assessment of outcomes.

Event	Number	Rate per 100 patient-years	95% Confidence Interval
TIA	1	2.23	0.1-12.4
Stroke	2	4.46	0.5-16.1
Lead failure	1	2.23	0.1-12.4
VT/VF	2	4.46	0.5-16.1
Transplant	1	2.23	0.1-12.4
Death	6	13.38	4.9-29.1

Table 27 - Summary of adverse events during combined registry and trial patients follow-up, over 44.8 patient-years. Poisson Confidence Intervals are shown.

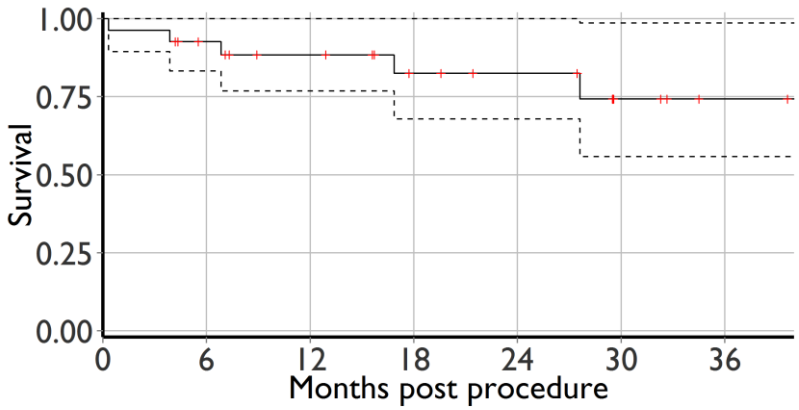


Figure 66 - Kaplan-Meier survival curve for the combined study and registry cohorts

Discussion

Summary of results

- I recruited 20 patients for endocardial LV pacing, in all of whom a lead was placed successfully, with 85% free of acute procedural complications
- Clinical improvement based on the CCS was observed in 69% of patients, and echocardiographic response by the ESV in 73%.
- Long-term complications in the entire cohort I followed up included a rate of 4.5 strokes per 100 patient-years
- Endocardial LV lead electrical function appeared to be stable over time
- About 75% of patients were alive at 3 years

Procedure

The procedure appears from this cohort to be reasonably safe, with 85% of patients free of acute complications. Those that did occur were manageable. It was shown in the BRUISE-CONTROL study that performing CRT procedures on therapeutic anticoagulation is safe (Birnie 2013). This trial's 10% rate of significant haematoma is higher than the 3.5% observed in their warfarin arm and also higher than in the ALSYNC study, where there was a 3% haematoma rate (Morgan 2015). This may be chance, or due to the additional intra-procedural heparin given during the pacing protocol.

Displacement of a 1-year old RV lead was unexpected but is unlikely to be specifically related to our technique.

The procedure can also be performed in a reasonable time, 25 ±19 minutes to access the left ventricle, probably faster than in the ALSYNC study where the investigators reported 18 ± 14 minutes to reach the fossa ovalis, 11 ± 21 minutes to puncture the septum, and

33 ± 26 minutes to place the lead. As a result of the electro-anatomical mapping and AHR protocol we did not place the LV lead immediately after gaining access and thus were unable to directly compare the two procedures. Placing the lead was generally relatively straightforward, as the puncture direction leads the sheath towards the lateral basal LV, where the late activation areas we targeted are in most patients.

The equipment used is all adapted for the purpose, and not designed for this use. Our use of electro-cautery onto a standard vascular access wire provided an inexpensive method of puncturing the septum, and appeared safe in Dr Betts' hands. In some cases it was challenging to direct the steerable Agilis sheath up onto the septum, again as it is not designed for this. In the final patient where vascular access was difficult, it was particularly challenging to manipulate the Agilis sheath. Steering the lead to its final position was also challenging in some patients.

CRT response

Response results were broadly within the range expected and are comparable to those of standard CRT (Chung 2008, McAlister 2007). Our trial's echocardiographic response rate at 70-90% was higher than the 60% seen in most studies (Chung 2008) and our clinical response rates based on the CCS were as expected, as 65-70% of patients are expected to improve with this metric (Chung 2008). In particular, our response rates based on ≥ 1 class increase in NYHA class, at 44% were low (the discrepancy between NYHA response and CCS is due to several patients improving by less than a full class).

It may well be that this relatively low clinical response rate is a feature of the high-risk and comorbid patient group recruited, rather than a limitation of the technique. Candidates who were relatively well and had failed conventional lead placement were unlikely to be recruited as they were suitable for surgical lead placement, leaving the study with a complex and extensively comorbid patient group in whom response was often limited by

cardiopulmonary comorbidities. This level of comorbidity is relatively hard to demonstrate in patient demographics. This is supported by the higher echocardiographic response rates, supporting the clinical suggestion that there were several patients in whom cardiac function was not the limiting factor.

In addition, 78% of our patients had atrial fibrillation. Most trials show worse response outcomes in patients with AF (Wilton 2011), although others have shown that if patients are managed optimally with AV node ablation where needed the outcomes are improved (Gasparini 2013). Our patients all had AV node ablation if ventricular rate control was not good.

Assessment of both response and safety in our small cohort is unavoidably limited by the small number of patients recruited, resulting in very wide confidence intervals. In addition, it is well-established that response rates in small unblinded trials like mine may often be higher than found in larger trials with more bias-resistant design (Jabbour 2015), as I showed in my meta-analysis of other trials of endocardial pacing.

Long-term adverse events

It is clear that long term adverse events are the key issue after LV endocardial pacing. In Chapter 3, I attempted to assess this in trials published so far, and found with 365 patients and 535 patient-years of follow-up, a rate of stroke of 2.4 events per 100 patient-years (95% CI 1.4-4.2). The rate in my combined trial and registry cohort of 4.5 strokes per 100 patient-years is not statistically significantly different (P=0.42). This fits clinically, as although the higher stroke rate I have found in our group is concerning, it would seem unwise to make any definite conclusions based on two patients.

Another method to estimate the expected stroke risk in the LVCONSEPT patient group is the use of published data to calculate personalised risk based on the CHA_2DS_2-VASC

score (Olesen 2011). This gave a mean annual risk of stroke or embolism of 2.4 ±1.2% on warfarin therapy. Despite evidence to suggest that the CHA_2DS_2-VASc score does not fully account for higher risks in heart failure patients (Melgaard L 2015), this would suggest that there is probably a small increase in the stroke rate over that expected in this patient group, which could be attributed to the effect of the endocardial lead.

As has been reported in other similar studies, at least one of the strokes which occurred was associated with poor control of INR levels, and careful screening for optimal INR control is essential. It is not however valid to make the conclusion that strokes in these patients at the time of low INR are due to thrombosis on the endocardial lead material. A meta-analysis of 30 studies of patients with AF taking warfarin showed that 57% of reported thromboembolic events were associated with an INR <2 (Mearns 2014). So we know that patients with AF have strokes when their INRs fall, even when they *do not* have lead material in their LV.

The same meta-analysis also investigates time in therapeutic range, and in a somewhat concerning result finds that the average was 61%. This is the reason why we chose an INR target of 2.5-3.5 for our patients, on the basis that this should result in patients more often being in therapeutic range. Most, although not all, of the prior trials of endocardial pacing have used this range, although there is not any comparison evidence to support this. The higher range may increase the risk of bleeding.

It might be that the use of non-warfarin direct oral anticoagulants (NOACs) would provide more reliable anticoagulation and thus be safer. There is minimal experience of NOACs in patients with endocardial LV leads, with only one trial reporting this in a small number of patients (Elencwajg 2012). The anticoagulant effect of NOACs is generally considered to be equivalent to an INR of 2-3, and a trial of the use of dabigatran in patients with prosthetic valves versus warfarin at a higher INR showed dabigatran to be

worse (Eikelboom 2013), which would suggest that NOACs would not be suitable for this indication. Despite this, the benefit of NOACs in their trials against warfarin in AF largely appears to be due to more reliable INR control, and their benefit was greatest in patients with poor time in therapeutic range, suggesting that NOACs might be superior in the endocardial pacing context, in particular in patients who find warfarin INR control difficult.

To what extent LV endocardial pacing increases the risk of stroke remains unclear. Comparison with CHADS-VASc predictions would suggest an increase of ~3 events per 100 patient-years, but as discussed this is probably an over-estimate due to the inability of CHADS-VASc scores to fully account for higher risks in heart failure patients. In terms of consenting patients for endocardial pacing, a 1-2 additional events per 100 patient-years range seems reasonable. This should be accompanied by advice about extreme caution in controlling INR levels and warfarin dosing to maximise time in therapeutic range.

Conclusions

- LV endocardial pacing across the interventricular septum as a second-line option for LV lead placement is acutely and chronically acceptably safe.
- Response rates are broadly comparable to those expected in the patient group recruited.
- There is likely to be an increase in the rate of stroke over that expected in these patients, of the order of 1-2 per 100 patient-years.

Chapter Eight – **Left ventricular lead location, electrical and mechanical delay**

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Introduction

In these experiments I aimed to investigate methods to optimise the LV lead position for CRT. As discussed before, it remains unclear which method of selecting the LV lead site results in the best acute or chronic response.

In IDEAL-CRT I aimed primarily to investigate the relationship between the acute haemodynamic response to biventricular pacing within the vein identified as the site of latest mechanical activation compared to other accessible veins. In addition, I assessed the influence of electrical delay at the pacing sites on response. The aims of the study were

predominantly related to acute outcomes, but patients were followed up at 6 months additionally.

In LVCONSEPT the primary outcomes, as discussed in prior chapters, were safety and clinical. During the implant procedure we also assessed AHR to BiVP at several endocardial LV pacing sites, investigating similar outcomes for this related cohort.

IDEAL-CRT study results

Methods

These were discussed in detail in the methods section, but are summarised here. Patients with standard indications for CRT were recruited. Speckle-tracking echocardiography was used to identify the segment of latest mechanical activation (LMA) as in the TARGET and STARTER trials. AHR was recorded using a pressure wire as change in LV dP/dt max from a baseline of A-V sequential DDD-RV pacing to DDD-BiV pacing over 30 seconds.

In each patient, the vein in the LMA was accessed, as well as the other best available vein in the opinion of the operator. We assessed AHR in both veins, using unipolar pacing at each pole of a quadripolar lead, 3 times, in a randomised order. Veins were classified as lateral if they were in one of the four lateral 17-segment model segments (basal and mid anterolateral and posterolateral).

We measured the QLV time from surface ECG Q wave onset to LV electrode activation at each pole during RV pacing. GLMM methodology was primarily used for analysis.

Results – acute haemodynamic studies

Patients

22 patients were recruited over 9 months. Summary patient characteristics are shown in Table 28 below, representing a reasonably typical population receiving CRT.

Parameter	Result
Age	69 ± 18
Male	17 (77%)
QRS Duration	153 ± 24
Ischaemic aetiology	14 (64%)
Persistent atrial fibrillation	4 (18%)
Baseline NYHA class	2.7 ± 0.5

Table 28 – Baseline clinical characteristics of the IDEAL-CRT patient population. Mean ± Standard Deviation or n (percent of total) shown

Baseline echocardiography

Target segment	Patients
Anterior	5 (23%)
Lateral	13 (59%)
Posterior	4 (18%)
Basal	12 (55%)
Mid-ventricular	10 (45%)

Table 29 – Echocardiographic baseline results and target segments identified on speckle-tracking echocardiography

Baseline LV EF was relatively high at 29 ± 8%. 3 patients had baseline EF ≥35%. One of these had an indication for CRT of moderate LV impairment (EF ~40%) and a need for pacing (CRT is known to prevent LV deterioration in this situation (Curtis 2013)), and two patients had standard indications for CRT, prior imaging suggesting an EF of <35%, but an EF on my research echo of 35-40%.

17 (77%) of patients had LBBB, 3 (14%) had intraventricular conduction delay, and 2 (9%) had RBBB. Of the 17 patients with LBBB, 6 had underlying RV pacing, and 10 met Straus' criteria for the 'strict' diagnosis of LBBB (Strauss 2011).

Four patients screened were excluded before recruitment as speckle-tracking image quality was too poor for reliable identification of a target site.

Acute haemodynamic results

In two cases safe arterial access was not possible, and in one case equipment failure prevented assessment, thus some acute haemodynamic measurements were possible in 19/22 patients (86%). We accessed 1.9 ± 0.4 veins per patient, which by testing each available quadripolar lead cathode, resulted in 6.9 ± 1.9 pacing sites per patient and 3.7 ± 0.7 sites per vein. It was possible to access the vein in the LMA segment and a comparator vein in 16 patients (73%); in the remaining three patients one or two veins could be accessed, but not both the LMA segment vein and a comparator, such that we assessed 37 veins in total.

Mean baseline dP/dt max was 962 ± 190 mmHg/s, increasing to 1061 ± 230 mmHg/s with biventricular pacing, representing a mean absolute AHR of 98 ± 81mmHg/s, and a percentage AHR of +10 ± 8%.

Per-patient vein choice results

Moving on to analyse the results on an individual patient basis, the LMA vein had a mathematically greater AHR in 50% of patients, but testing the difference using GLMM to compare between veins in each patient found only showed a significantly greater AHR in the LMA vein in 2 patients (13%), and a significantly greater AHR in the comparator vein in 4 patients (25%).

The vein with the highest AHR was lateral 65% of the time, but 5/6 (83%) of the veins that had a significantly higher AHR were lateral. The vein containing the longest QLV measurement had the highest AHR in 59% of patients, but again 5/6 (83%) of the significantly higher AHRs were in the vein with the longest QLV.

None of these per-patient results achieved significance due to the small patient numbers.

Quadripolar pole selection

Using GLMM to assess AHR to BiVP factored by the pole of the quadripolar lead used as the cathode, there was no pole that was significantly greater than the others across all patients. The results of GLMM analysis of AHR by pole are shown in Figure 80 in the discussion section below.

On an individual vein basis, a pole with significantly greater AHR than others in that vein could be identified in 76% of 35 assessed veins by GLMM comparison of differential least-squares means of AHR from each pole, allowing for multiple comparisons in each vein. The AHR difference between the best and worst poles in each vein was 5.6 ± 6.5%, and the difference between the best and worst veins in each patient was 6.5 ± 4.9%. The difference between poles was greater than the difference between veins in 54% of patients.

The effect of the LMA vein and mechanical delay

Using a simple mean method as in other studies, percentage AHR in comparator veins was 11.3 ± 2.0% (mean ± standard error), and in LMA veins 9.4 ± 1.5%. Making a comparison of these by a t-test for n=16 patients, the difference was not significant at P= 0.45, although as discussed this methodology is overly simplistic.

From univariate analysis of every beat by GLMM, mean percentage AHR in Comparator veins was 11.3 ± 1.5%, higher than that in the LMA veins at 9.8 ± 0.6%, with this difference achieving significance (P= 0.012). This is illustrated in Figure 82 in the discussion section below.

The mechanical delay values, i.e. the time to peak strain in each segment as assessed by speckle-tracking echocardiography were not predictive of AHR using a GLMM model in the IDEAL-CRT cohort (P=0.74).

Electrical delay

GLMM analysis of the overall relationship between electrical delay, as measured by QLV, and AHR to BiVP in the IDEAL-CRT cohort found no overall significant relationship (P of non-zero relationship 0.56). On an individual patient level, there was a significant relationship by GLMM in 7/19 patients (37%).

Within each vein, the pole with the longest electrical delay had a greater AHR for 13/37 (35%, P=NS) of assessed poles, and a significantly greater AHR for 8/14 (57%; P=NS).

When QLV results were dichotomised, (as in other studies (Gold 2011b, Zanon 2014)) as being greater or less than 100ms, there was a significant effect. QLV <100ms was associated with a 2.9% (95% CI -3.5 to -2.5%; P<0.001) decrease in AHR.

Pacing site

There was a significant effect of the LV segment paced on AHR, with in general lateral segments having a higher AHR than non-lateral, in the 8 targeted basal and medial segments. Considering a simplified 4-segment model, the only segment that was significantly worse than the others was the posterior segment, as shown in Figure 67 below, although it is important to note that no leads were truly anterior.

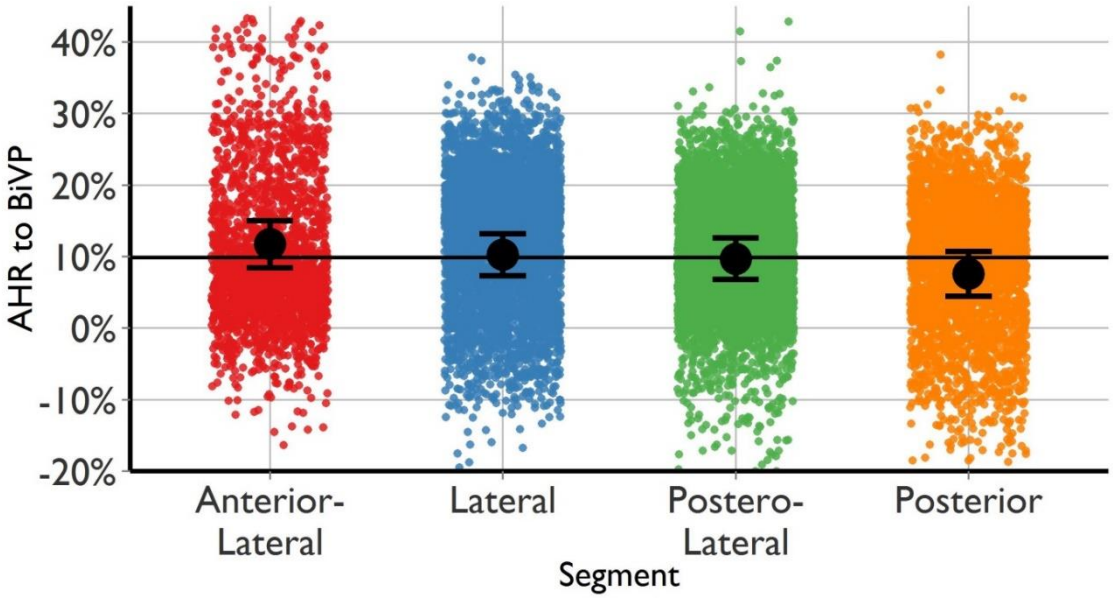


Figure 67 - Four-segment model comparison in the IDEAL-CRT epicardial pacing cohort. There were no significant differences from the overall mean, apart from the posterior segment, which was significantly worse (P=0.028).

Lateral lead positioning was not a significant predictor of AHR in univariate analysis, with a predicted increase in AHR of 0.6% (-0.8 to +1.9%; P=0.39).

The presence of scar suggested by echocardiography in the segment of the pacing site, which from prior work would be expected to reduce response to CRT, was associated with a significantly *higher* AHR to BiVP by 3.3% (95% CI 0.9-5.6%; P=0.007).

Other clinical factors

I tested the association of pre-procedural clinical factors with AHR to BiVP. The presence of LBBB ECG morphology, age, and baseline QRS duration were not significantly associated with AHR.

Multivariate Analysis of predictors of AHR

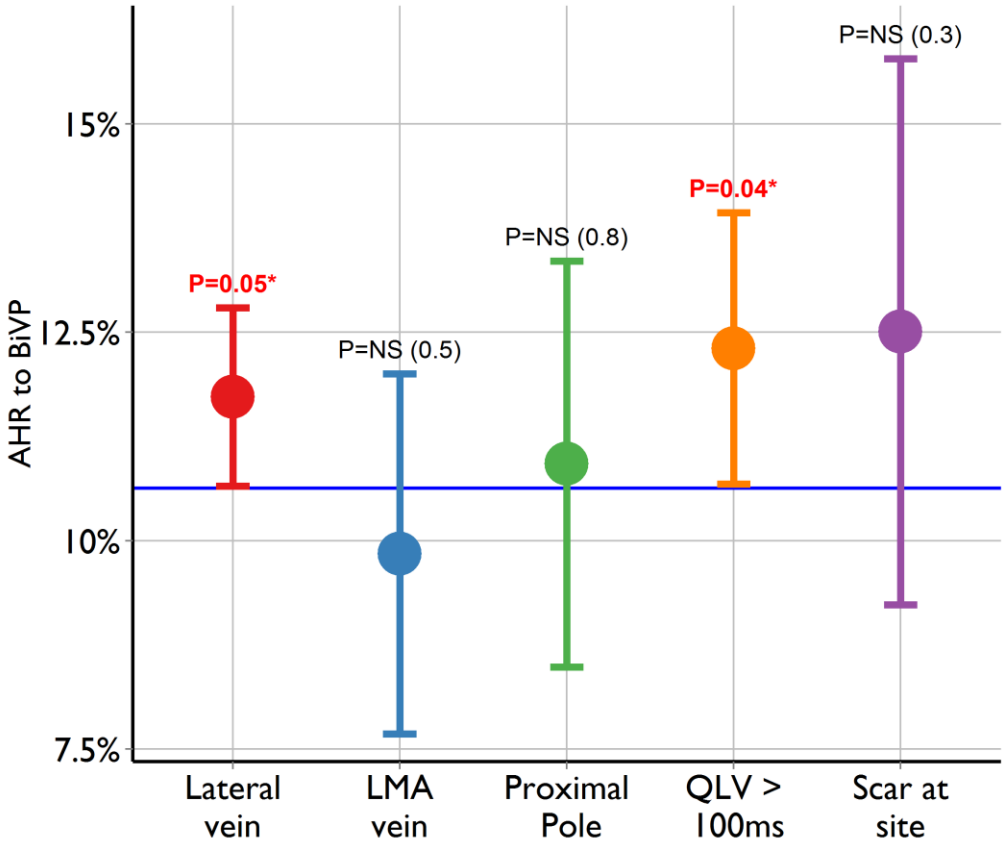


Figure 68 - Overall effects on percentage AHR of different parameters commonly proposed as methods to select LV lead pacing site in the IDEAL-CRT study. Mean effect and 95% confidence intervals are plotted, with probability of significant difference from the overall mean, shown in blue.

Finally, I used a multivariate GLMM model with all of the factors commonly suggested as methods to select a pacing site as binary predictors. For this model I separated poles into proximal (M-3 and P-4) and distal (D-1 and M-2), and dichotomised QLV using a cut-off of 100ms as above. In this model there were significant effects of lateral positioning and QLV>100 ms. The results are shown in Figure 68 above using percentage AHR for clarity, although they were the same using absolute change in AHR.

Results – clinical follow-up

Four patients were unable to return to Oxford for follow-up, and only limited response information was available for them. One patient died of a stroke 2 months post-procedure. The 3 patients in whom the acute haemodynamic measurements were not possible were considered to have exited the study at that stage and were not followed up. Thus 15 patients were seen for full follow-up, at 7.5 ± 2 months after the implant procedure, and 18 patients had some follow-up data available.

Based on the Packer Clinical Composite Score assessment 11/19 patients (58%) improved, 3 (16%) were unchanged, and 5 (26%) worsened or died.

QRS width decreased by 26ms, to 130 ± 20ms, suggesting good resynchronisation.

Other response rates were variable depending on the criterion used, as shown in Table 31 and Figure 69 below. Clinical response rates were low in this cohort, with a response based on NYHA class and 6-minute walk test being particularly low. The clear discrepancy between NYHA class and CCS was due to patients improving by less than one class, or not changing NYHA class but feeling better and improving on the quality of life assessment.

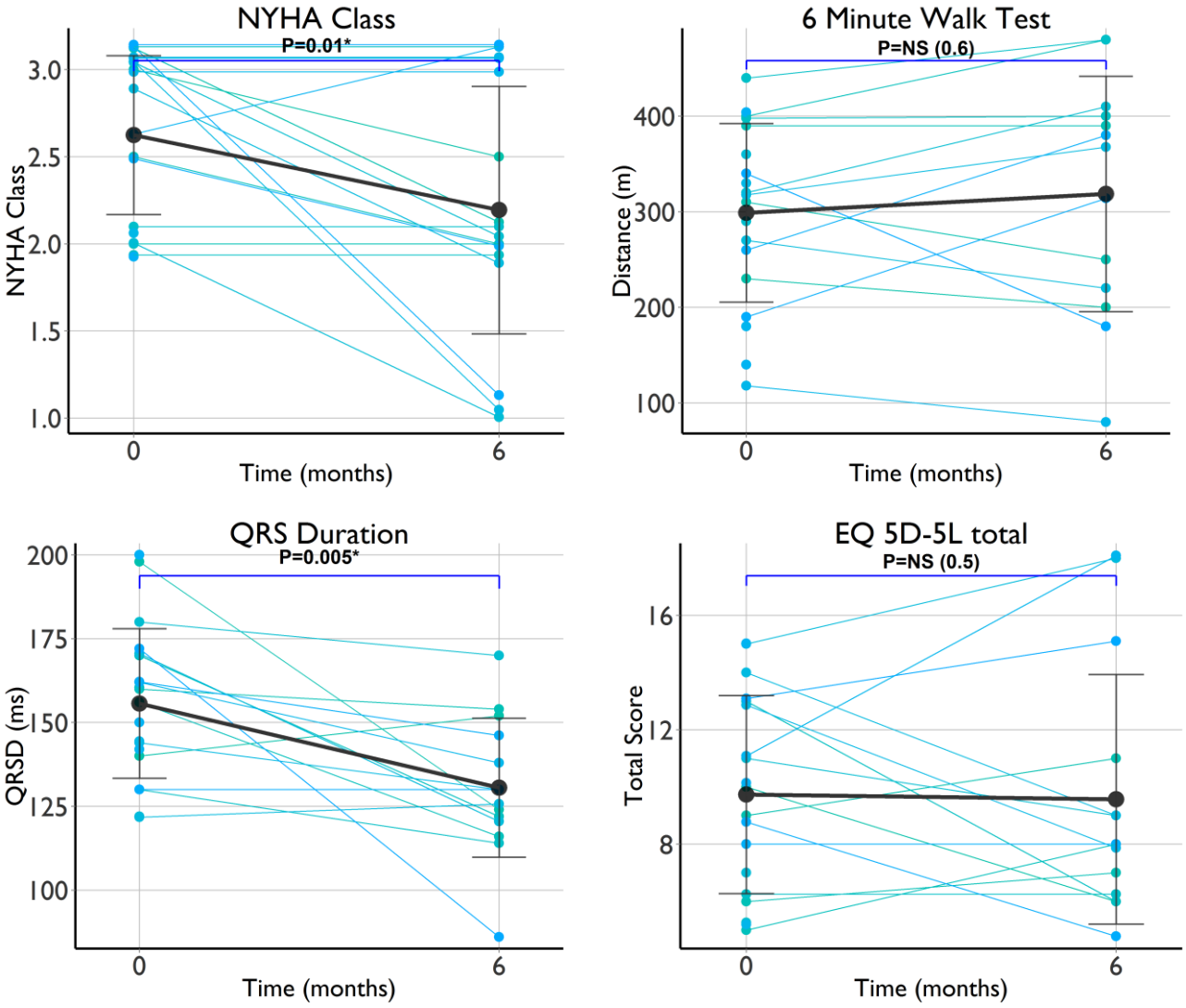


Figure 69 - Clinical response to CRT in the IDEAL-CRT cohort. P values from tests as per Table 30 below.

	Baseline	6m	Mean Change	Response	P	Criterion	Test
NYHA Class	2.7 ± 0.4	2.2 ± 0.7	-0.5	6/18 (33%)	0.01*	≥1 class decrease	W
6 MWT (m)	306 ± 92	319 ± 123	13	5/13 (38%)	NS (0.6)	≥10% increase	T
EQ 5D-5L Total	10 ± 3	10 ± 4	-1	6/14 (43%)	NS (0.5)	>1 decrease	W
EQ 5D-5L VAS %	63 ± 17	65 ± 23	2	7/14 (50%)	NS (0.3)	>5 increase	W

Table 30 – Clinical response rates. Tests performed: T- paired T-tests; W-Wilcoxon signed-rank test.

Echocardiographic response rates based on LVEF were higher, as shown in Figure 70 and Table 31, and although fewer patients met the criteria for response based on LV ESV, there was a clear trend towards a decrease in this parameter.

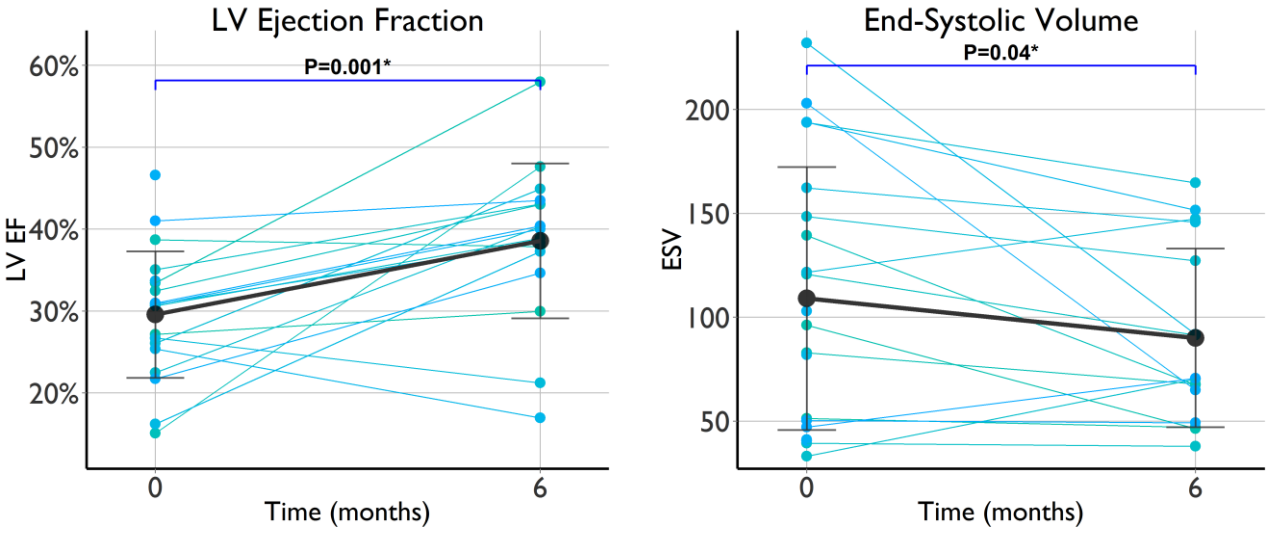


Figure 70 – Echocardiographic response to CRT in the IDEAL-CRT cohort. P values from paired T-tests.

	Baseline	6m	Mean Change	Response	P	Criterion
ESV (mL)	120 ± 65	90 ± 43	-30	7/16 (44%)	0.04*	≥15% decrease
EF %	29 ± 7%	39 ± 9%	10.1%	12/17 (71%)	0.001*	≥5% increase

Table 31 - Echocardiographic response to CRT. Paired T-tests were performed for both.

LVCONSEPT acute haemodynamic results

Methods

The methods used were similar to those used before, and were discussed in the methods section. The LMA site was identified from speckle-tracking echocardiography. The site of latest electrical activation (during RV pacing) was identified using electro-anatomic mapping. It was relatively hard to move between pacing sites (unlike simply changing quadripolar lead pole in IDEAL-CRT) and so rather than multiple 30-second recordings at each site, I made one 2-minute recording.

We assessed the following sites (where possible) in each patient:

6. LMA
7. LEA
8. Empirical positioning on the baso-lateral wall
9. At the LV apex

In addition, we assessed the LV endocardial site that was as close as possible to any pre-existing LV leads, although this was only possible in 6 patients with pre-existing LV leads.

Results

I was able to assess AHR in 18/20 patients at 3.9 ± 0.4 sites per patient (range 3 - 5). As mentioned in the prior chapter, in two patients AHR results were not possible due to procedural challenges. There was adequate image quality to allow assessment of the LMA site in 19/20 patients. The LEA site could be identified in all of the 18 patients in whom we attempted this.

Mean baseline dP/dt max was 623 ± 187 mmHg/s, increasing to 700 ± 186 mmHg/s with biventricular pacing, a mean absolute AHR of 81 ± 76 mmHg/s, and percentage AHR of 15 ± 17 %.

Endocardial pacing site

The LMA site derived from echocardiography and the LEA site from the electro-anatomic map were the same segment in 3 patients (18%), and in 43% of patients they were within one segment.

On an individual patient basis, I assessed the best pacing site with GLMM analysis. In all 18 patients an optimal site could be identified. The best site was most often in the LEA segment, as shown in Figure 71 below.

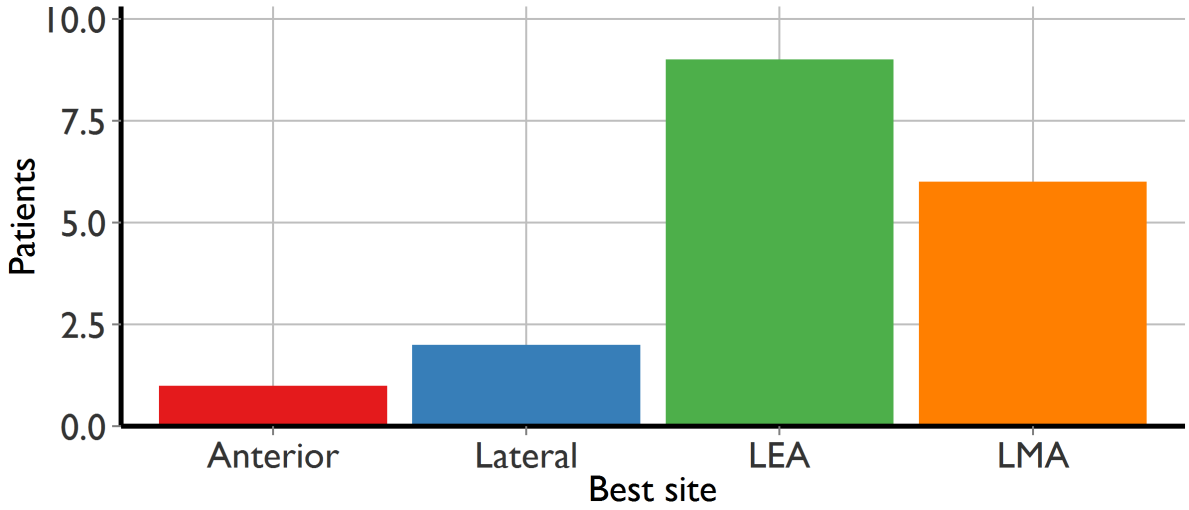


Figure 71 – The endocardial pacing site with the greatest AHR in each patient.

I used a GLMM analysis to compare AHR at all sites across all patients. As shown in Figure 78 in the discussion section below, positioning at the empirical lateral site, and at both of the LMA and LEA sites was associated with a significantly higher AHR than the overall mean.

I made a direct comparison based on AHR between the LEA and LMA sites in each patient, and again there was a significant difference in all 16 patients in whom both sites were assessed. The mean difference in AHR between the two was 9.2%. The LMA site was better in 7/16 (44%) patients.

Across all patients, there was a non-significant trend for the LMA site to have a greater AHR by 0.3% (95%CI -6.6 to +7.4%; P=NS (0.9)) as shown in Figure 81 in the discussion section below.

Electrical and mechanical delay

Unlike in the IDEAL-CRT cohort, there was a significant effect of QLV on AHR in univariate analysis across the range of QLV values, with a 3.2% increase in AHR per 20ms increase in QLV (95%CI +1.3 to +5.0%; P=0.003). Similarly, there was a significant effect of dichotomised QLV on AHR, such that sites with QLV >100ms had an 11.3% greater AHR (95%CI +5.4 to +17.2%; P<0.001).

Mechanical delay at each site, as measured by speckle-tracking echocardiography, was not associated with AHR. Both of these results are considered in more detail when combined with the IDEAL-CRT results below.

Multivariate analysis of predictors of AHR, similarly to the IDEAL-CRT epicardial pacing cohort, showed that the only significant predictor was QLV>100ms (P=0.03) although ischaemic aetiology was of borderline significance (P=0.053). There was a trend for a lateral pacing site to be associated with higher AHR, although this did not reach significance (P=0.16).

AHR via coronary sinus lead versus endocardial to the lead

In 6 patients with a pre-existing coronary sinus lead I was able to compare AHR via the CS lead with AHR at the endocardial aspect of that lead. The existing LV lead was connected

to the electroanatomic mapping system, and the endocardial catheter was manipulated to the endocardial aspect of it. There was no significant difference (trend of lower AHR at endocardial aspect by -5.7%; 95%CI -27.3 to +15.9%; P=NS (0.6)).

AHR during biventricular pacing and LV only pacing at the final site

In 17 patients pacing at the final site was conducted both as biventricular pacing and as LV only pacing. LV only pacing was associated with a lower AHR by -7.1% (95%CI -12.1 to -1.8%; P=0.01), as illustrated in Figure 72 below.

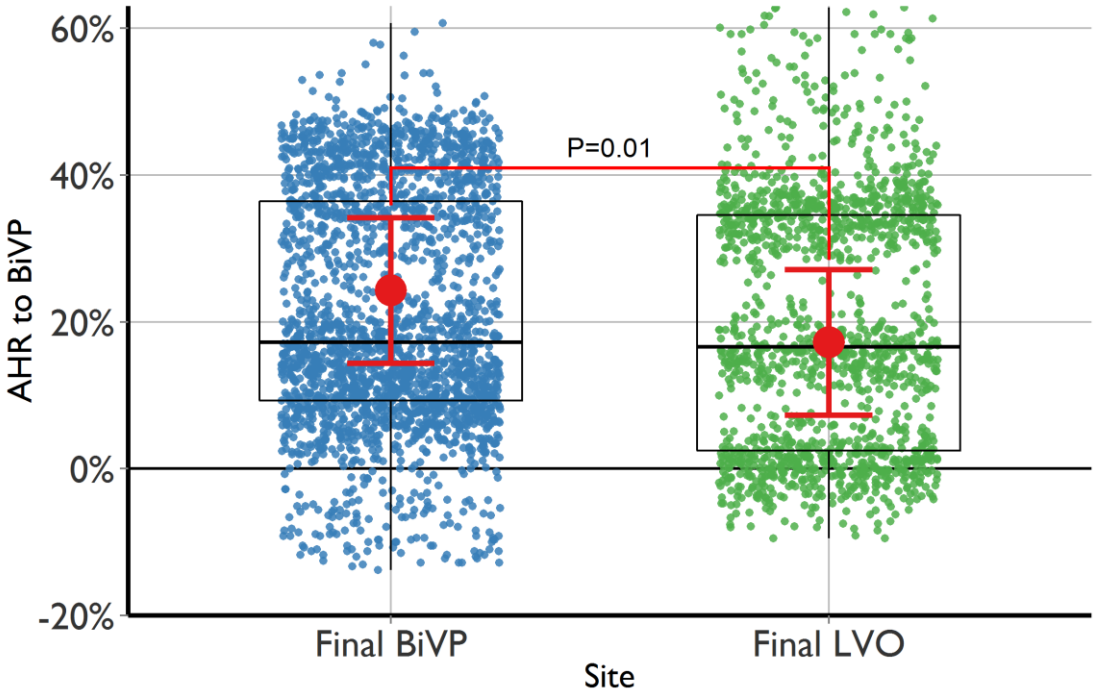


Figure 72 – Pacing at the final LV lead site in BiVP and LV only modes. Boxplot with GLMM estimates in red.

Synthesis of results

As the methods of my studies were similar, the opportunity arises to pool data, in order to look for predictors of both acute haemodynamic response and of chronic clinical and echocardiographic response in a larger data set. I will now report the results of this pooled analysis.

Pooled population

	All	Epicardial	Endocardial	P
N	40	22	20	
Age	66 ± 15	69 ± 18	67 ± 12	0.6
Male	33 (83%)	77%	80%	0.8
QRS Duration	155 ± 21	153 ± 24	157 ± 14	0.4
Ischaemic aetiology	23 (58%)	64%	45%	0.2
NYHA class	2.6 ± 0.5	2.7 ± 0.5	2.9 ± 0.4	0.7
EF	29 ± 7%	29 ± 8%	28 ± 7%	0.5
Atrial Fibrillation	16 (40%)	18%	60%	0.005*

Table 32 – Baseline clinical characteristics of the pooled LVCONSEPT and IDEAL-CRT patient populations. P values for comparison of LVCONSEPT (endocardial) and IDEAL-CRT (epicardial) groups by T-tests or Chi-square tests as appropriate.

There were 38 patients with AHR data available, in whom I assessed 208 pacing sites, 5.5 ± 2 sites per patient (range 1 - 8). Mean baseline dP/dt max was 861 ± 243 mmHg/s, increasing to 976 ± 270 mmHg/s with biventricular pacing, a mean absolute AHR of 93 ± 81 mmHg/s, and a percentage AHR of 11 ± 11%.

Combined speckle-tracking results

I analysed the combination of the mechanical delay timings derived from speckle-tracking echocardiography. As expected and as shown in Figure 73 below, mean delays were

shorter in the septal segments and the anterior segments, although these differences did not reach statistical significance. When the study was included as a modifier, patients in LVCONSEPT had significantly shorter mean delays, by 88 ± 18 ms (mean ± SE).

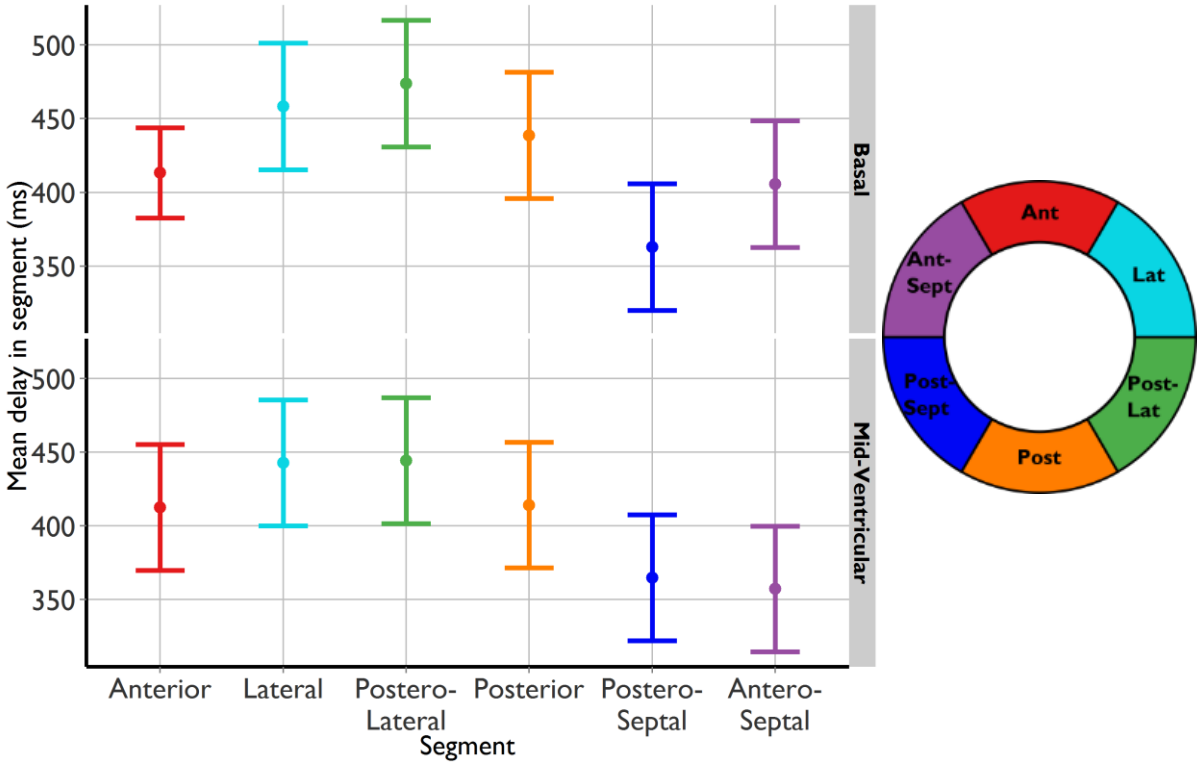


Figure 73 - Mechanical delay as estimated by speckle-tracking echocardiography, by segment and level. Mean figures calculated by GLMM. Mean and standard errors shown.

Mechanical delay was not significantly related to AHR to BiVP in the whole cohort, nor in either of the studies, although as would be expected there was a positive correlation (P=0.8 of no significant relationship; graph not shown).

QRS width as related to AHR in the combined population

QRS width was significantly related to AHR overall (overall trend of -2.0% decrease in AHR per 20ms increase in QLV (95%CI -3.2 to -0.7%; P=0.005), as shown in Figure 74 below.

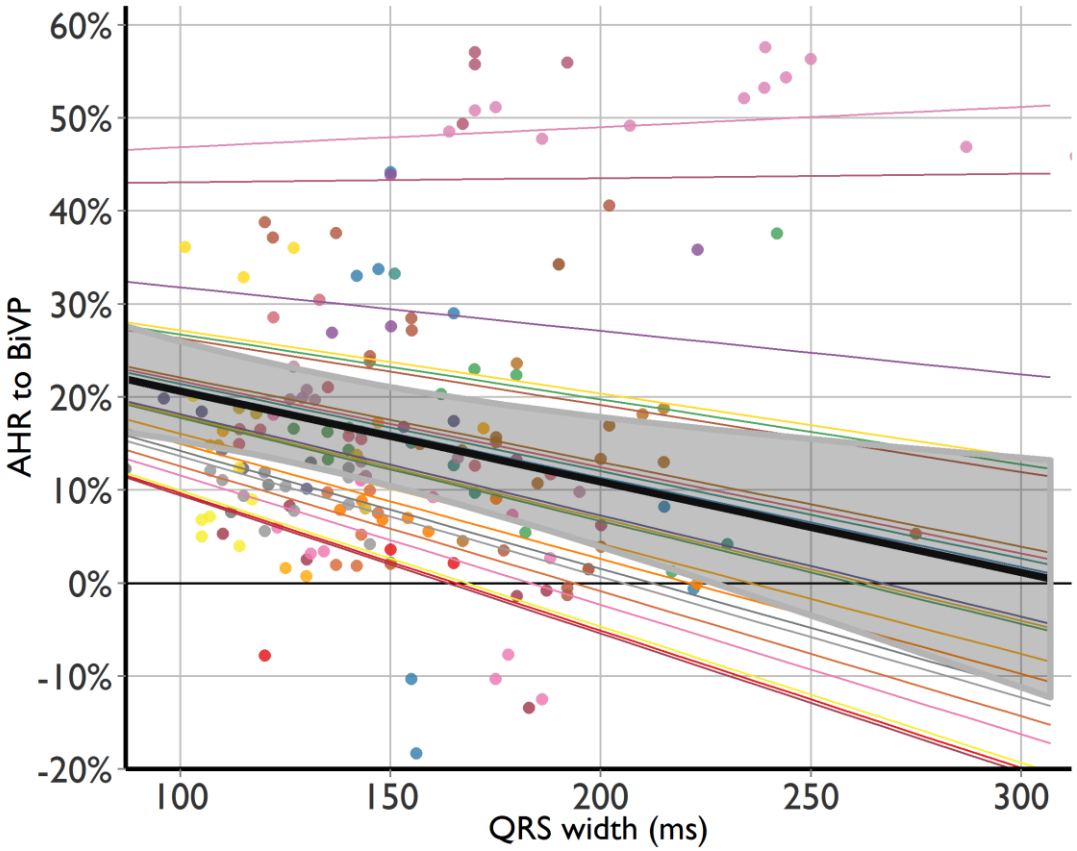


Figure 74 - QRS width versus AHR. GLM regression lines are shown for each patient, with the overall line and 95% CI in black and grey.

QLV results in the combined population

QLV was significantly related to AHR in the LVCONSEPT endocardial pacing group (+3.2% increase in AHR per 20ms increase in QLV; 95%CI +1.3 to +5.0%; P=0.003), but in the IDEAL-CRT epicardial pacing group there was not a significant relationship across the range of QLV values (0.3% increase in AHR per 20ms increase in QLV, 95%CI -0.69 to 1.3%, p=0.56 of no difference). The overall relationship between QLV and AHR, which was 1.3% increase in AHR per 20ms increase in QLV (95%CI +0.2 to +2.3%; P=0.02), is illustrated in Figure 84 in the discussion section below.

A cut-off value of QLV>100ms was predictive of response in both groups and overall, associated with an 11.3% increase in AHR in the LVCONSEPT group (p<0.001) and a 2.9% increase in AHR in the IDEAL-CRT group relative to QLV<100ms (p=0.007).

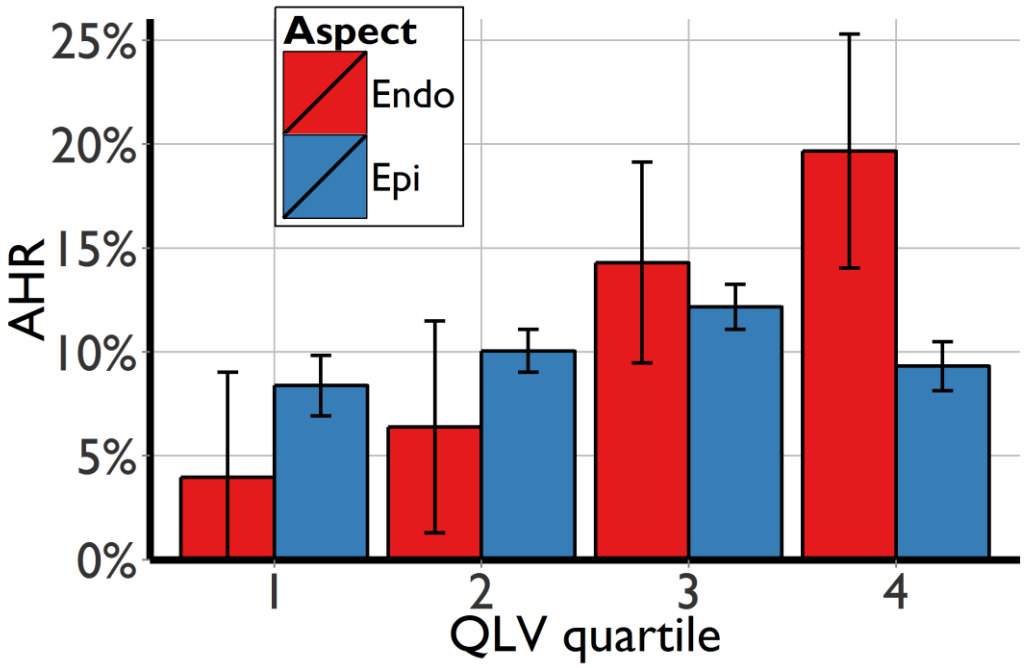


Figure 75 – AHR to BiVP by quartile of QLV, in the IDEAL-CRT cohort (Epi) and the LVCONSEPT cohort (Endo). Both cohorts are divided based on the combined group quartiles to allow for valid comparison. Range and median of both groups were similar.

The differential relationship of QLV to AHR in the two groups is illustrated in Figure 75 above, showing a relatively flat relationship across quartiles of QLV in the IDEAL-CRT cohort and a much steeper one in the LVCONSEPT patients.

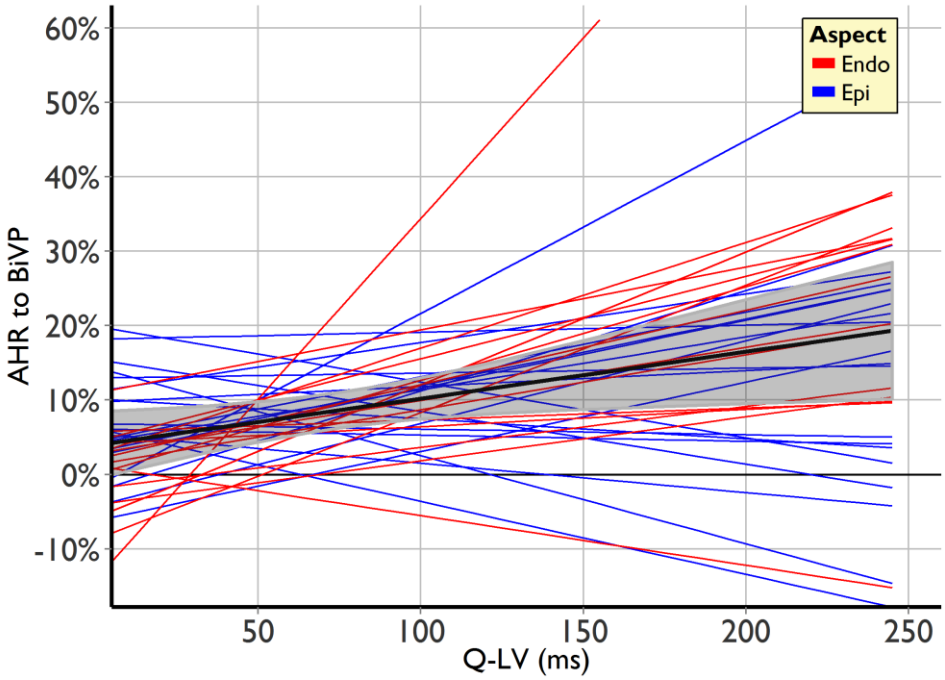


Figure 76 – GLMM lines for individual patients by pacing aspect. As can be seen, several of the blue lines representing epicardial pacing patients from the IDEAL-CRT study have a negative QLV-AHR relationship.

As shown in Figure 76 above it appears that the overall lack of linkage between AHR and QLV in the epicardial pacing (IDEAL-CRT study) is due to a greater degree of heterogeneity in the relationship between AHR and QLV. Only one patient with endocardial pacing had a negative AHR-QLV relationship, but 8/19 of the epicardial pacing group did. When the epicardial pacing group were subdivided by positive or negative QLV response, those with a positive response have a similar QLV-AHR relationship to the overall result of a 1.4% increase in AHR per 20ms increase in QLV (95%CI +0.8 to +2.0%; P<0.001), although this is still lower than the response for the endocardial pacing group, whereas the remainder have a significant negative response of -2.1% decrease in AHR per 20ms increase in QLV (95%CI -2.7 to -1.5%; P<0.001).

No significant clinical predictors of this group with a negative QLV-AHR relationship were found on analysis, although this was limited by the small numbers of patients in this group.

Similar results were found for QLV ratio (QLV divided by pre-procedure QRS width). QLVR was a powerful predictor of AHR (P=0.01), although the previously described QLVR cut-off of > 0.7 was not associated with significantly greater AHR.

Combined pacing site results

Considering the segment at which the LV was paced, as expected the septal segments were significantly worse than all other segments. AHR at the posterior segment was also significantly worse than the mean, with a 3.6% decrease in AHR (P<0.001 of significant difference from the mean AHR).

Pacing at a basal segment was associated with a significantly higher AHR than pacing at a mid or apical LV site, by +2.4% (95%CI +0.5 to +4.3%; P=0.01).

Scar at the pacing site, as detected by speckle-tracking echocardiography, was not predictive of AHR in the combined cohort, although there was an unexpected trend towards higher AHR at sites with scar of 2.2% (95%CI -0.2 to +4.5%; P=NS (0.07)). On univariate analysis, lateral pacing position was associated with a 2.6% increase in AHR (95%CI +1.1 to +4.0%; P<0.001).

Clinical predictors of AHR to BiVP

On univariate analysis, the presence of neither LBBB, P=NS (0.8), nor 'strict' LBBB, P=NS (0.2), were significant predictors of a higher AHR, although there was a positive trend associated with both. Ischaemic aetiology was associated in univariate analysis with a lower AHR by -6.5% (95%CI -12.8 to -0.3%; P=0.04). Persistent atrial fibrillation at baseline was not a significant predictor of AHR.

Only QLV >100ms and ischaemic aetiology were significant predictors of AHR to BiVP on multivariate GLMM analysis in the combined cohort. Lateral positioning, positioning at the site of latest mechanical activation, position at a site with scar, and pre-existing LBBB were

not significant predictors. These results are illustrated in Figure 85 in the discussion section below.

Chronic clinical response as related to AHR results

Clinical response was not associated with AHR, when measured by NYHA class change, ESV or EF (all P values>0.1). The reverse association also appeared to hold, and AHR was not a predictor of clinical response.

AHR of >10%, used as a predictor of response by other groups (Duckett 2011), was not a predictor of response by ESV, EF or NYHA class. The area under the Receiver-Operator Curve (ROC) for AHR>10% to predict response by ESV was 0.56, suggesting a poor ability of this factor to predict response with my data.

I attempted to replicate the methods of the Rinaldi group (Duckett 2011), by using ROC curve optimisation to select the optimal dP/dt max cutpoint from my data to predict response. To do this is I used the OptimalCutpoints R package (Lopez-Raton 2014, Zweig 1993). I derived a cut-point of 13.3% AHR, associated with a marginally better area under the curve of 0.58, as shown in Figure 77 below. This was still not significantly predictive of clinical response in GLM analysis.

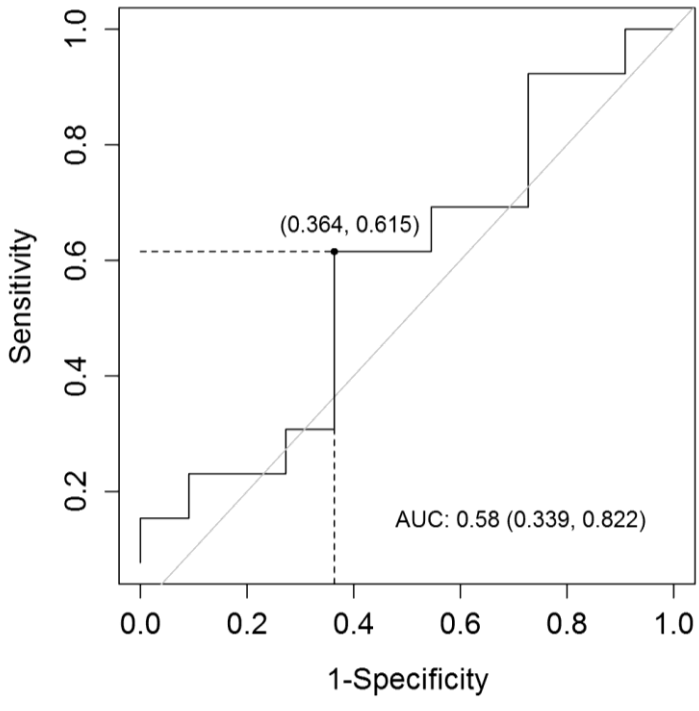


Figure 77 – Receiver-operating characteristics curve identifying the optimal dP/dt max cut-point to predict response by ESV.

QLV as a predictor of clinical response

Similarly, I assessed the utility of QLV as a predictor of clinical response. The ROC-optimised value of QLV to predict response by ESV was 153ms, giving an area under the curve of 0.57. This cut-off value was again not significantly predictive of response in GLMM analysis.

As discussed above, a negative relationship between QLV and AHR was seen in 9 patients. This negative relationship showed a trend towards predicting response by ESV on GLMM analysis (P=0.1), and produced a ROC AUC of 0.66, which although still not a good predictor is the best identified from my data.

Other predictors of clinical response

Permanent AF was not a significant predictor of clinical response in my data, and neither were baseline LBBB or ischaemic aetiology (all P>0.1).

Discussion

Summary of results

In summary, I have shown that:

- In the epicardial pacing IDEAL-CRT cohort:
    - There was no quadripolar lead pole that was consistently superior
    - The LMA vein was not better than the comparator vein, and in fact was overall worse in terms of AHR to BiVP
    - QLV greater than 100ms was associated with greater AHR, and on multivariate analysis only this and lateral lead position were predictors of AHR to BiVP
- In the endocardial pacing LVCONSEPT cohort:
    - Pacing at the LMA site was not associated with a significantly greater AHR than at the LEA site
    - Again, late electrical activation was a significant multivariate predictor of greater AHR
    - LV only pacing at the final site was significantly worse than biventricular pacing

Further results could be obtained from the combined cohort:

- QRS width during pacing is inversely associated with acute haemodynamic response to pacing
- Mechanical delay as estimated by speckle-tracking echocardiography was not associated with AHR

- Although longer QLV was associated with greater AHR in both cohorts, there was no significant linear relationship in the epicardial group, and pacing at a given delay endocardially was associated with a greater AHR increase
- Pacing at a basal site was associated with greater AHR than mid-ventricular or apical sites
- Only QLV >100ms and ischaemic aetiology were significant predictors of AHR to BiVP in multivariate analysis
- Neither AHR or QLV were significant predictors of chronic clinical response

Where to put LV leads?

There is relatively little existing evidence to guide endocardial LV lead site placement, and although as discussed previously there have been several studies investigating epicardial LV lead placement, it remains unclear if any method is superior.

I have shown clearly from my data that the pacing site is relevant in terms of acute haemodynamics, with some sites significantly worse than others, and a site with significant acute haemodynamic differences from others able to be identified in all patients. It certainly appears that it is not appropriate to simply place the lead anywhere.

Even in the endocardial cohort, where conduction around the ventricle is likely to be rapid, significant differences are still observed between pacing site. Once the selection is narrowed down to non-apical pacing sites, in my data the three sites chosen to be likely to be beneficial pacing sites, i.e. the LMA, LEA, and lateral sites, all had a greater AHR than the mean. This does not assist with choosing whether any one of them is superior.

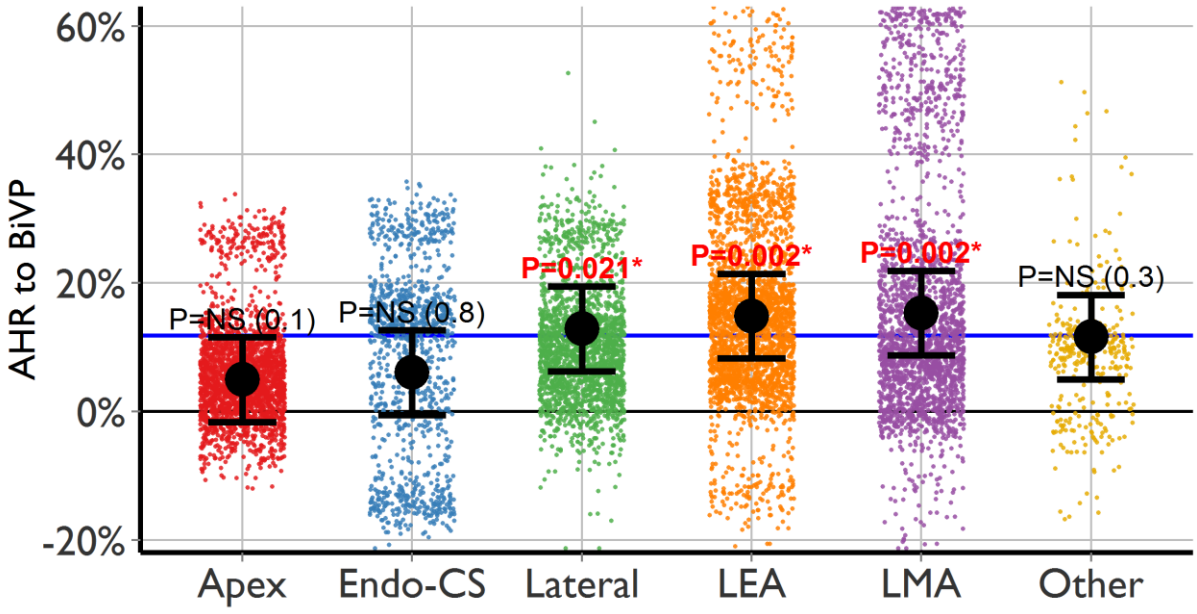


Figure 78 – AHR according to endocardial pacing site. The points and error bars show the GLMM estimate of AHR attributable to pacing at that site, and the probability of significant difference from the overall mean, shown in blue.

In the IDEAL-CRT group a vein with a significant overall difference from the other could be identified in only 40% of patients, but this was limited by comparing the average of all sites in each vein with each other. More relevantly, a significantly better optimal pole/vein combination could be identified in 76% of cases, again suggesting that there is potential to identify relevant differences, both between veins and between sites within them. Finding practical ways to do this is key. Potential candidate techniques previously discussed are quadripolar pole selection, lateral lead positioning, positioning at the LMA site, or selecting late electrical activation. I will discuss my results investigating each of these modalities.

Pacing site by segment

The combined results of pacing site by LV segment are shown below in Figure 79. Only the two septal and posterior segments were significantly worse than the lateral segment.

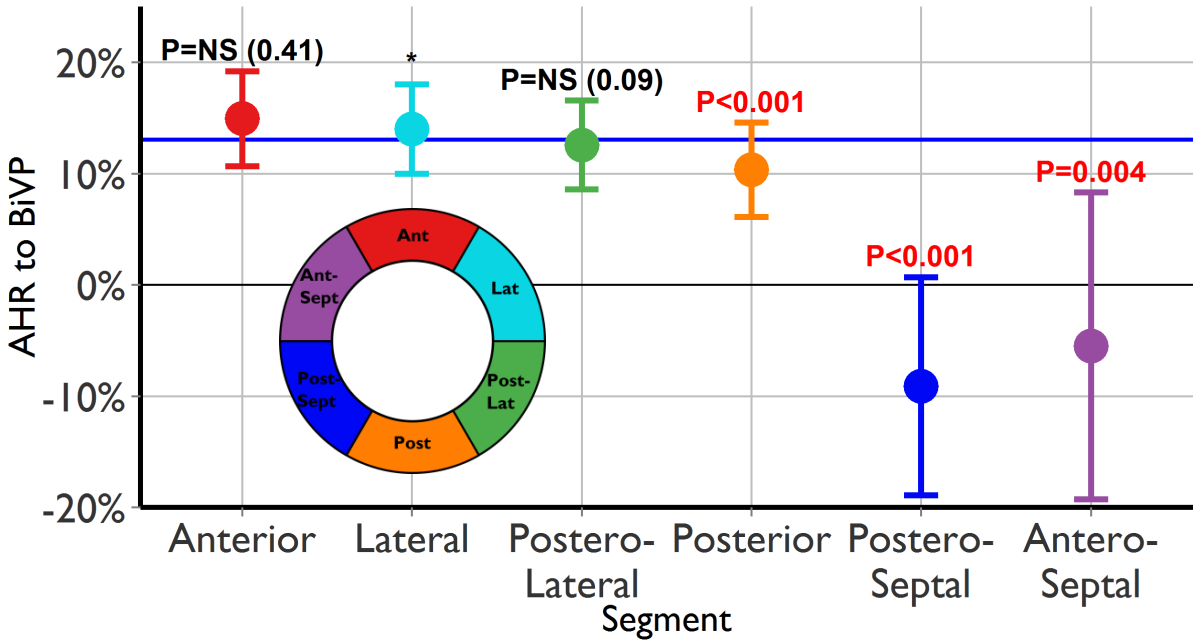


Figure 79 – AHR by the LV transverse segment of pacing, in the combined data set. The blue line is the overall mean. The P values show the probability of a statistically significant difference from the lateral segment. The posterior and septal segments were significantly worse.

Prior studies have also suggested that posterior positioning may be adverse (Saxon 2009), although other studies have also suggested that anterior lead positioning may also be associated with negative haemodynamic effects (Derval 2010).

This data suggests that a wide arc of 3 LV segments, from antero-lateral through to posterolateral is associated with better AHR on average, but does not suggest where within this segment optimal LV lead placement for a given patient would lie. This does in fact support much of the pre-clinical data discussed in the background chapter, which suggested that the optimal site would be relatively large and lateral.

Basal LV lead positioning was associated with a significantly higher AHR compared to non-basal sites. This would be expected from likely left ventricular activation patterns; our RV leads were placed apically and so during RV pacing the base would be expected to be a site of later activation. This result is consistent with the prior clinical studies of lead

positioning showing better outcomes in patients with non-apical lead sites (Singh 2011, Thébault 2012, Wilton 2014).

This analysis may be limited by the relatively inaccurate methods used to localise lead position. In the IDEAL-CRT epicardial group these were the same as in the TARGET and STARTER studies of targeted LV lead positioning (Khan 2012, Saba 2013). As in these trials we were essentially judging the segmental positioning of the LV lead by eye, and although we used left lateral CS views to try and make this systematic and comparable to echo views, it is clear that inaccuracy could easily be introduced. In particular the 'high lateral' position, which is commonly used for CRT, could be assessed as either being in the lateral or antero-lateral segments, and is frequently on the border between the two. Prior studies have shown that physician assessment of LV lead positioning during the implant procedure does not correlate well with careful post-procedural assessment by multiple x-rays (Wilton 2014). It may well be that the relatively high AHR in the anterior segment represents misclassification of leads that were in the lateral segment. This area is also confused by the multiple lead position classification schemes in use, as discussed in my prior meta-analysis chapter. True anterior lead positioning in the great cardiac vein is likely to result in poor outcomes as the lead is anatomically near to the RV. The anterolateral segment however, covers an area of relatively lateral LV territory that is probably a viable LV lead target. Similar limitations apply to the endocardial pacing group, where we could localise lead position accurately on the mapping system, but segmental position was still an estimate.

In addition, base-apical assessment was also an estimate; in particular within the epicardial pacing group we did not repeat a RAO view at each pacing site to assess longitudinal lead position. There was a preponderance of basal pacing sites, probably due to this effect. Again, this may make these results unreliable.

It is notable that pacing at a segment with scar (as suggested by low peak strain values on speckle-tracking echocardiography) was not associated with lower AHR. Several prior studies, as discussed in the background chapter, have showed that scar at the pacing site is a powerful negative predictor of response (Bilchick 2014, Delgado 2011, Leyva 2011, Marsan 2009, Shetty 2013). I suspect that the reason for the contrary finding in my data is that I did not pace at many scarred sites. The LMA targeting technique avoided scarred segments, so I only paced in scar very infrequently (19/133 (14%) tested sites). In addition, sites with severe scar may not have provided LV capture, so will not have been assessed at all. In IDEAL-CRT, we assessed 3.7 poles per vein; in a proportion of veins not all poles could be assessed. This was due to a mixture of high thresholds, often due to scar although potentially due to poor contact between the lead and myocardium, and sometimes due to intolerable phrenic stimulation at the site.

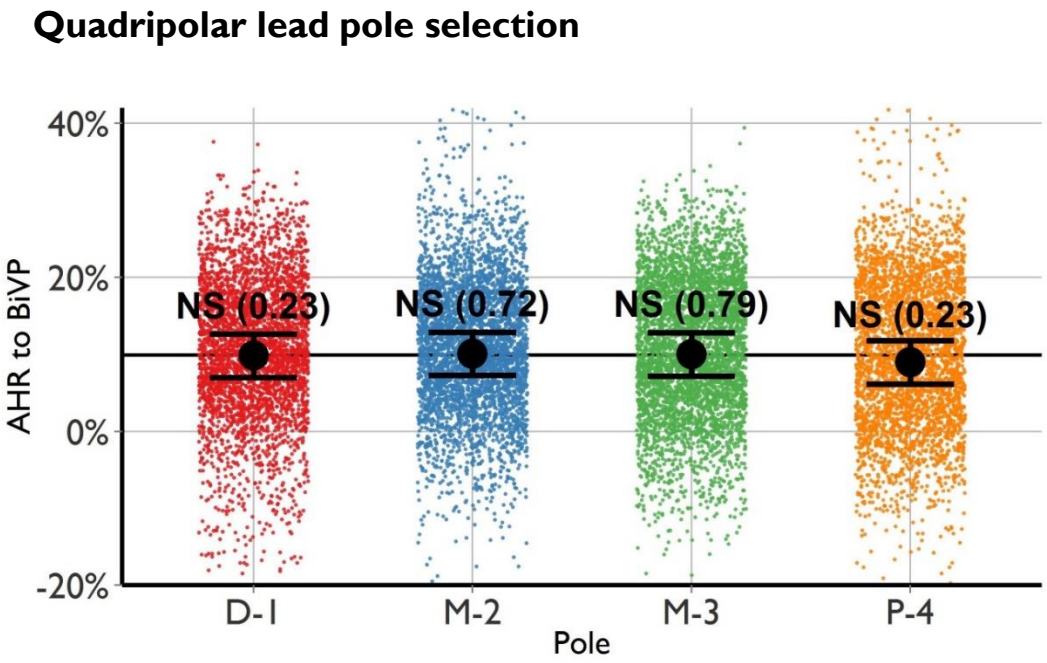


Figure 80 - Percentage AHR to BiVP by poles across all patients in the IDEAL-CRT epicardial pacing cohort, shown as scatter plots of each-beat AHR. Mean AHR and 95% confidence intervals at each pole, as assessed by GLMM, are shown in black. P values for significant difference from the overall mean (the horizontal black line) are shown.

As is clearly shown in Figure 80 above, there was no overall effect of quadripolar lead cathode selection in the IDEAL-CRT epicardial pacing cohort. This would be expected, as in each patient and vein the poles will be in different positions depending upon venous anatomy, and local factors such as proximity to remaining native conduction tissue may influence the efficiency of biventricular pacing from a pole. It was notable that significant increases in AHR in a given vein could be achieved by quadripolar pole selection in the majority of cases. In 76% of veins, one pole was significantly better than the others when carefully assessed using my methodology. It is particularly interesting that the potential increase achievable by quadripolar cathode selection was frequently greater than that between veins, suggesting that there are potentially relevant gains to be made by choosing the right quadripolar cathode.

Some authors have suggested that more proximal cathodes may be a better empirical choice (Valzania 2013), but this was not clearly shown in my data, attractive as this principle might seem for easy cathode choice. Treating the two proximal poles (P-4, M-3) as a binary GLMM predictor, there was still no effect of this on AHR (P=0.39). These results are consistent with the finding of other groups that there is no consistently better cathode in all patients (Asbach 2013, Cabrera Bueno 2013, Pappone 2013a, Valzania 2013). Despite this negative finding, in the overall analysis, basal segment pacing was superior to pacing at non-basal sites. This agrees with several trials previously discussed, showing an outcome benefit of basal or non-apical LV pacing (Singh 2011, Wilton 2014), and would support choosing basal electrodes where possible.

It is unfortunate that no 'easy' rules can be derived to assist in empirical pole selection, as although the methodology I used provides a precise method to choose an optimal quadripolar cathode, it took about 10-12 minutes per vein. This was also only assessing the four available unipolar vectors, pacing between the pole and the generator (or a plate

standing in for the generator). I did not assess the other 8 available vectors in the St Jude Medical Quartet lead; and up to another 4 are available in other quadripolar leads. This complexity of potential pacing options may limit the clinical applicability.

My use of GLMM analysis of every beat does provide an improvement over the methods used by most others, and will identify an optimal pole faster if used well. It might be that automated algorithms based on this could be developed to allow more rapid assessment of the AHR at each pole.

Latest electrical or mechanical?

I think my data can shed further light on how we might individualise endocardial and epicardial pacing sites. In the endocardial pacing group I was able to make a direct comparison between the LMA and LEA sites, showing no overall significant difference between pacing at the LMA site and the LEA site.

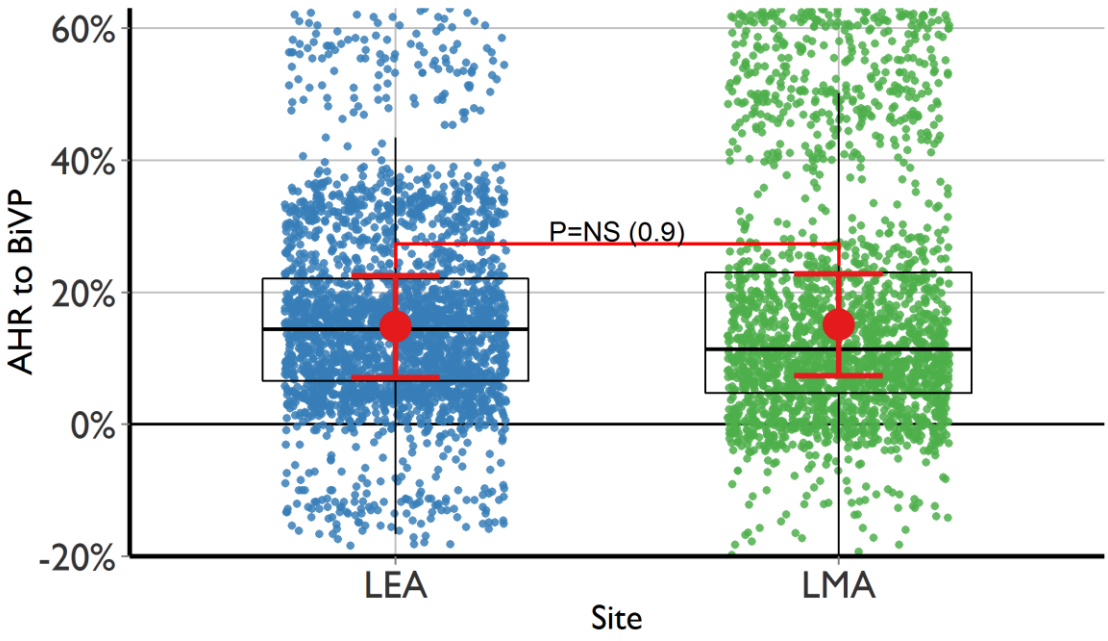


Figure 81 – Boxplot comparison of the AHR at the LMA and LEA sites in the endocardial pacing LVCONSEPT cohort. The GLMM estimates are shown in red, along with the probability of a significant difference between the two.

The LMA and LEA were only in the same segment in 19% of cases, although in 44% of patients they were adjacent. In all patients there were statistically significant differences between the two however, and the best site varied between patients. As shown in the technique accuracy chapter, the localisation of the LMA segments was only accurate to about one segment, so it is hard to assess from this number of patients how frequently they are not the same place. This individual patient data is also limited by the small numbers of patients.

In the IDEAL-CRT cohort I could not specifically identify a single LEA site with the same degree of accuracy, but again there was no overall benefit of pacing in the LMA vein versus the comparator. On an individual patient basis there was a greater AHR in the LMA about half of the time, consistent with no significant benefit (but limited by patient numbers).

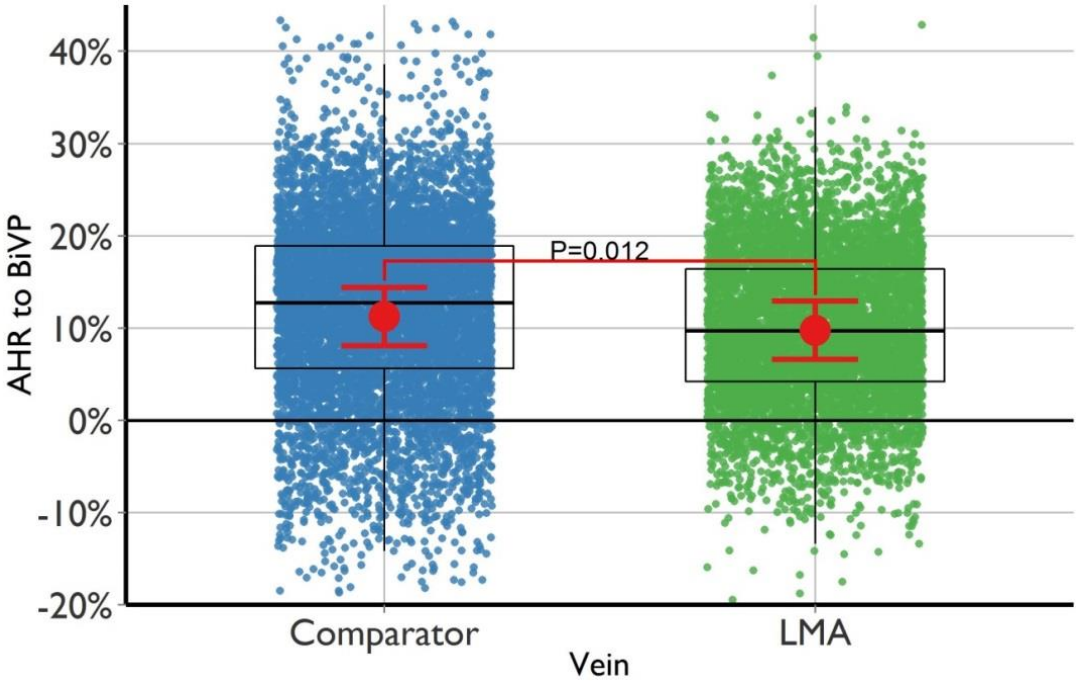


Figure 82 - AHR to BiVP by vein in the IDEAL-CRT epicardial pacing cohort. The box-plot overlay in black shows the median AHR and the interquartile range, with whiskers extending to the furthest point that is within 1.5 times the IQR. The red dots and error bars illustrate the mean and 95% confidence interval of the AHR as calculated by univariate GLMM.

In both studies there did not appear to be a clear benefit of pacing at the site of latest mechanical activation versus other sites. This was borne out by multivariate GLMM analysis, in which pacing at the LMA site was not a significant predictor of AHR.

These results may be limited by the relatively small distances between sites. As mentioned above, in the endocardial pacing cohort the LEA and LMA segments were within one segment in about half of the cases. In IDEAL-CRT, the two veins were a mean of 2.5 segments apart, but there were 5/17 patients in whom they were adjacent. This suggests that I was largely testing two veins that would be expected to have a different AHR. In both the TARGET and STARTER trials of lead targeting there was benefit as long as the lead was in a segment adjacent to the target segment. This may have reduced the difference between the two, as in 5 patients they were in adjacent segments. Ideally I would have assessed a greater number of veins in the IDEAL-CRT cohort, but this would have presented significant practical difficulties in terms of procedure length.

The finding that the extent of mechanical delay from speckle-tracking does not correlate with AHR also supports these results – the consistent finding seems to be that mechanical delay does not predict AHR.

Why does the LMA site not increase AHR?

There are several possible interpretations of why pacing at the LMA site does not increase AHR, but does seem to improve clinical outcomes. Firstly, it is possible that the technique of identifying the LMA segment and choosing a pacing site within it is simply too inaccurate. The speckle-tracking echocardiography technique depends upon small differences in mechanical delay, and this mechanical delay measurement is undoubtedly subject to error. Furthermore, there will be additional sources of error introduced by mapping the echo findings onto the epicardial venous or endocardial anatomy. If the

technique only identifies a very broad area within which the LMA site *could* be located then my assessments of AHR at this site will be inaccurate, and it may be that there are LMA sites within the targeted area that are associated with a greater AHR. This interpretation would be supported by the poor reproducibility of the LMA assessment technique.

An additional explanation, consistent with my data, is that the benefits seen in the trials of LMA targeting were not mediated by changes in acute haemodynamics. This is supported by multiple pieces of evidence. In the trials, the distribution of pacing sites was very similar between the targeted and non-targeted groups. As discussed in the background chapter, data from the long-term follow up of the TARGET trial suggests that the primary determinant of outcome was scar at the pacing site, not lead concordance with the LMA site (Kydd 2014).

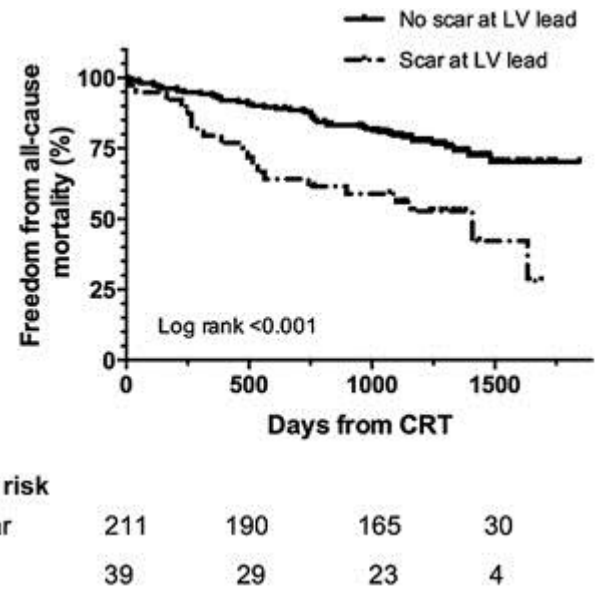


Figure 83 - long-term follow-up of the TARGET trial. Kaplan-Meier curves of all-cause mortality divided by the presence or absence of scar at the lead site. From Kydd et al (Kydd 2014).

A further study, from Taylor et al, used a large retrospective cohort of cardiac MRI data to investigate concordance of the LV lead with the LMA segment (derived from the MRI equivalent of speckle-tracking, called feature-tracking). They found that the main predictor of outcomes was scar at the LV lead site, and that although placement of the lead in the

LMA segment predicted echocardiographic reverse remodelling, it did not predict clinical outcomes. Scar at the pacing site did however predict clinical outcomes (Taylor 2016).

Another study has found similar results to mine. Derval used tissue Doppler imaging to identify the latest activated segment, a technique which is probably less accurate than speckle-tracking but is well-established. They found that pacing at this site did not produce the highest AHR by dP/dt max (Derval 2014).

These results, along with mine, would suggest that placement at the LMA site does not improve the efficiency of CRT, and that the significant benefit seen in these studies was most likely due to the avoidance of pacing on scarred myocardium.

Of course dP/dt is only one measurement of AHR, and it may be that it does not fully reflect the benefit of the LMA targeting strategy. Another measure of AHR might be more predictive, or AHR may simply not reflect chronic outcomes. Whilst this alternative interpretation remains possible, the clinical results above do support my results.

Electrical delay and AHR

I found that electrical delay as measured by QLV was a good predictor of AHR. In both cohorts a QLV of greater than 100ms was a strong positive predictor of response. This is consistent with previously published data, also showing that this was a good predictor of both acute and chronic response. A QLV of less than 100ms suggests minimal intra-ventricular electrical delay, and so this is a marker of a lead position where there is not dys-synchrony to treat, and thus it is not surprising that there is less AHR.

It would perhaps be expected that the longer the electrical delay, and thus presumably the greater the dys-synchrony, the greater the potential for haemodynamic response to pacing at the site. This relationship was found in the overall cohort, with a strong linear relationship between AHR and QLV. Other groups have found this result, in particular

Zanon et al, who found that in 96% of a 32-patient cohort the longest QLV coincided with the greatest AHR (Zanon 2014). They found, using GLMM in a similar methodology, a consistent linear relationship between QLV and AHR. Howard et al found similar results in a dog model (Howard 2011). Gold et al found that QLV correlated with dP/dt max in an acute haemodynamic study in humans (Gold 2014).

Pappone et al measured the delay to electrical activation of the myocardium along a quadripolar lead and then determined the relationship of AHR to CRT to this delay (Pappone 2013a). Pacing at the site with the longest electrical delay increased dP/dt max by a statistically significant 2% versus the earliest activation site, but only if the difference was over 10ms.

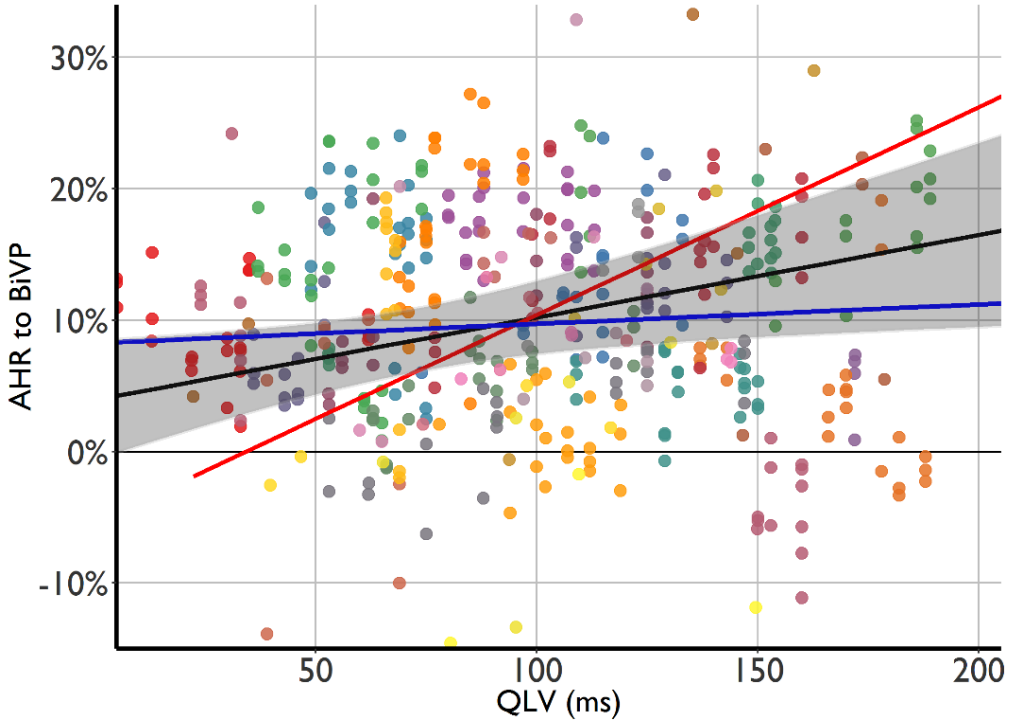


Figure 84 – QLV versus AHR in the combined group, with the overall GLM line and confidence interval in black and grey. The line for the LVCONSEPT group is shown in red, and for the IDEAL-CRT group in blue.

In my data, these results were not consistent between the epicardial and endocardial groups. There was a very clear relationship in the endocardial group, but not a significant one in the epicardial pacing patients. This was due to greater heterogeneity in the QLV-

AHR relationship within the epicardial group. Several epicardial patients had a negative relationship between QLV and AHR. This heterogeneity was not seen in Zanon et al's data.

I cannot find any significant difference between these patients with the negative response and the rest of the group. This finding is interesting however, as a negative QLV-AHR response acutely appears in my data to have some ability to predict long-term clinical response. The utility of this may be limited in clinical practice, as deriving this result requires a detailed AHR protocol such as mine. Despite this, it appears that I am identifying a group who do not respond to CRT in a normal way and therefore have worse chronic outcomes. I was not able to find any significant clinical differences between this group and the rest of the cohort, so there does not appear to be an obvious way to identify these patients clinically.

I did not formally assess the reproducibility of QLV measurements. This technique has however been widely used, and has been previously found to be consistent (Gold 2011b, Singh 2006). QRS width measurement was quite reproducible with a mean scatter between measurements of the same setting in the same patient of 12ms, and so given the similar methodology I would expect similar reproducibility for QLV.

In multivariate analysis, QLV >100ms was a significant predictor of AHR. This was true for both the endocardial and epicardial groups. Ischaemic aetiology had a significant trend (P=0.045) towards a lower AHR in the combined group. Along with my results suggesting that the LMA is not a site that predicts better AHR, this supports targeting a long QLV, a strategy that is viable for both endocardial and epicardial pacing.

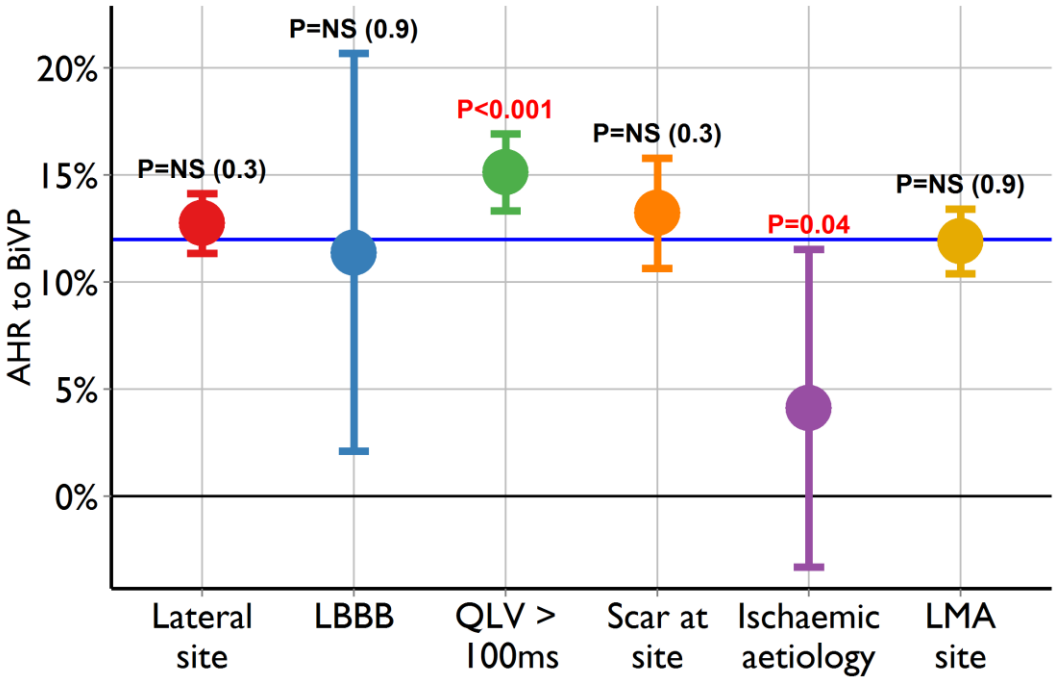


Figure 85 – The change from the overall mean AHR (blue line) attributable to various factors on multivariate analysis of both studies. Only pacing at a site with a long electrical delay, as measured by QLV, was associated with a significant improvement over the mean AHR. Ischaemic aetiology was associated with a significant decrease.

Epicardial and endocardial QLV and AHR

The flatter AHR-QLV relationship in the epicardial pacing cohort is a relevant result. Prior studies have shown that the epicardium is activated after the endocardium, so if the two are equivalent one would expect a greater response in the endocardial group, as the QLV would be longer epicardially for a given electrical delay at an area. The difference in activation times from endocardial to epicardial was 24ms in an animal study, and about 7ms in a human imaging study (Berger 2011, Russell 1979).

It may be that endocardial pacing provides superior acute response at a given extent of electrical delay and dys-synchrony. The endocardium provides more rapid access to the cardiac conduction system, and in addition the length of the activation path will be shorter. There is normally faster conduction along the LV endocardium than the

epicardium, and this differential is exaggerated in failing hearts, to a variable extent between patients (Glukhov 2012).

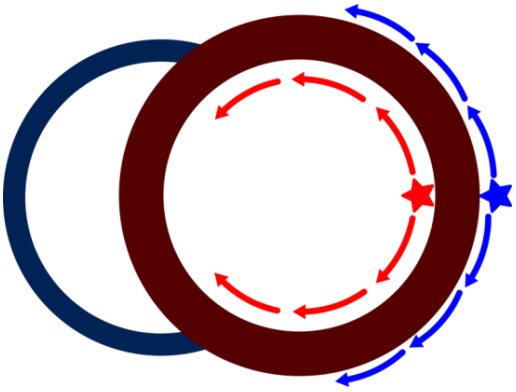


Figure 86 – LV endocardial and epicardial activation. Stimulation at a given site will result in a quicker spread of activation endocardially than epicardially.

Similarly, another group have found that, in a dog model, the increase in dP/dt max with endocardial BiVP correlated with the extent of electrical delay (i.e. the time for the electrical depolarisation started at a right ventricular electrode to reach the LV pacing site) (Howard 2011). This was not found for epicardial pacing. Another study used high-fidelity computer simulation to assess the response endocardially and epicardially, and found more rapid activation from endocardial stimulation, consistent with the animal data, when a rapidly conducting endocardial tissue layer was included in the model (Hyde 2015). Some of this effect may be due to specific access to the remaining Purkinjie network within the LV endocardium, which can persist even in patients with LBBB (Hamaoka 2015).

These data support a haemodynamic benefit of endocardial pacing which is intrinsic to the endocardial positioning, rather than to the freedom to choose an endocardial pacing site.

It is worth noting that our permanent endocardial pacing was not actually truly endocardial, as the cathodal tip of the active fixation leads used ends up in the mid-myocardium, although it will still be closer to the endocardium than a lead in the coronary sinus. The acute endocardial haemodynamics were measured via a catheter, which was truly endocardial.

QRS width

My data showed a significant negative correlation between QRS width and AHR during biventricular pacing. This would fit with the general theory of CRT as achieving electrical resynchronisation. In general, better electrical resynchronisation of the left ventricle would be expected to result in a shorter QRS. This is complicated by the contribution of the RV, as QRS includes the depolarisation of both ventricles. A non-optimal site would result in less coordinated electrical and mechanical activation, and thus wider QRS and lower AHR.

Another two acute haemodynamic studies have found similar results, showing that a decrease in QRS width was associated with higher AHR (Derval 2014, Trolese 2014).

Despite these findings, clinical results have been inconsistent. An analysis of the 610 patients in the REVERSE trial by Gold et al found that change in QRS width was not, after correction for baseline variables, an independent predictor of clinical response (Gold 2012). A retrospective analysis of 179 patients referred to the advanced HF service in Birmingham found that change in QRS width was a univariate predictor of response, but this was not significant in multivariate analysis (Wan 2015).

An analysis of 426 patients from the PROSPECT study found that the difference between preimplantation QRS width and BIVP QRS width was a multivariate predictor of clinical and echocardiographic response. Several other smaller trials have found that achieving a narrower QRS does predict clinical response (Arbelo 2014, Molhoek 2004, Rickard 2011).

Although my data are not conclusive, they do provide some additional support of the strategy of aiming for the shortest possible QRS width, although the evidence for this is rather less convincing than for the QLV and QLV-QRS ratio strategies.

LV only pacing

In my sample of LV endocardial pacing, LV only pacing produced a significantly lower AHR than BiV pacing. Prior reports of this assessment have generally shown little significant difference. Rinaldi's group assessed endocardial BiVP and LVP in ten patients, and found no significant difference in AHR between the two, which from LV electrical activation mapping they attributed to slow trans-septal conduction limiting fusion in BiVP (Sohal 2014).

Thibault et al undertook a clinical cross-over trial to assess this. In a group of 211 patients 8-10 weeks after CRT implantation they randomised to LV only or BiV pacing, and found no overall significant difference in clinical or echocardiographic response. However, 30% of non-responders to LV pacing responded to BiVP, and 17% of BiVP non-responders responded to LV pacing (Thibault 2011). A meta-analysis including three studies (but not Thibault's) similarly found no significant difference in clinical outcomes between the two (Boriani 2012).

The reason for these different results in my cohort is unclear. It may simply represent a chance finding in my relatively small sample. It is clear from Thibault's study that some patients do derive a significantly greater benefit from one or other of these modalities, and it would seem likely that my sample happens to include more patients benefiting from BIVP.

Clinical results in the IDEAL-CRT cohort

Clinical response in the IDEAL-CRT cohort was relatively low. Using my primary outcome measure of Packer CCS, 58% of patients improved (and 74% improved or were unchanged). This is similar to prior studies using this measure (Chung 2008).

There was a marked discrepancy between clinical and echocardiographic response rates. Given that we replicated the methods of the TARGET study where they had 70% echocardiographic response based on ESV reduction (Khan 2012), our response rates were significantly lower than theirs, although there was a marked disconnect in my data between ESV and EF response. The reasons for this are not clear. TARGET excluded patients with AF and we had 18% persistent AF patients, who are known to have lower response to CRT (Wilton 2011), so this may partially explain the result. In addition, our cohort had a low prevalence of broad LBBB meeting Straus' criteria (45%), so it might be expected that we would find low response rates.

Finally, conclusions based on these clinical results are clearly extremely limited by the small size of the cohort. I think it is worth stressing again that clinical results were not the focus of the study, and are reported for completeness.

Conclusions

- Lead placement at a site of late mechanical activation was not associated with greater acute haemodynamic response
- Placement at a site of late electrical activation as illustrated by a long QLV time was strongly associated with better acute response
- QRS width was negatively associated with AHR

Chapter Nine – **Conclusions**

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Endocardial LV pacing

I have shown that our novel technique for trans-ventricular septal endocardial pacing appears to be acceptably safe and effective, within the limitations of a small study. Response rates are comparable to standard CRT. It was notable in my meta-analysis of endocardial pacing that many prior trials reported high response rates. It is possible that my trial had actual lower rates, but I suspect the explanation may be that I was more rigorous in our response reporting than many of the other trials. My response rates were similar to those in the robust ALSYNC study (Morgan 2016).

The technique does appear to be acutely safe. Although all of the procedures in this paper were performed in Oxford, we are aware of other groups using the technique, either having been taught directly by Dr Betts or from reading our prior descriptions of the technique (Gamble 2013, 2015). We are aware of use in London, Brighton, Liverpool, as well as Spain, The Netherlands (Scheffer 2014), and the Ukraine (Karpenko 2015).

Long term safety and thrombotic risk is the key issue for endocardial pacing and I have been able to make a contribution to the literature on this by adding to the total body of patients included in trials, and in particular with a cohort of patients followed up over the medium term. We intend to continue to follow-up all of our trial patients to 2 years, and then to include as many as possible in a further registry to look at long term outcomes. My current data represent an addition of about 10% to the current worldwide endocardial pacing follow-up time, and this will increase over time.

The safety events reported in my data are concerning, largely due to the two strokes and one TIA which occurred. Most of the events that occurred in my patients have been less than 6 months post-procedure, which suggests that there may be a period of higher risk before lead endothelialisation occurs. I have made every effort to maintain accurate

follow-up of the patients included in the study, so I believe I have captured all of the events which have occurred in them to date, although conclusions are limited as at the time of writing follow-up remains relatively limited for some patients. As we add additional follow-up time and further studies it should become clearer to what extent thromboembolic events will limit this technique.

Benefit of endocardial pacing

Do my results bear out any significant benefits of endocardial pacing? We were able to successfully target chosen optimal pacing sites with this technique, providing an opportunity for truly targeted CRT that is not limited by venous anatomy.

My acute haemodynamic data did show that endocardial pacing appears to produce a greater AHR than epicardial pacing at a given extent of electrical delay. This does support the prior results suggesting that endocardial pacing may have some intrinsic benefit in terms of haemodynamics over epicardial pacing via the coronary sinus (Bordachar 2012, Derval 2010, Ginks 2012a, Howard 2011, Spragg 2010, Van Deursen 2009), although this has not been consistent (Hamaoka 2015). There are limitations of my haemodynamic data, which I will discuss in more detail below.

Despite the above acute haemodynamic findings, our clinical results were no better than expected for standard CRT, which does not support a major benefit of lead targeting or endocardial pacing. Some of this could potentially be explained by the challenging cohort of patients recruited, or even by the fact that our chronic pacing site was from the tip of a lead placed in the endocardial aspect of the mid-myocardium rather than truly endocardial.

I have also reported our small experience of endocardial CRT in non-responders to conventional CRT. These patients had a clinical and echocardiographic response rate that was similar to that in the overall cohort, although the tiny numbers make comparisons

difficult. Subjectively, patient selection seemed to be the key in this group. In retrospect, the non-responders who did not improve were probably unlikely to do so, due to very severely impaired cardiac function, even though we attempted to select patients in whom we felt LV lead position was a contributor to non-response. ALSYNC also reported response rates in the 31 patients recruited on the basis of non-response, which were similar to mine at 40-60% based on response modality (Morgan 2016).

Future studies

The small cohort included in my data is an obvious limitation of my results, and more trials and patients are clearly needed.

Key questions about management of these patients remain unanswered. Could non-vitamin K oral anticoagulants be used? Additional trials would be needed to answer this question, although in practice the numbers of patients needed to identify relatively subtle differences between warfarin and NOAC anticoagulation would be very large, making such trials impractical in this area.

Systematic imaging of the endocardial leads in these patients, perhaps with intra-cardiac echocardiography or trans-oesophageal echocardiography, might allow assessment of the timing of lead endothelialisation, and thus potentially the time-scale of increased thrombotic risk. An undoubted concern is the current need to continue all patients on warfarin for the long-term; we empirically selected a higher INR range of 2.5-3.5. Whether this level of anticoagulation needs to be maintained for years is unknown, but if it could be shown that all leads are endothelialised by 6 months there would be potential to reduce the target INR then.

Access to the LV via the interventricular septum with a pacing lead provides the opportunity of pacing the septum as well as the LV free wall. Multipolar leads are in

common use via the coronary sinus, and so a potential lead with a pole to pace the septum and another to pace the LV endocardium is not hard to conceive. We are already investigating the haemodynamic effects of dual-site pacing at the LV septum and endocardial LV free wall in the DoUbLE-CRT study (Dual Site Left Endocardial Pacing for Cardiac Resynchronisation Therapy), some data from which were included in the NICOM comparison chapter. This trial is not yet complete, but should answer the question as to whether septal to lateral LV biventricular pacing is superior to RV to LV biventricular pacing.

In terms of the future use of endocardial pacing in a non-commercial situation, collaborative efforts between centres performing endocardial LV pacing are needed in order to gather larger patient cohorts and to follow them up over the longer term. This should allow us to accurately assess the rate of endocardial LV lead-related thrombosis. With bigger cohorts it may be possible to make a comparison between the trans-ventricular and trans-atrial septal techniques for LV endocardial pacing, both in terms of safety and in cost. We are already involved in discussions about setting up such a registry of endocardial pacing cases across the UK.

If a larger trial of trans-ventricular septal endocardial pacing were to be performed, the most obvious target population would be CRT candidates with AF, who are already on warfarin. These patients are known to respond less well to CRT, and so there is potential to improve response with endocardial pacing. A multicentre trial would be needed in order to recruit a reasonable number of patients, and would potentially show that the technique can safely be 'exported' elsewhere, overcoming the limitation of our current study that all procedures were performed by a single extremely experienced operator.

Randomisation of patients to conventional epicardial or endocardial pacing would allow a genuine assessment of the comparative risks and benefits. However, I think it is hard to

justify such a trial based on my data and my meta-analysis of prior studies, as the overall findings suggest that there is a significant increase in thromboembolic risk attributable to endocardial pacing without any clear evidence of significant benefit over epicardial pacing via the CS. A better next stage study might be to build a registry of non-randomised patients and propensity-match them with control CRT patients. This would potentially allow a valid assessment of additional risk attributable to the LV lead, which is extremely hard to assess in the current data without comparators.

Who needs endocardial pacing?

Given the risks and lack of evidence of additional benefit of endocardial pacing discussed above, I feel that at least for the moment it needs to remain as a second or third line therapy for patients in whom conventional CRT is impossible to attain or maintain. This will include patients in whom (despite all efforts being made) CS access or lead placement is not viable, as well as those who have already responded to CRT but in whom LV lead failure and a lack of additional CS targets prevents re-establishment of CRT. The first group are probably now infrequent, as I showed in my meta-analysis that CRT is now achievable in >97% of patients, and even in those in whom it initially fails another operator may well succeed, although the lead position achieved may not be optimal.

There is no clear evidence that well-performed surgical epicardial lead placement is inferior to CS LV leads. Once the additional perioperative risk has passed, the long-term risks of epicardial leads are probably less than endocardial, particularly in terms of thrombotic risk. Hence this is a reasonable second-line option for most patients, as long as the surgeon will place the lead in a baso-lateral site that is likely to result in response.

As is often the case in CRT, personalisation to the patient is needed. In a significant cohort of patients, such as those with comorbidities or prior thoracotomy, the surgical risk may

be prohibitive, and endocardial pacing will be a better option. Those who are already on warfarin would not be exposed to additional bleeding risk from endocardial pacing (other than potentially the incremental risk of an INR target increase from 2.5 to 3.) Some patients may not want to go through the risk and pain of surgery, although they must be properly informed about the long-term risks. Although we used general anaesthesia in our patients, this is not a necessity for the procedure, and the avoidance of the need for a GA is a potential advantage.

Neither my data nor the cohort of non-responders included in ALSYNC have shown that this is an obvious therapy for all non-responders, but about 50-60% of included non-responder patients did respond. Again, careful personalisation will be needed. We found the best results in patients where the LV lead was clearly badly positioned, and where (most importantly) no other factors were the main reason for non-response. Patients with declining heart failure due to worsening of their aetiological condition, or with severe limiting comorbidities, will still not respond wherever their lead is placed.

Future technology

The future of endocardial pacing is hard to assess. In the short term it remains unclear whether the ALSYNC trial sponsors (Medtronic) or any other company are likely to invest significantly in endocardial pacing; I understand that the Medtronic endocardial pacing kit used in the study remains unavailable commercially.

Leadless pacing technology will probably have an important role. The two currently available leadless right ventricular pacing systems are both about 0.8mL volume, and are probably too thrombogenic to safely place in the left ventricle (Reddy 2014, Reynolds 2016). They can also both only pace in VVI mode, so there is no current option for AV or

VV synchrony. Future versions may be smaller, designed to endothelialise, and able to communicate with additional devices in other chambers.

The EBR Systems WISE endocardial pacing device discussed in the background chapter already allows synchronised LV pacing, albeit with a rather cumbersome first-generation additional subcutaneous device. The endocardial transducer is small, and may represent a safer long-term option than a lead. Similar energy delivery systems could be combined with a defibrillator to reduce the number of boxes required by the patient.

For now, trans-septal LV endocardial pacing represents a viable alternative for suitably selected patients without other options, but I suspect the need for endocardial leads will be replaced in the medium term by leadless solutions.

Where is the best LV lead site?

LMA and scar

I have shown that there are significant differences in acute haemodynamics between patients, and there is a reasonable body of clinical data suggesting that lead position can change patient outcomes. Retrospective clinical data certainly support basal rather than apical lead position (Singh 2011, Thébault 2012, Wilton 2014), and even though data from large trials did not consistently show benefit of a particular lead position in the lateral plane, smaller trials would suggest that important clinical benefits can be gained by personalising LV lead position (Khan 2012, Saba 2012, Zanon 2014).

In both of my trials there was no significant overall haemodynamic benefit of placing the LV lead at the LMA site, the LMA site was not a predictor of AHR, and the extent of mechanical delay was not a predictor of AHR. These data support the conclusion that scar avoidance, and not a haemodynamic benefit of pacing at the LMA site, is the major benefit of the speckle-tracking technique. This agrees with several other studies using different methodology to show that LV lead placement at a scarred site carries an adverse prognosis (Bilchick 2014, Delgado 2011, Leyva 2011, Marsan 2009, Shetty 2013). In addition, studies of longer term clinical follow-up assessing outcomes relative to LV lead position at the LMA or near scar suggest that the benefit is due to avoidance of scar rather than to placement at the LMA site specifically (Kydd 2014, Taylor 2016).

From my data it is hard to assess the impact of scar. I actively avoided pacing at scarred sites, as the echocardiographic LMA segment localisation excludes scarred segments, and when picking the LMA segment we also avoided sites of electrical scar.

Electrical delay

My data suggest that placement at an electrically late activated site is important. I found that the extent of electrical delay at a pacing site was a positive predictor of haemodynamic response at that site. QLV >100ms was a multivariate predictor of AHR in both studies.

This is consistent with the developing concept that CRT is an electrical therapy, and so targeting electrical delay is key to its benefits. The ECHO-CRT trial results are certainly confirmation that targeting mechanical dyssynchrony in the absence of electrical dyssynchrony does not produce beneficial outcomes, as are the analyses showing that the most benefit from CRT is in patients with LBBB (Cleland 2013, Ruschitzka 2013). My results agree with prior findings that the AHR to BiVP as assessed with dP/dt max correlates with the extent of electrical delay (Gold 2014, Pappone 2013a, Zanon 2014). Despite the limited data linking AHR to clinical outcomes, it is notable that clinical response to CRT as separated by QLV quartile shows a similar distribution to that of AHR as illustrated in Figure 87 on the subsequent page.

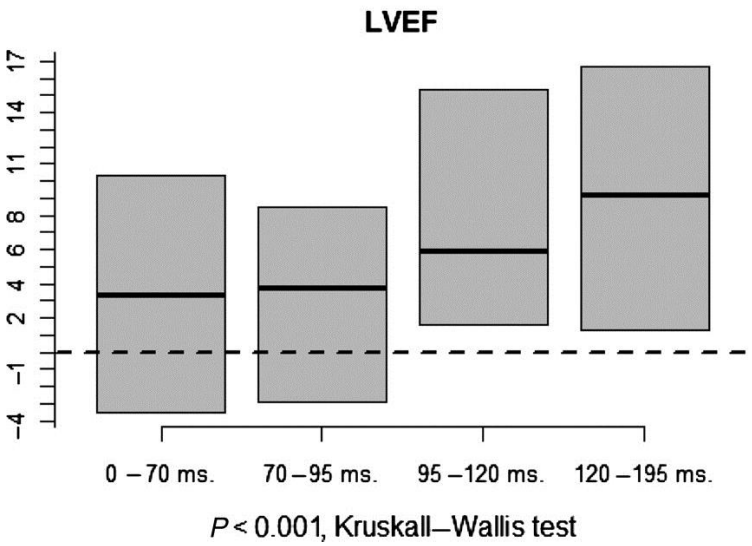
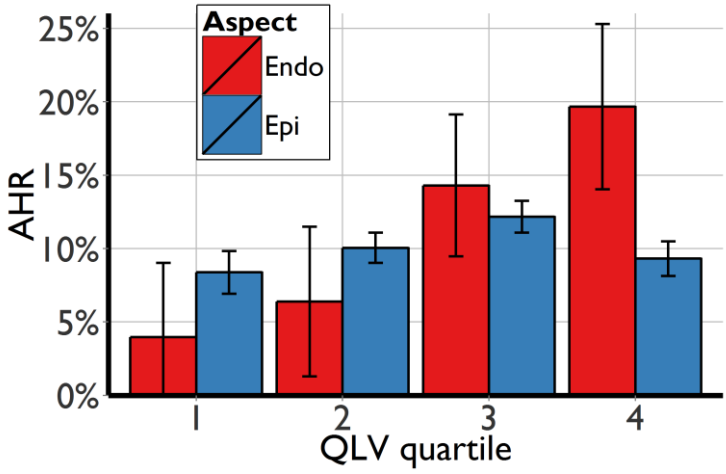


Figure 87 – Top: Response to CRT as measured by change in LVEF, as per quartile of QLV. From Gold et al (Gold 2011b).

Bottom: Response to CRT as per quartile of QLV, from my data.



Other authors have also found that electrical delay predicts clinical response. Kandala showed that patients with LV lead electrical delay >50% of QRS width were more likely to show reverse remodelling (Kandala 2013a). Kutifya found similar results in a retrospective analysis of 494 patients (Kutyifa 2013b). Stabile showed that the RV-LV lead electrical delay was a predictor of clinical response (Stabile 2015).

Taken with the prior literature, my data strongly support a strategy of targeting late electrical activation.

Positioning at the latest electrical activation site is a particularly promising strategy for endocardial pacing. It is relatively easy to map electrical activation endocardially and

although we created a relatively full map for this study a much more limited map could be performed clinically to roughly localise a late site. This is a more practical way of identifying a good site than use of the site of latest mechanical activation.

When pacing via the coronary sinus, mapping late electrical activation is less straightforward. QLV measurements from the LV lead can be used to assess each vein, but most operators are reluctant to sample multiple veins with the LV lead due to the technical difficulty of moving the lead. Some studies have used leads to map the coronary sinus, but others have combined a coronary wire which can measure electrical activation at its tip with electroanatomic mapping, a more straightforward option (Niazi 2014, Rad 2015b). Although due to its cost it is unlikely that formal electroanatomic mapping will be performed in all cases, use of a coronary wire able to measure electrical activation times is a relatively plausible way of rapidly assessing electrical activation in the one or two veins that are plausible targets for CRT (Khan 2009).

Liang et al have published a small prospective study of targeting CRT based on electrical delay. They assessed each viable coronary sinus branch with the LV lead, and placed the lead in the one with the longest QLV. In 29 patients treated with this strategy, echocardiographic response (assessed by change in ESV) was significantly greater at 6 months than in a (non-randomised, but contemporaneous) control group, at the cost of a procedure that was on average 15 minutes longer (Liang 2015).

My data support multiple prior studies finding that a cut-off value for QLV of ~100ms predicts both AHR (Zanon 2014) and clinical response (Gold 2011b, Singh 2006). This would suggest a benefit from assessing other veins if the longest available QLV in a given vein is <100ms. Although I used a fixed cut-off value of 100ms for comparison with other studies, clearly the maximum available electrical delay will be a factor of the baseline QRS width. Although most evidence supports selecting patients with a broader QRS for CRT,

when patients in the 'intermediate zone' of QRSD 120-150 are paced it would be expected to be harder to find a QLV >100ms. Similarly, in a patient with QRS width of 180ms, a QLV of only 100ms is probably not the best achievable. Accordingly use of a QLV/QRS ratio is probably more useful as a one-off assessment of whether a given electrical delay is likely to be beneficial. In a retrospective analysis QLV/QRS >0.7 was a predictor of survival (Roubicek 2015). Once comparing electrical delays within a patient, the ratio is unnecessary and the 'raw' QLV time can be used.

Once a quadripolar lead has been placed within a coronary vein it is relatively easy to assess activation times at each pole, and in fact this can be performed in an automated way with at least one company's CRT device software platform (SJM), although not yet easily via the pacing systems analyser. My data would certainly support choosing the latest activated site along a quadripolar lead; this is relatively easy to implement even when only one vein site is felt to be suitable or the patient clinical state precludes assessing multiple veins.

Comparability of the LMA and LEA sites

As discussed above, it is relatively hard to identify the LEA site, so could the LMA site be used as a predictor of the LEA site? From my endocardial mapping data, the two were only the same segment in 18% of patients, even though they were often nearby.

Other human electro-mechanical mapping data has suggested that there is a differential relationship between the LMA and LEA (Constantino 2013, Kroon 2015). In one study of 10 patients Kroon et al found that although there was significant concordance between electrical and mechanical activation patterns, the latest activated sites were often not identical. Fujiwara et al attempted to correlate electrical activation in the coronary sinus and mechanical activation from speckle tracking echocardiography, and found that the sites

only matched in 3/16 patients (Fujiwara 2014). Another study produced different results by correlating the results of coronary venous electroanatomic mapping and mechanical activation delays derived from speckle-tracking echocardiography, and reported that in 19/23 the LMA and LEA corresponded (Mafi Rad 2015).

I think overall my data tie into the majority of studies suggesting that the LMA and LEA sites are not identical, and so the LMA cannot be used as a non-invasive method to predict the LEA site.

Lateral or LEA

I have suggested that placement at a late electrically activated site appears to be beneficial. An alternative hypothesis would be that all that the latest electrical activation site predicts is that a lateral pacing site is beneficial, as the late electrical activation is commonly lateral. Simulation work from Prinzen's group would suggest that pacing at a lateral site is the most haemodynamically beneficial, but that the LEA site often happens to coincide with the lateral site (Pluijmert 2015). This is supported by data showing that when QLV times are mapped in multiple veins, the lateral area is on average the one with the longest electrical delay (Schricker 2015).

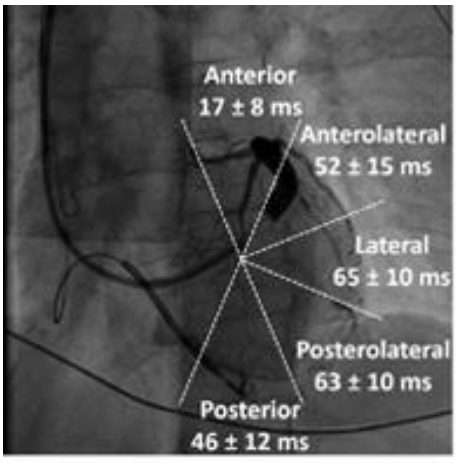


Figure 88 – Average RV to LV activation times in the available CS branches in 18 patients, showing that lateral sites are on average latest (Schricker 2015).

In my data, lateral lead position was not a significant predictor of AHR, but QLV was. This would support the alternative hypothesis that QLV does provide further incremental benefit over lateral positioning alone, although in many, and probably most, patients the longest QLV will be laterally.

Positioning at a basal site was associated with a significantly greater AHR, supporting prior clinical data.

Limitations

Some of the limitations of these results have been discussed already. The major overall limitation of my lead targeting results is that they are very largely based upon acute haemodynamic response. As discussed in the second background chapter, AHR is used as a surrogate for clinical response. Patients will be unlikely to be concerned about how their cardiac haemodynamics change unless this is reflected in symptoms or prognosis. The link between the two remains uncertain, with mixed positive (Duckett 2011, de Roest 2013) and neutral (Bogaard 2011, Prinzen 2012, Suzuki 2010) results in prior studies.

Despite this, assessment by AHR is widely used, and appears to be a valid way to generate hypotheses about lead positioning without requiring very large numbers of patients. Furthermore, it allows the identification of relatively subtle differences between sites that would be hard to assess at all in a clinical trial, as the clinical correlates would be small – although potentially important to the patient. As mentioned above, the QLV AHR data is supported by clinical studies showing that longer QLV also predicts clinical outcomes (Gold 2011b, Roubicek 2015, Singh 2006).

The pooled results of the two studies will be influenced by the slightly different AHR assessment protocols used. The rigorously repeated protocol in IDEAL-CRT should minimise order effects and maximise data significance. In LVCONSEPT the longer but non-repeated measurements would potentially be open to more bias from order effects. The long 2-minute recordings minimise this, as does the every-beat GLMM analysis by considering the whole dataset and allowing for the repeated measures.

Conclusions about the benefits of targeting to the LMA site are limited by the poor reproducibility of the technique for identifying the site. Some of this variability may have been my ability and technique, and the absence of a significant institutional experience of this technique. It may also be that the TomTec software I used is less accurate than the GE software used in the studies. However, having spoken to researchers in Cambridge, it appears that the technique is similarly only accurate to within about 1-2 segments in their hands. This does cast significant doubt on the ability of the speckle-tracking technique to reproducibly and accurately identify scar or late activation, despite the results of the studies of it.

I have not considered CRT timing interval optimisation at all in this work. In all patients procedures were performed with fixed AV intervals and simultaneous RV and LV pacing. At the end of the procedure we chose permanent intervals according to our normal clinical practice, which is to use empirical values and to adjust these based on ECG parameters. Further increases in acute haemodynamic and clinical response might be achievable in some patients with interval optimisation. In addition, my patient cohorts had a 40% overall incidence of persistent atrial fibrillation, driven in particular by the LVCONSEPT endocardial pacing cohort. This could impact on response rates.

Future technological developments

The development of CRT technology may assist in lead site selection and optimisation. St Jude Medical have developed the MediGuide technology which allows 3-D visualisation of catheter and wire positions, and has been used to allow reduced fluoroscopy during CRT implant procedures (Richter 2013, Sommer 2014, Thibault 2015). An extension of this system allows assessment of both electrical and mechanical activation patterns at the site of the sensor-equipped wires or leads. This could potentially allow relatively easy electro-mechanical activation mapping during CRT implants. The Biosense Webster NOGA

electro-anatomic mapping system has similar capability, and has been used in CRT research (Kroon 2015). This technology might potentially allow easy assessment of an optimal lead position during the implant procedure with little additional time and effort.

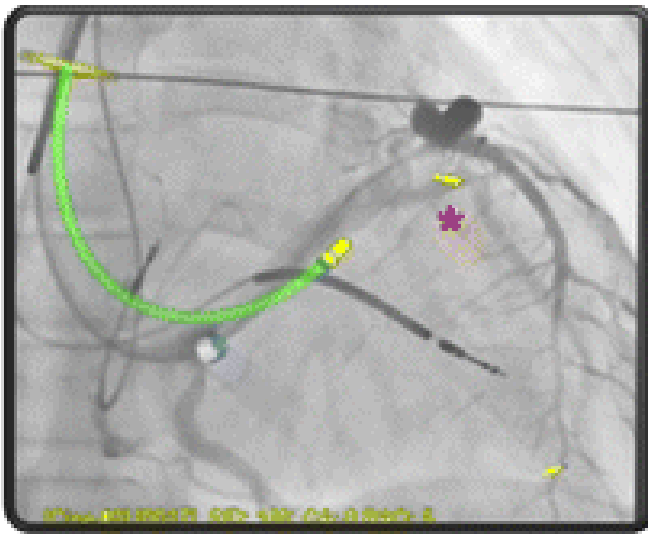


Figure 89 – Use of the MediGuide system for CRT to allow CS branch access without radiographic screening. The CS catheter, green with yellow tip, is shown. The yellow bar with asterisk is the sub-selector tip, and the lower yellow tip is the end of a coronary wire.

The ECVUE multi-electrode ECG mapping system (CardioInsight, recently purchased by Medtronic) is a vest with 252 electrodes. The detailed surface ECG data produced by this is combined with structural data from a CT scan and used to non-invasively image cardiac electrical activation. Data derived from this have already been shown to predict CRT response better than QRS width (Ploux 2013). Future use of this technology may allow targeting of the LV lead to a site of electrical delay identified by non-invasive mapping.

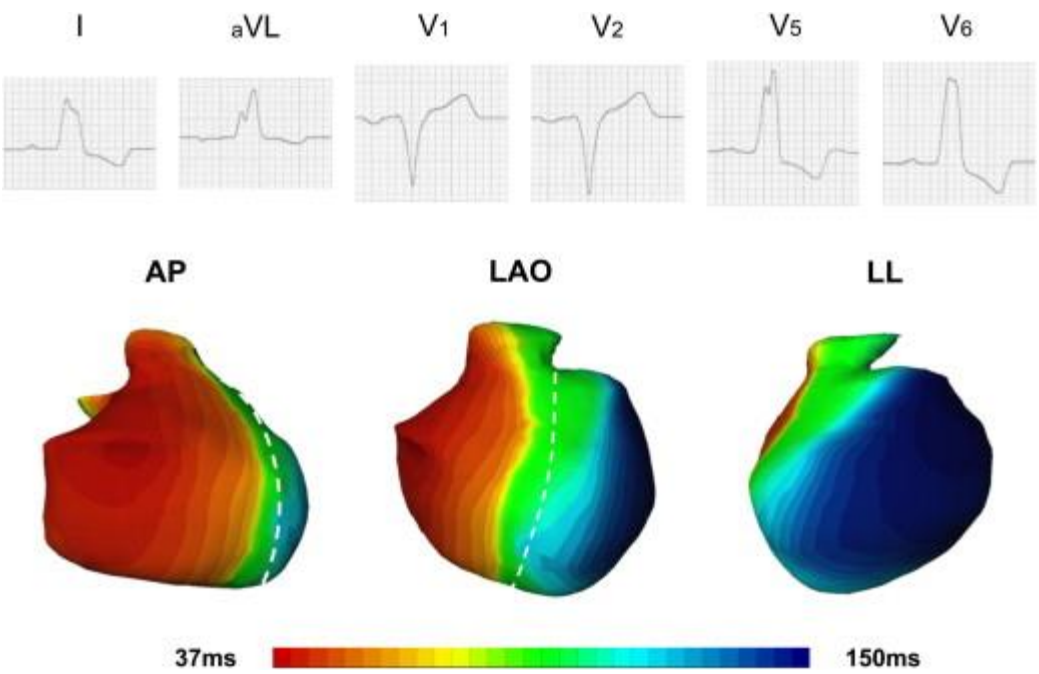
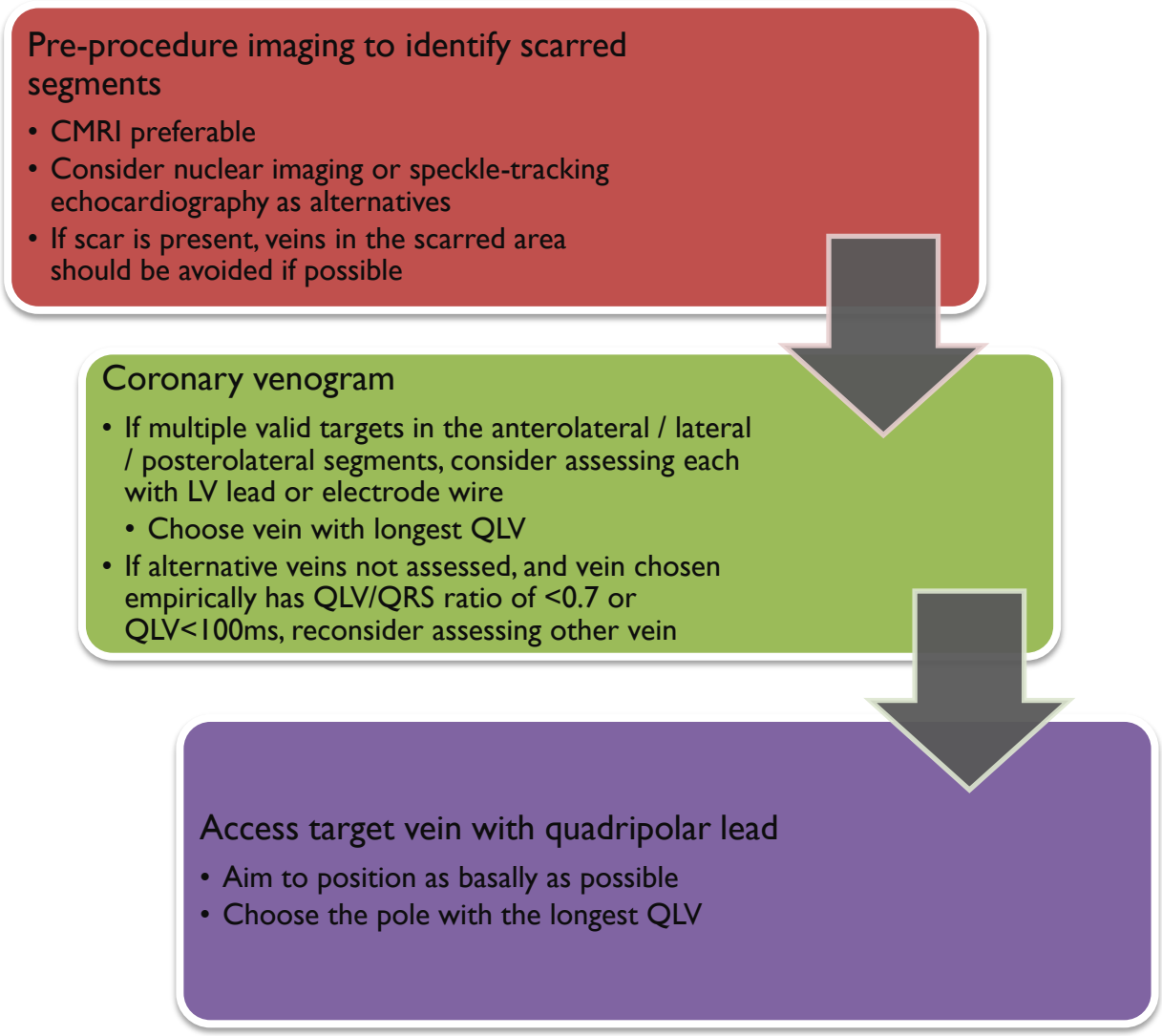


Figure 90 – Image of electrical activation and ECG in a patient, derived from the ECVUE system. From Ploux et al (Ploux 2013).

Multi-point pacing (MPP) provides a potential alternative strategy to the lead placement optimisation I have discussed, as it could be argued that by activating a large area of myocardium there is no longer a need to target the lead. This is not borne out by evidence so far; a study assessed standard biventricular and multipoint pacing in multiple veins in each patient, and found that biventricular pacing at the haemodynamically best site was still better than multipoint pacing at the worst site (Zanon 2015). It seems most likely that multipoint pacing will be an addition to targeted LV lead placement rather than a replacement of it.

Proposed optimal strategy of lead targeting

Based on the conclusions above, I would propose a strategy for lead targeting.



The strategy detailed in the diagram above is designed to be relatively practical, and to minimise the additional time added. As discussed above, there is quite convincing evidence (not arising from my data) that pre-procedure imaging to identify and avoid scarred segments of myocardium will improve outcomes.

Assessing each vein is time consuming, exposes the patient and operator to additional radiation, and potentially the patient to increased risk of venous dissection. Use of the electrode wire would minimise this (Rad 2015b), as may radiation reduction with a electroanatomic mapping system (Sommer 2014), but these remain experimental.

In the absence of these techniques, and given that many patients only have one vein that is an obvious target (Khan 2009), I believe it is reasonable to start by empirically accessing a lateral vein, and to check the QLV/QRS ratio in it. The ratio is probably more sensitive than the QLV as a one-off measure. If this suggests that the site chosen has a short electrical delay, then we should consider assessing QLV in another vein.

Once the vein has been accessed, the lead should be placed as basally as possible within the limits of achieving a stable position. Then the pole with the longest QLV should be selected – once comparing between poles the simpler QLV can be used.

Future studies

I believe based on my data and previously published work that the strategy I outline above would be likely to result in improved response to CRT. It would clearly need to be prospectively tested. A trial would not require any specific equipment. Ideally it would be outcome driven. The expected difference in response rates would probably be of the order of 5-10%, and so a considerable number of patients will be required. If a binary outcome of response (either clinical or echocardiographic) was used, with an expected response rate in the control arm of 65% then a trial of 874 patients would be needed to show a hypothesised improvement of 10% with a power of 90%. This would imply a large and expensive multinational trial. Use of a continuous outcome measure such as change in ESV or 6-minute walk distance would reduce the numbers needed into the 3-400 patient range.

The best strategy may be to start with a pilot study of CRT using this strategy. Response rates could then be assessed in this group and compared to historical controls. This would provide a more accurate estimate of the likely benefit of the strategy before planning and attempting to fund a larger outcome driven trial.

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Vitally, I must offer my thanks to all of the patients who have selflessly agreed to participate in the studies.

Finally, many thanks to my wife for her support and tolerance of long days, late nights, and grumbling about statistics.

Thank you for your time in reading my thesis. I hope you have found it interesting and look forward to discussing it with you at the viva.

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Appendix

List of papers included in meta-analysis of LV lead success rates in Chapter Two

Full list of included papers, years of recruitment , study type (RCT or other), and number of recruited patients.

*Recruitment time period estimated from data provided, but not directly stated in the paper.

$As there was only one study reported for each of 2012 and 2013, these were considered with the 2011 cohort.

Study	Citation	Years	Type	N
InSync 2002	Gras, D et al. (2002). Cardiac resynchronization therapy in advanced heart failure the multicenter InSync clinical study. *Eur. J. Heart Fail.* 4:311–320.	1997-1998	Other, 10 centres	117
Albertsen 2005	Albertsen, AE et al. (2005). Left Ventricular Lead Performance in Cardiac Resynchronization Therapy: Impact of Lead Localization and Complications. *Pacing Clin. Electrophysiol.* 28:483–488.	1997-2002	Other, 1 centre	120
MUSTIC 2001	Cazeau, S et al. (2001). Effects of Multisite Biventricular Pacing in Patients with Heart Failure and Intraventricular Conduction Delay (MUSTIC). *N. Engl. J. Med.* 344:873–880.	1998-1999	RCT, 15 centres	67
MUSTIC 2002	Leclercq, C et al. (2002). Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur. Heart J.* 23:1780–1787.	1998-1999	RCT, 15 centres	64
CONTAK CD 2003	Higgins, SL et al. (2003). Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J. Am. Coll. Cardiol.* 42:1454–1459.	1998-2000	RCT, 47 centres	565
MIRACLE 2002	Abraham, WT et al. (2002). Cardiac resynchronization in chronic heart failure (MIRACLE). *N. Engl. J. Med.* 346:1845–1853.	1998-2000	RCT, 45 centres	567
Auriccho 2003	Auricchio, A et al. (2003). Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J. Am. Coll. Cardiol.* 42:2109–2116.	1998-2001	RCT, 9 centres	27
Ollitrault 2003	Ollitrault, J et al. (2003). Long-Term Experience with a Preshaped Left Ventricular Pacing Lead. *Pacing Clin. Electrophysiol.* 26:185–188.	1999-2000	Other, 12 centres	14
Pürerfellner 2000	Pürerfellner, H et al. (2000). Transvenous left ventricular lead implantation with the EASYTRAK lead system: the European experience. *Am. J. Cardiol.* 86:157K–164K.	1999-2000	Other, 63 centres	194
Daoud 2002	Daoud, EG et al. (2002). Implantation Techniques and Chronic	1999-2001	Other, 1	66

Study	Citation	Years	Type	N
	Lead Parameters of Biventricular Pacing Dual-Chamber Defibrillators. *J. Cardiovasc. Electrophysiol.* 13:964–970.		centre	
Kautzner 2004	Kautzner, J et al. (2004). Technical Aspects of Implantation of LV Lead for Cardiac Resynchronization Therapy in Chronic Heart Failure. *Pacing Clin. Electrophysiol.* 27:783–790.	1999-2001	Other, 1 centre	46
MIRACLE ICD 2003	Young, JB et al. (2003). Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *J. Am. Med. Assoc.* 289:2685–2694.	1999-2001	RCT, 45 centres	421
Schuchert 2004	Schuchert, A et al. (2004). Two-year performance of a preshaped lead for left ventricular stimulation. *Pacing Clin. Electrophysiol.* 27:1610–1614.	1999-2001	Other, 6 centres	102
Léon 2002	Leon, AR et al. (2002). Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: Effect of upgrading to biventricular pacing after chronic right ventricular pacing. *J. Am. Coll. Cardiol.* 39:1258–1263.	1999-2001*	Other, 1 centre	20
Gasparini 2003	Gasparini, M et al. (2003). Is the Left Ventricular Lateral Wall the Best Lead Implantation Site for Cardiac Resynchronization Therapy? *Pacing Clin. Electrophysiol.* 26:162–168.	1999-2002	Other, 1 centre	159
Koos 2004	Koos, R et al. (2004). Comparison of left ventricular lead placement via the coronary venous approach versus lateral thoracotomy in patients receiving cardiac resynchronization therapy. *Am. J. Cardiol.* 94:59–63.	1999-2002	Other, 1 centre	57
Mair 2005	Mair, H et al. (2005). Surgical epicardial left ventricular lead versus coronary sinus lead placement in biventricular pacing. *Eur. J. Cardiothorac. Surg.* 27:235–242.	1999-2003	Other, 3 centres	79
Bleeker 2005	Bleeker, GB et al. (2005). Comparison of Effectiveness of Cardiac Resynchronization Therapy in Patients <70 Versus ≥70 Years of Age. *Am. J. Cardiol.* 96:420–422.	1999-2004*	Other, 1 centre	170
Reitan 2014	Reitan, C et al. (2014). Patient-assessed short-term positive response to cardiac resynchronization therapy is an independent predictor of long-term mortality. *Europace* 16:1603–1609.	1999-2010	Other, 1 centre	296
BELIEVE 2006	Gasparini, M et al. (2006). Comparison of 1-year effects of left ventricular and biventricular pacing in patients with heart failure who have ventricular arrhythmias and left bundle-branch block: The Bi vs Left Ventricular Pacing: An International Pilot Evaluation on Heart Failure Patients with Ventricular Arrhythmias (BELIEVE) multicenter prospective randomized pilot study. *Am. Heart J.* 152:155.e1-155.e7.	2000-2002	RCT, 15 centres	100
COMPANION 2004	Bristow, MR et al. (2004). Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure (COMPANION). *N. Engl. J. Med.* 350:2140–2150.	2000-2002	RCT, 128 centres	617
Insync III 2005	León, AR et al. (2005). Safety of Transvenous Cardiac Resynchronization System Implantation in Patients With Chronic Heart Failure: Combined Results of Over 2,000 Patients From a Multicenter Study Program. *J. Am. Coll. Cardiol.* 46:2348–2356.	2000-2002	Other, 28 centres	422
MIRACLE ICD II 2004	Abraham, WT et al. (2004). Effects of Cardiac Resynchronization on Disease Progression in Patients With Left Ventricular Systolic Dysfunction, an Indication for an Implantable Cardioverter-Defibrillator, and Mildly Symptomatic Chronic Heart Failure. *Circulation* 110:2864–2868.	2000-2002	RCT, 1 centre	210
RD-CHF 2007	Leclercq, C et al. (2007). Upgrading from Single Chamber Right	2000-	RCT,	56

Study	Citation	Years	Type	N
	Ventricular to Biventricular Pacing in Permanently Paced Patients with Worsening Heart Failure: The RD-CHF Study. *Pacing Clin. Electrophysiol.* 30:S23–S30.	2002	11 centres	
Blanc 2004	Blanc, J-J et al. (2004). Midterm Benefits of Left Univentricular Pacing in Patients With Congestive Heart Failure. *Circulation* 109:1741–1744.	2000-2002*	Other, 1 centre	34
PAVE 2005	Doshi, RN et al. (2005). Left Ventricular-Based Cardiac Stimulation Post AV Nodal Ablation Evaluation (The PAVE Study). *J. Cardiovasc. Electrophysiol.* 16:1160–1165.	2000-2003	RCT, 7 centres	124
Macias 2007	Macías, A et al. (2007). Cardiac resynchronization therapy: predictive factors of unsuccessful left ventricular lead implant. *Eur. Heart J.* 28:450–456.	2000-2005	Other, 1 centre	212
Rolink 2009	Rolink, AM et al. (2009). Cardiac resynchronisation therapy: results from daily practice in Rijnstate Hospital, Arnhem. *Neth. Heart J.* 17:6–8.	2000-2006	Other, 1 centre	119
Ahsan 2013	Ahsan, SY et al. (2013). An 8-year single-centre experience of cardiac resynchronisation therapy: procedural success, early and late complications, and left ventricular lead performance. *Europace* 15:711–717.	2000-2009	Other, 1 centre	490
Martin 2013	Martin, A et al. (2013). The Green Lane and Auckland City Hospital cardiac resynchronisation therapy experience. *N. Z. Med. J.* 126:54–61.	2000-2011	Other, 1 centre	137
MIRACLE ICD General phase 2005	León, AR et al. (2005). Safety of Transvenous Cardiac Resynchronization System Implantation in Patients With Chronic Heart Failure: Combined Results of Over 2,000 Patients From a Multicenter Study Program. *J. Am. Coll. Cardiol.* 46:2348–2356.	2001-2002	Other, 45 centres	664
Kühlkamp 2002	Kühlkamp, V (2002). Initial experience with an implantable cardioverter-defibrillator incorporating cardiac resynchronization therapy. *J. Am. Coll. Cardiol.* 39:790–797.	2001-2002*	Other, 26 centres	84
CARE-HF 2005	Cleland, JGF et al. (2005). The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure. *N. Engl. J. Med.* 352:1539–1549Gras, D et al. (2007). Implantation of Cardiac Resynchronization Therapy Systems in the CARE-HF Trial: Procedural Success Rate and Safety. *Europace* 9:516–522.	2001-2003	RCT, 82 centres	469
Da Costa 2006	Da Costa, A et al. (2006). Prospective validation of stress echocardiography as an identifier of cardiac resynchronization therapy responders. *Heart Rhythm* 3:406–413.	2001-2003	Other, 1 centre	71
Díaz-Infante 2005	Díaz-Infante, E et al. (2005). Predictors of Lack of Response to Resynchronization Therapy. *Am. J. Cardiol.* 95:1436–1440.	2001-2003	Other, 6 centres	177
VecToR 2004	US Food and Drug Administration (2005). PMA P030035/S3 - St. Jude Medical FrontierTM model 5508L and FrontierTM II model 5586 cardiac resynchronization therapy pacemakers (CRT-P): summary of safety and effectiveness. (Silver Springs (MD)).	2001-2003	RCT, 41 centres	144
Bax 2004	Bax, JJ et al. (2004). Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J. Am. Coll. Cardiol.* 44:1834–1840.	2001-2003*	Other, 1 centre	85
Delarche 2007	Delarche, N et al. (2007). Importance of Anterograde Visualization of the Coronary Venous Network by Selective Left Coronary Angiography Prior To Resynchronization. *Pacing Clin. Electrophysiol.* 30:70–76.	2001-2004	Other, 1 centre	185
RHYTHM II ICD 2006	Boriani, G et al. (2006). Randomized comparison of simultaneous biventricular stimulation versus optimized	2002-2003	RCT, 19	127

Study	Citation	Years	Type	N
	interventricular delay in cardiac resynchronization therapy: The Resynchronization for the HemodYnamic Treatment for Heart Failure Management II implantable cardioverter defibrillator (RHYTHM II ICD) study. *Am. Heart J.* 151:1050–1058.		centres	
Sawhney 2004	Sawhney, NS et al. (2004). Randomized prospective trial of atrioventricular delay programming for cardiac resynchronization therapy. *Heart Rhythm* 1:562–567.	2002-2003*	Other, 1 centre	40
Chung 2007	Chung, ES et al. (2007). Feasibility of Biventricular Pacing in Patients With Recent Myocardial Infarction: Impact on Ventricular Remodeling. *Congest. Heart Fail.* 13:9–15.	2002-2004	RCT, 2 centres	9
RHYTHM ICD 2004	US Food and Drug Administration (2004). St. Jude Medical® EpicTM HF System including the EpicTM HF model V-338 cardiac resynchronization therapy defibrillator, the AesculaTM LV model 1055K lead, the QuickSiteTM LV model 1056K lead, and the model 3307, v4.5m programmer software: summary of safety and effectiveness. (Silver Springs (MD)).	2002-2004	RCT, 50 centres	205
Piccirillo 2006	Piccirillo, G et al. (2006). Influence of cardiac-resynchronization therapy on heart rate and blood pressure variability: 1-year follow-up. *Eur. J. Heart Fail.* 8:716–722.	2002-2004*	RCT, 1 centre	16
Díaz-Infante 2007	Díaz-Infante, E et al. (2007). Usefulness of Ventricular Dyssynchrony Measured Using M-Mode Echocardiography to Predict Response to Resynchronization Therapy. *Am. J. Cardiol.* 100:84–89.	2002-2005	Other, 1 centre	91
PREVENT-HF 2011	Stockburger, M et al. (2011). Preventing ventricular dysfunction in pacemaker patients without advanced heart failure: results from a multicentre international randomized trial (PREVENT-HF). *Eur. J. Heart Fail.* 13:633–641.	2002-2008	RCT, 14 centres	57
RHYTHM ICD/QuickSite Lead 2004	US Food and Drug Administration (2004). St. Jude Medical® EpicTM HF System including the EpicTM HF model V-338 cardiac resynchronization therapy defibrillator, the AesculaTM LV model 1055K lead, the QuickSiteTM LV model 1056K lead, and the model 3307, v4.5m programmer software: summary of safety and effectiveness. (Silver Springs (MD)).	2003-2003	Other, 49 centres	162
DECREASE-HF 2007	Rao, RK et al. (2007). Reduced Ventricular Volumes and Improved Systolic Function With Cardiac Resynchronization Therapy A Randomized Trial Comparing Simultaneous Biventricular Pacing, Sequential Biventricular Pacing, and Left Ventricular Pacing. *Circulation* 115:2136–2144.	2003-2004	RCT, 57 centres	358
Murphy 2006	Murphy, RT et al. (2006). Tissue Synchronization Imaging and Optimal Left Ventricular Pacing Site in Cardiac Resynchronization Therapy. *Am. J. Cardiol.* 97:1615–1621.	2003-2004	Other, 1 centre	54
RENEWAL-AVT 2006	Saxon, LA et al. (2006). Results of the Multicenter RENEWAL® 3 AVT Clinical Study of Cardiac Resynchronization Defibrillator Therapy in Patients with Paroxysmal Atrial Fibrillation. *J. Cardiovasc. Electrophysiol.* 17:520–525.	2003-2004	Other, 38 centres	168
Gold 2005	Gold, MR et al. (2005). Comparison of stimulation sites within left ventricular veins on the acute hemodynamic effects of cardiac resynchronization therapy. *Heart Rhythm* 2:376–381.	2003-2004*	Other, 1 centre	24
Abraham 2012	Abraham, WT et al. (2012). Randomized controlled trial comparing simultaneous versus optimized sequential interventricular stimulation during cardiac resynchronization therapy. *Am. Heart J.* 164:735–741.	2003-2005	RCT, 32 centres	247
Albertsen	Albertsen, AE et al. (2011). Adverse effect of right ventricular	2003-	Other,	25

Study	Citation	Years	Type	N
2011	pacing prevented by biventricular pacing during long-term follow-up: a randomized comparison. *Eur. J. Echocardiogr.* 12:767–772.	2005	1 centre	
OVID 2006	Biotronik (2011). Corox Family of OTW LV Leads Technical Manual (Berlin, Germany).	2003-2005	Other, 33 centres	132
TRIP-HF 2008	Leclercq, C et al. (2008). A Randomized Comparison of Triple-Site Versus Dual-Site Ventricular Stimulation in Patients With Congestive Heart Failure. *J. Am. Coll. Cardiol.* 51:1455–1462.	2003-2005	RCT, 7 centres	40
OPTION CRT/ ATx 2006	Bersohn, MM et al. (2006). OPTION CRT/ATX: An Original CRT-Defibrillator Study Design. In AHA 2006, (Circulation), p. II_606US Food and Drug Administration (2006). PMA050023 - Biotronik Tupos LV/ATx CRT-D and Kronos LV-T CRT-D: summary of safety and effectiveness. (Silver Springs (MD)).	2003-2005*	RCT, 25 centres	200
D'Ivernois 2008	D'Ivernois, C et al. (2008). Where Are the Left Ventricular Leads Really Implanted? A Study of 90 Consecutive Patients. *Pacing Clin. Electrophysiol.* 31:554–559.	2003-2006	Other, 1 centre	89
MASCOT 2008	Padeletti, L et al. (2008). Atrial fibrillation in recipients of cardiac resynchronization therapy device: 1-year results of the randomized MASCOT trial. *Am. Heart J.* 156:520–526.	2003-2006	RCT, 34 centres	402
Sorin Group 2008	US Food and Drug Administration (2008). PMA060027 -Sorin Ovatio CRT-D Model 6750 and Situs OTW Left Ventricular Over-the-Wire Lead: summary of safety and effectiveness. (Silver Springs (MD)).	2003-2006	RCT, 27 centres	177
Fatemi 2008	Fatemi, M et al. (2008). Primary failure of cardiac resynchronization therapy: what are the causes and is it worth considering a second attempt? A single-centre experience. *Europace* 10:1308–1312.	2003-2007	Other, 1 centre	100
GREATER-EARTH 2011	Thibault, B et al. (2011). Left Ventricular Versus Simultaneous Biventricular Pacing in Patients With Heart Failure and a QRS Complex ≥120 Milliseconds. *Circulation* 124:2874–2881.	2003-2009	RCT, 11 centres	211
RAFT 2010	Tang, ASL et al. (2010). Cardiac-Resynchronization Therapy for Mild-to-Moderate Heart Failure (RAFT). *N. Engl. J. Med.* 363:2385–2395.	2003-2009	RCT, 34 centres	888
BLOCK-HF 2013	Curtis, AB et al. (2013). Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction (BLOCK-HF). *N. Engl. J. Med.* 368:1585–1593.	2003-2011	RCT, 58 centres	809
LESSER-EARTH 2013	Thibault, B et al. (2013). Cardiac Resynchronization Therapy in Patients With Heart Failure and a QRS Complex <120 Milliseconds The Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) Trial. *Circulation* 127:873–881.	2003-2011	RCT, 12 centres	159
Delnoy 2008	Delnoy, PP et al. (2011). Upgrading to Biventricular Pacing Guided by Pressure–Volume Loop Analysis During Implantation. *J. Cardiovasc. Electrophysiol.* 22:677–683.	2004-2005	Other, 1 centre	40
LOLA ROSE 2007	Sirker, A et al. (2007). Cardiac resynchronization therapy: left or left-and-right for optimal symptomatic effect—the LOLA ROSE study. *Europace* 9:862–868.	2004-2005	RCT, 1 centre	19
PROSPECT 2008	Chung, ES et al. (2008). Results of the Predictors of Response to CRT (PROSPECT) Trial. *Circulation* 117:2608–2616.	2004-2005	RCT, 53 centres	473
Hua 2006	Hua, W et al. (2006). Short-term effect of cardiac resynchronization therapy in patients with ischaemic or nonischaemic cardiomyopathy. *Chin. Med. J. (Engl.)* 119:1507–	2004-2005*	Other, 1 centre	149

Study	Citation	Years	Type	N
	1510.			
Zanon 2006	Zanon, F et al. (2006). Implantation of Left Ventricular Leads Using a Telescopic Catheter System. *Pacing Clin. Electrophysiol.* 29:1266–1272.	2004-2005*	Other, 1 centre	74
Boriani 2010	Boriani, G et al. (2010). A randomized double-blind comparison of biventricular versus left ventricular stimulation for cardiac resynchronization therapy: The Biventricular versus Left Univentricular Pacing with ICD Back-up in Heart Failure Patients (B-LEFT HF) trial. *Am. Heart J.* 159:1052–1058.e1.	2004-2006	RCT, 26 centres	186
everesT 2000	Biotronik (2011). Corox Family of OTW LV Leads Technical Manual (Berlin, Germany).	2004-2006	Other, 78 centres	148
Mischke 2009	Mischke, K et al. (2009). Initial experience with remote magnetic navigation for left ventricular lead placement. *Acta Cardiol.* 64:467–475.	2004-2006	Other, 1 centre	123
REVERSE 2009	Linde, C et al. (2008). Randomized Trial of Cardiac Resynchronization in Mildly Symptomatic Heart Failure Patients and in Asymptomatic Patients With Left Ventricular Dysfunction and Previous Heart Failure Symptoms (REVERSE). *J. Am. Coll. Cardiol.* 52:1834–1843.	2004-2006	RCT, 73 centres	642
Van Geldorp 2010	van Geldorp, IE et al. (2010). Beneficial effects of biventricular pacing in chronically right ventricular paced patients with mild cardiomyopathy. *Europace* 12:223–229.	2004-2006	RCT, 1 centre	39
Gallagher 2007	Gallagher, P et al. (2007). Initial Clinical Experience with Cardiac Resynchronization Therapy Utilizing a Magnetic Navigation System. *J. Cardiovasc. Electrophysiol.* 18:174–180.	2004-2006*	Other, 1 centre	102
Imanishi 2012	Imanishi, J et al. (2012). Utility of combined assessment of baseline dyssynchrony and its acute improvement to predict long-term outcomes after cardiac resynchronization therapy. *Am. J. Cardiol.* 110:1814–1819.	2004-2006*	Other, 2 centres	121
Piepoli 2008	Piepoli, MF et al. (2008). Time Course of Effects of Cardiac Resynchronization Therapy in Chronic Heart Failure: Benefits in Patients with Preserved Exercise Capacity. *Pacing Clin. Electrophysiol.* 31:701–708.	2004-2006*	RCT, 1 centre	44
Champagne 2011	Champagne, J et al. (2011). The effect of electronic repositioning on left ventricular pacing and phrenic nerve stimulation. *Europace* 13:409–415.	2004-2007	Other, 15 centres	260
Ciampi 2009	Ciampi, Q et al. (2009). Identification of responders to cardiac resynchronization therapy by contractile reserve during stress echocardiography. *Eur. J. Heart Fail.* 11:489–496.	2004-2007	Other, 3 centres	69
Crossley 2010	Crossley, GH et al. (2010). Chronic performance of an active fixation coronary sinus lead. *Heart Rhythm* 7:472–478.	2004-2007	Other, 20 centres	428
O'Mara 2012	O'Mara, JE et al. (2012). Regional Patterns of Dyssynchrony: Lateral Wall Delay Is Desirable but Not Essential for Left Ventricular Remodeling in Biventricular Pacing. *Echocardiography* 29:554–559.	2004-2007	Other, 1 centre	32
Pinter 2009	Pinter, A et al. (2009). Assessment of Resynchronization Therapy on Functional Status and Quality of Life in Patients Requiring an Implantable Defibrillator. *Pacing Clin. Electrophysiol.* 32:1509–1519.	2004-2007*	RCT, 5 centres	90
AVAIL CLS/CRT	Orlov, MV et al. (2010). Biventricular pacing improves cardiac function and prevents further left atrial remodeling in patients	2004-2008	RCT, 22	139

Study	Citation	Years	Type	N
2010	with symptomatic atrial fibrillation after atrioventricular node ablation. *Am. Heart J.* 159:264–270.		centres	
Ciampi 2010	Ciampi, Q et al. (2010). Clinical and prognostic role of pressure-volume relationship in the identification of responders to cardiac resynchronization therapy. *Am. Heart J.* 160:906–914.	2004-2008	Other, 3 centres	72
MADIT-CRT 2009	Moss, AJ et al. (2009). Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events (MADIT-CRT). *N. Engl. J. Med.* 361:1329–1338.	2004-2008	RCT, 110 centres	1089
Rafique 2010	Rafique, AM et al. (2010). A revised approach to patient selection for cardiac resynchronization treatment using multiple asynchrony parameters in Narrow- and Wide-QRS cardiomyopathy causes cardiac reverse. *Europace* 12:1127–1135.	2004-2008	Other, 1 centre	90
Hsu 2012	Hsu, JC et al. (2012). Predictors of Fluoroscopy Time and Procedural Failure During Biventricular Device Implantation. *Am. J. Cardiol.* 110:240–245.	2004-2011	Other, 1 centre	272
Duray 2008	Duray, GZ et al. (2008). Upgrading to biventricular pacing/defibrillation systems in right ventricular paced congestive heart failure patients: prospective assessment of procedural parameters and response rate. *Europace* 10:48–52.	2005-2006	Other, 1 centre	77
António 2010	António, N et al. (2010). Cardiac resynchronization therapy is effective even in elderly patients with comorbidities. *J. Interv. Card. Electrophysiol.* 27:61–68.	2005-2007	Other, 1 centre	87
RETHINQ 2007	Beshai, JF et al. (2007). Cardiac-Resynchronization Therapy in Heart Failure with Narrow QRS Complexes. *N. Engl. J. Med.* 357:2461–2471.	2005-2007	RCT, 34 centres	172
Sedláček 2010	Sedláček, K et al. (2010). Isolated left ventricular pacing results in worse long-term clinical outcome when compared with biventricular pacing: a single-centre randomized study. *Europace* 12:1762–1768.	2005-2007	Other, 1 centre	40
CLEAR 2012	Ritter, P et al. (2012). A randomized pilot study of optimization of cardiac resynchronization therapy in sinus rhythm patients using a peak endocardial acceleration sensor vs. standard methods. *Europace* 14:1324–1333.	2005-2008	RCT, 51 centres	261
Leenders 2012	Leenders, GE et al. (2012). Septal Deformation Patterns Delineate Mechanical Dyssynchrony and Regional Differences in Contractility Analysis of Patient Data Using a Computer Model. *Circ. Heart Fail.* 5:87–96.	2005-2008	Other, 1 centre	109
MENDMI 2010	Chung, ES et al. (2010). Effect of Peri-Infarct Pacing Early After Myocardial Infarction Results of the Prevention of Myocardial Enlargement and Dilatation Post Myocardial Infarction Study. *Circ. Heart Fail.* 3:650–658.	2005-2008	RCT, 29 centres	44
PACE 2009	Yu, C-M et al. (2009). Biventricular pacing in patients with bradycardia and normal ejection fraction. *N. Engl. J. Med.* 361:2123–2134.	2005-2008	RCT, 4 centres	193
Sénéchal 2009	Sénéchal, M et al. (2010). Usefulness and Limitation of Dobutamine Stress Echocardiography to Predict Acute Response to Cardiac Resynchronization Therapy. *Echocardiography* 27:50–57.	2005-2008	Other, 1 centre	51
Brignole 2011	Brignole, M et al. (2011). Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur. Heart J.* 32:2420–2429.	2005-2009	RCT, 19 centres	190
Oto 2012	Oto, A et al. (2012). Percutaneous Coronary Sinus Interventions	2005-	Other,	255

Study	Citation	Years	Type	N
	to Facilitate Implantation of Left Ventricular Lead: A Case Series and Review of Literature. *J. Card. Fail.* 18:321–329.	2010	1 centre	
STARTER 2013	Saba, S et al. (2013). Echocardiography-Guided Left Ventricular Lead Placement for Cardiac Resynchronization Therapy Results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region Trial. *Circ. Heart Fail.* 6:427–434.	2005-2011	RCT, 1 centre	187
Faran 2008	Faran, A et al. (2008). Cardiac resynchronisation therapy in patients with end-stage heart failure--long-term follow-up. *Kardiol. Pol.* 66:19–26; discussion 27.	2006-2006	Other, 1 centre	28
Haghjoo 2009	Haghjoo, M et al. (2009). Effect of right ventricular lead location on response to cardiac resynchronization therapy in patients with end-stage heart failure. *Europace* 11:356–363.	2006-2007	Other, 1 centre	73
Rogers 2012	Rogers, DPS et al. (2012). A randomized double-blind crossover trial of triventricular versus biventricular pacing in heart failure. *Eur. J. Heart Fail.* 14:495–505.	2006-2007	RCT, 1 centre	43
Delgado 2008	Delgado, V et al. (2008). Assessment of left ventricular dyssynchrony by speckle tracking strain imaging comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. *J. Am. Coll. Cardiol.* 51:1944–1952.	2006-2007*	Other, 1 centre	161
Stockburger 2008	Stockburger, M et al. (2008). Baseline Doppler parameters are useful predictors of chronic left ventricular reduction in size by cardiac resynchronization therapy. *Europace* 10:69–74.	2006-2007*	Other, 1 centre	73
Bonakdar 2009	Bonakdar, HR et al. (2009). Prediction of response to cardiac resynchronization therapy using simple electrocardiographic and echocardiographic tools. *Europace* 11:1330–1337.	2006-2008	Other, 1 centre	82
LODO-CRT 2010	Muto, C et al. (2010). Presence of left ventricular contractile reserve predicts midterm response to cardiac resynchronization therapy—results from the LODO-CRT Trial. *Heart Rhythm* 7:1600–1605.	2006-2008	Other, 24 centres	297
Bank 2009	Bank, AJ et al. (2009). Results of the PROspective MInnesota Study of ECHO/TDI in Cardiac Resynchronization Therapy (PROMISE-CRT) Study. *J. Card. Fail.* 15:401–409.	2006-2008*	Other, 9 centres	65
Luedorff 2010	Luedorff, G et al. (2010). Improved success rate of cardiac resynchronization therapy implant by employing an active fixation coronary sinus lead. *Europace* 12:825–829.	2006-2009	Other, 1 centre	678
Taylor 2010	Taylor, AJ et al. (2010). Combined dyssynchrony and scar imaging with cardiac magnetic resonance imaging predicts clinical response and long-term prognosis following cardiac resynchronization therapy. *Europace* 12:708–713.	2006-2009*	Other, 1 centre	40
Wang, J 2014	Wang, J et al. (2014). Elevated pulmonary artery pressure predicts poor outcome after cardiac resynchronization therapy. *J. Interv. Card. Electrophysiol.* Advance online publication.	2006-2012	Other, 1 centre	187
Garikipati 2014	Garikipati, NV et al. (2014). Comparison of Endovascular Versus Epicardial Lead Placement for Resynchronization Therapy. *Am. J. Cardiol.* 113:840–844.	2006-2012*	Other, 1 centre	12
Lee 2014	Lee, SH et al. (2014). Mid-Term Outcomes in Patients Implanted with Cardiac Resynchronization Therapy. *J. Korean Med. Sci.* 29:1651–1657.	2006-2013	Other, 3 centres	47
Medtronic Inc 2009	US Food and Drug Administration (2009). PMA080006 - Medtronic Attain AbilityTM Model 4196 Lead: summary of safety and effectiveness. (Silver Springs (MD)).	2007-2007	Other, 22 centres	146
Bertini 2009	Bertini, M et al. (2009). Effects of Cardiac Resynchronization Therapy on Left Ventricular Twist. *J. Am. Coll. Cardiol.* 54:1317–	2007-2008*	Other, 1	80

Study	Citation	Years	Type	N
	1325.		centre	
Diab 2011	Diab, IG et al. (2011). Does ventricular dyssynchrony on echocardiography predict response to cardiac resynchronisation therapy? A randomised controlled study. *Heart* 97:1410–1416.	2007-2009	RCT, 1 centre	49
Giannola 2011	Giannola, G et al. (2011). Efficacy of a tool combining guide-wire and stylet for the left ventricular lead positioning. *Europace* 13:244–250.	2007-2009	Other, 7 centres	117
MOMIJI 2012	Momomura, S et al. (2012). Clinical efficacy of cardiac resynchronization therapy with an implantable defibrillator in a Japanese population: results of the MIRACLE-ICD outcome measured in Japanese indication (MOMIJI) study. *Circ. J.* 76:1911–1919.	2007-2009	RCT, 22 centres	85
RESPOND 2011	Foley, PWX et al. (2011). Cardiac resynchronisation therapy in patients with heart failure and a normal QRS duration: the RESPOND study. *Heart* 97:1041–1047.	2007-2009	RCT, 1 centre	28
Zhang 2011	Zhang, B-C et al. (2011). Initial clinical experience with implantation of left ventricular lead guided by Overlay Ref for the treatment of congestive heart failure. *Arch. Cardiovasc. Dis.* 104:11–16.	2007-2009	Other, 1 centre	88
Rönn 2011	Rönn, F et al. (2011). Right ventricular lead positioning does not influence the benefits of cardiac resynchronization therapy in patients with heart failure and atrial fibrillation. *Europace* 13:1747–1752.	2007-2009*	Other, 1 centre	33
Jackson 2013	Jackson, KP et al. (2013). Impact of Using a Telescoping-Support Catheter System for Left Ventricular Lead Placement on Implant Success and Procedure Time of Cardiac Resynchronization Therapy. *Pacing Clin. Electrophysiol.* 36:553–558.	2007-2011	Other, 1 centre	437
Bisch 2010	Bisch, L et al. (2010). Predictive factors of difficult implantation procedure in cardiac resynchronization therapy. *Europace* 12:1141–1148.	2008-2009	Other, 1 centre	106
Döring 2012	Döring, M et al. (2013). Individually tailored left ventricular lead placement: lessons from multimodality integration between three-dimensional echocardiography and coronary sinus angiogram. *Europace* 15:718–727.	2008-2009	Other, 1 centre	38
Klein 2012	Klein, N et al. (2012). Clinical efficacy of left ventricular pacing vector programmability in cardiac resynchronization therapy defibrillator patients for management of phrenic nerve stimulation. *Europace* 14:826–832.	2008-2009	Other, 10 centres	131
MUSIC 2011	Lim, P et al. (2011). Multicentre study using strain delay index for predicting response to cardiac resynchronization therapy (MUSIC study). *Eur. J. Heart Fail.* 13:984–991.	2008-2009	Other, 4 centres	189
Ussen 2011	Ussen, B et al. (2011). Safety and feasibility of cephalic venous access for cardiac resynchronization device implantation. *Pacing Clin. Electrophysiol.* 34:365–369.	2008-2009	Other, 1 centre	103
Becker 2010	Becker, M et al. (2010). Analysis of LV Lead Position in Cardiac Resynchronization Therapy Using Different Imaging Modalities. *JACC Cardiovasc. Imaging* 3:472–481.	2008-2009*	Other, 1 centre	56
Girsky 2010	Girsky, MJ et al. (2010). Prospective Randomized Trial of Venous Cardiac Computed Tomographic Angiography for Facilitation of Cardiac Resynchronization Therapy. *Pacing Clin. Electrophysiol.* 33:1182–1187.	2008-2009*	Other, 1 centre	25
Tolosana 2012	Tolosana, JM et al. (2012). Cardiac resynchronization therapy in patients with permanent atrial fibrillation. Is it mandatory to	2008-2009*	Other, 6	202

Study	Citation	Years	Type	N
	ablate the atrioventricular junction to obtain a good response? *Eur. J. Heart Fail.* 14:635–641.		centres	
NARROW-CRT 2013	Muto, C et al. (2013). A Randomized Study of Cardiac Resynchronization Therapy Defibrillator Versus Dual-Chamber Implantable Cardioverter-Defibrillator in Ischemic Cardiomyopathy With Narrow QRS The NARROW-CRT Study. *Circ. Arrhythm. Electrophysiol.* 6:538–545.	2008-2010	RCT, 6 centres	56
TRUST-CRT 2012	Lenarczyk, R et al. (2012). Implantation feasibility, procedure-related adverse events and lead performance during 1-year follow-up in patients undergoing triple-site cardiac resynchronization therapy *J. Cardiovasc. Electrophysiol.* 23:1228–1236.	2008-2010	RCT, 1 centre	100
Bai 2011	Bai, R et al. (2011). Positioning of Left Ventricular Pacing Lead Guided by Intracardiac Echocardiography with Vector Velocity Imaging During Cardiac Resynchronization Therapy Procedure. *J. Cardiovasc. Electrophysiol.* 22:1034–1041.	2008-2010*	Other, 3 centres	104
Serdoz 2011	Serdoz, LV et al. (2011). Predictors for Restoration of Normal Left Ventricular Function in Response to Cardiac Resynchronization Therapy Measured at Time of Implantation. *Am. J. Cardiol.* 108:75–80.	2008-2010*	Other, 2 centres	75
ECHO-CRT 2013	Ruschitzka, F et al. (2013). Cardiac-Resynchronization Therapy in Heart Failure with a Narrow QRS Complex (ECHO-CRT). *N. Engl. J. Med.* 369:1395–1405.	2008-2013	RCT, 115 centres	855
Sperzel 2012	Sperzel, J et al. (2012). First prospective, multi-centre clinical experience with a novel left ventricular quadripolar lead. *Europace* 14:365–372.	2009-2009	Other, 15 centres	75
Sterliński 2010	Sterliński, M et al. (2010). Success rate of transvenous left ventricular lead implantation for cardiac resynchronisation therapy - recent experience of a single centre. *Kardiol. Pol.* 68:903–909.	2009-2009	Other, 1 centre	122
aCRT 2012	Martin, DO et al. (2012). Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac resynchronization therapy: Results of the adaptive CRT trial. *Heart Rhythm* 9:1807–1814.	2009-2010	RCT, 94 centres	492
Burger 2011	Burger, H et al. (2011). New generation of transvenous left ventricular leads - first experience with implantation of multipolar left ventricular leads. *Exp. Clin. Cardiol.* 16:23–26.	2009-2010	Other, 1 centre	30
Mehta 2012	Mehta, PA et al. (2012). Elimination of phrenic nerve stimulation occurring during CRT: follow-up in patients implanted with a novel quadripolar pacing lead. *J. Interv. Card. Electrophysiol.* 33:43–49.	2009-2010	Other, 1 centre	40
Strauss 2013	Strauss, M et al. (2013). Comparison of a new quadripolar coronary sinus lead with the conventional bipolar coronary sinus lead in patients undergoing CRT-ICD therapy. *Eur. Heart J.* 34:P3191.	2009-2010	Other, 1 centre	61
TARGET 2012	Khan, FZ et al. (2012). Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy. *J. Am. Coll. Cardiol.* 59:1509–1518.	2009-2010	RCT, 1 centre	207
Tomassoni 2013	Tomassoni, G et al. (2013). Postoperative Performance of the Quartet® Left Ventricular Heart Lead. *J. Cardiovasc. Electrophysiol.* 24:449–456.	2009-2010	Other, 24 centres	178
CLEPSYDRA 2014	Auricchio, A et al. (2014). Long-term effectiveness of the combined minute ventilation and patient activity sensors as	2009-2011	RCT, 63	516

Study	Citation	Years	Type	N
	predictor of heart failure events in patients treated with cardiac resynchronization therapy. *Eur. J. Heart Fail.* 16:663–670.		centres	
Forleo 2012	Forleo, GB et al. (2012). Clinical and procedural outcome of patients implanted with a quadripolar left ventricular lead: Early results of a prospective multicenter study. *Heart Rhythm* 9:1822–1828.e3.	2009-2011	Other, 4 centres	154
Arora 2012	Arora, S et al. (2012). Peak oxygen uptake during cardiopulmonary exercise testing determines response to cardiac resynchronization therapy. *J. Cardiol.* 60:228–235.	2009-2011*	Other, 1 centre	76
Bogaard 2012	Bogaard, MD et al. (2012). Cardiac resynchronization therapy beyond nominal settings: who needs individual programming of the atrioventricular and interventricular delay? *Europace* 14:1746–1753.	2009-2011*	Other, 1 centre	50
ERACE 2013	Goetze, S et al. (2013). Phrenic nerve stimulation in CRT patients and benefits of electronic lead repositioning: the ERACE trial. *J. Interv. Card. Electrophysiol.* 38:1–9.	2009-2012*	Other, 54 centres	305
Behar 2014	Behar, JM et al. (2014). Reduction in mortality and phrenic nerve stimulation with cardiac resynchronization therapy delivered via a multipolar compared to a bipolar left ventricular lead; long term follow-up from a multi-centre registry. *J. Cardiovasc. Electrophysiol.* In Press.	2009-2014	Other, 3 centres	1164
Da Costa 2012	Da Costa, A et al. (2012). Anatomical factors involved in difficult cardiac resynchronization therapy procedure: a non-invasive study using dual-source 64-multi-slice computed tomography. *Europace* 14:833–840.	2010-2010	Other, 1 centre	50
Arias 2012	Arias, MA et al. (2012). Acute and mid-term outcomes of transvenous implant of a new left ventricular quadripolar lead versus bipolar leads for cardiac resynchronization therapy: results from a single-center prospective database. *Cardiol. J.* 19:470–478.	2010-2011*	Other, 1 centre	42
Shetty 2011	Shetty, AK et al. (2011). Use of a quadripolar left ventricular lead to achieve successful implantation in patients with previous failed attempts at cardiac resynchronization therapy. *Europace* 13:992–996.	2010-2011*	Other, 1 centre	21
Thibault 2013	Thibault, B et al. (2013). Acute haemodynamic comparison of multisite and biventricular pacing with a quadripolar left ventricular lead. *Europace* 15:984–991.	2010-2011*	Other, 1 centre	27
Vado 2013	Vado, A et al. (2014). Single-center experience of a quadripolar pacing lead for cardiac resynchronization therapy. *J. Interv. Card. Electrophysiol.* 39:161–165.	2010-2012	Other, 1 centre	45
Wang 2014	Wang, L et al. (2014). Coronary sinus cannulation with a steerable catheter during biventricular device implantation. *Scand. Cardiovasc. J.* 48:41–46.	2010-2012	Other, 1 centre	182
Moubarak 2014	Moubarak, G et al. (2014). First experience of intraoperative echocardiography-guided optimization of cardiac resynchronization therapy delivery. *Arch. Cardiovasc. Dis.* 107:169–177.	2010-2012*	Other, 1 centre	91
Forleo 2014	Forleo, GB et al. (2014). Improved implant and postoperative lead performance in CRT-D patients implanted with a quadripolar left ventricular lead. A 6-month follow-up analysis from a multicenter prospective comparative study. *J. Interv. Card. Electrophysiol.* 1–8.	2010-2013	Other, 7 centres	428
Sommer, A	Sommer, A et al. (2014). Left and right ventricular lead positions	2011-	Other,	59

Study	Citation	Years	Type	N
2014	are imprecisely determined by fluoroscopy in cardiac resynchronization therapy: a comparison with cardiac computed tomography. *Europace* euu056.	2012	1 centre	
Jones 2014	Jones, MA et al. (2015). Inter- and Intravein Differences in Cardiac Output with Cardiac Resynchronization Pacing using a Multipolar LV Pacing Lead. *Pacing Clin. Electrophysiol.* 38:267–274.	2011-2012	Other, 1 centre	22
Pappone 2014	Pappone, C et al. (2015). Multipoint Left Ventricular Pacing in a Single Coronary Sinus Branch Improves Mid-Term Echocardiographic and Clinical Response to Cardiac Resynchronization Therapy. *J. Cardiovasc. Electrophysiol.* 26:58–63.	2011-2012	RCT, 1 centre	44
Sommer, P 2014	Sommer, P et al. (2014). Non-fluoroscopic catheter visualization using MediGuide™ technology: experience from the first 600 procedures. *J. Interv. Card. Electrophysiol.* 40:209–214.	2011-2012*	Other, 1 centre	115
Laksman 2014	Laksman, Z et al. (2014). Model-Based Navigation of Left and Right Ventricular Leads to Optimal Targets for Cardiac Resynchronization Therapy A Single-Center Feasibility Study. *Circ. Arrhythm. Electrophysiol.* 7:1040–1047.	2011-2013	Other, 1 centre	31
Crossley 2014	Crossley, GH et al. (2015). Performance of a novel left ventricular lead with short bipolar spacing for cardiac resynchronization therapy: Primary results of the Attain Performa Quadripolar Left Ventricular Lead Study. *Heart Rhythm* 12:751–758.	2011-2013*	Other, 126 centres	1124
Rad 2014	Rad, MM et al. (2015). Left ventricular lead placement in the latest activated region guided by coronary venous electroanatomic mapping. *Europace* 17:84–93.	2012-2013$	Other, 1 centre	25
Thibault 2014	Thibault, B et al. (2015). Reducing Radiation Exposure during CRT Implant Procedures: Early Experience with a Sensor-Based Navigation System. *Pacing Clin. Electrophysiol.* 38:63–70.	2013-2014$	Other, 1 centre	130