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Optimal site selection & image fusion guidance technology to facilitate cardiac resynchronisation therapy

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ABBREVIATIONS OF COMMON TERMS

AHR: Acute hemodynamic response

CMR: Cardiac MRI

CRT: Cardiac Resynchronisation Therapy

CS: Coronary sinus

ICM: Ischemic cardiomyopathy

LBBB: Left bundle branch block

LV: Left ventricle

LVEF: Left ventricular ejection fraction

LV_{ENDO}: Left ventricular endocardial

NICM: Non-ischemic cardiomyopathy

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

QRSd: QRS duration

RV: Right ventricle

ABSTRACT

Introduction: Cardiac resynchronisation therapy (CRT) has emerged as one of the few effective treatments for heart failure however, up to 50% of patients derive no benefit. Suboptimal LV lead position is a potential cause of poor outcomes whilst targeted lead deployment has been associated with enhanced response rates. Image-fusion guidance systems represent a novel approach to CRT delivery, allowing physicians to both accurately track and target a specific location during LV lead deployment.

Areas Covered: This review will provide a comprehensive evaluation of how to define the optimal pacing site. We will evaluate the evidence for delivering targeted LV stimulation at sites displaying favourable viability or advantageous mechanical or electrical properties. Finally, we will evaluate several emerging image-fusion guidance systems which aim to facilitate optimal site selection during CRT.

Expert Commentary: Targeted LV lead deployment is associated with reductions in morbidity and mortality. Assessment of tissue characterisation and electrical latency are critical and can be achieved in a number of ways. Ultimately, the constraints of CS anatomy have forced the exploration of novel means of delivering CRT including endocardial pacing which hold promise for the future of CRT delivery.

1. INTRODUCTION:

One in five people will suffer from HF during their life time and once diagnosed ~40% of patients die within one year[1]. Cardiac resynchronisation therapy (CRT) by pacing the left (LV) and right (RV) ventricles to re-coordinate cardiac electrical activation and produce a synchronous contraction, has emerged as one of the few effective treatments for HF(2,3). However, at present 30% of patients fail to respond clinically through improved quality of life, exercise capacity and New York Heart Association (NYHA) functional classification of HF and up to 50% show no beneficial changes in cardiac function[3]. Suboptimal LV lead position is a common culprit when evaluating poor outcomes after CRT [4–7]. Equally, several groups have reported enhanced response rates when targeting tissue which displays evidence of favourable viability [8–11] or advantageous mechanical [12–18] or electrical [19–23] properties. This review will evaluate how to define the optimal LV pacing site and the mechanisms by which it is possible to selectively deploy a pacing electrode at this site.

2. ACUTE AND CHRONIC MARKERS OF RESPONSE

In order to identify the optimal pacing location, it is necessary to perform an examination of the available sites and preferentially select the site which possesses the most favourable characteristics. Unfortunately, in the 20 years since the first description of resynchronisation pacing for heart failure [24], no consensus has been achieved on how to define “response” to CRT [25] making comparison of the various pacing sites problematic. A multitude of different clinical and event-based definitions of response to CRT have been described with rates of response varying from 32% to 91% depending on the criteria used. This review will predominantly focus on three indices; outcome based metrics which evaluate survival and mortality after device implantation. Markers

of left ventricular reverse remodelling (LVRR) following device implantation, of a reduction in LV end-systolic volume (LVESV) is the most widely accepted marker [26,27]. Finally, some metrics evaluate acute changes in LV contractility. Acute haemodynamic response (AHR) is a reproducible marker of LV contractility best expressed as the change in the maximum rate of left ventricular pressure (LV-dP/dt_{max}), from a baseline control state [28,29]. Previous work has evaluated the acute haemodynamic effects of CRT using LV-dP/dt_{max} as an outcome measure [29–32] and this metric has been used to compare the effects of biventricular pacing at different locations [28,29,33]. An improvement in LV-dP/dt_{max} of 10% during acute implantation has been shown to predict chronic LV reverse remodelling in patients receiving CRT [34].

3. TISSUE CHARACTERISATION:

3.1 Pathophysiology of Scar in Ischemic and Non-Ischaemic Cardiomyopathy

Ischaemic scar forms as a result of permanent myocyte death following an ischaemic insult. A reparative process is initiated to rebuild the infarcted myocardium and maintain the structural integrity of the ventricle. An initial inflammatory phase of healing is followed by a fibrogenic phase that eventually results in the formation of scar tissue as dead myocytes are progressively replaced by collagenous scar. Ischaemic scar tends to display a sub-endocardial or transmural distribution affecting a specific coronary territory. Histological evidence of myocardial fibrosis has also been described in non-ischaemic presentations [35–37]. Whilst the precise mechanism behind this scar formation, which typically follows an epicardial or mid-wall distribution, is unclear, interstitial and perivascular fibrosis ultimately results in myocardial necrosis [38].

3.2 Impact of scar on the mechanical properties of the heart

Almost immediately following coronary artery occlusion, the subtended area of myocardium becomes passive and non-contractile. The non-viability and reduced plasticity of infarcted scar tissue is associated with a reduction in efficient and effective mechanical function during systole. Nearly all of the determinants of systolic function are negatively impacted by the presence of scar including cardiac shape and dimensions, preload, afterload & contractility [39]. During systole, the scarred region stretches and bulges outward while the remaining myocardium contracts, causing a reduction in the mechanical efficiency of the heart as a pump. This effect is strongly dependant on the total area of scarred tissue [40].

3.3 Impact of scar on outcomes

The size, location and transmuralty of scar all impact LV remodelling after CRT. Global scar burden has been shown to be inversely proportional to LV reverse remodelling amongst both ischaemics [41], non-ischaemics [42] and mixed populations, [43–45]. Functional improvement [41,42,46] and survival [47] are also inversely proportional to scar burden. Retrospective analysis has confirmed that favourable markers for response include smaller scar size and fewer areas of transmural scar [45]. The location of scar is of equal importance, in particular when it is located in the postero-lateral region of the LV, a site empirically thought to be optimal for LV lead deployment. Scar in this area is associated with lower response rates following CRT [45,48].

3.4 Impact of scar on electrical activation

Scar prevents effective transmission of the electrical impulse, resulting in prolonged activation. Electrical activation in regions of fibrosis is characterised by localised delays and fractionated, low-amplitude extracellular electrograms [49]. This has been attributed to changes in patterns of excitation and conduction due to altered ion channel activity [50] and decreased cellular connectivity [51] compounded by tortuous conduction through areas of surviving myocytes. This delay in LV activation results in less haemodynamic improvement during biventricular pacing [52]. Electrical stimulation in regions of scar can also be pro-arrhythmic [53,54] and is associated with increased morbidity and mortality [8,55]. Significantly, the presence of myocardial scar at the site of LV stimulation during CRT is associated with non-response [8,56].

3.5 Scar Identification

Given the negative implications associated with stimulating scarred and fibrotic myocardial tissue, current evidence favours avoiding these areas and targeting viable tissue. Numerous mechanisms have been proposed in order to differentiate non-viable tissue and these can be categorised into anatomical, functional and biological modalities, see Table 1. Anatomical imaging involves direct visualisation of tissue defined as scarred. Functional imaging relies on surrogate markers of scar such as measures of wall motion, strain, voltage or contractile reserve. Biological imaging assesses metabolism or perfusion as a surrogate for viability.

3.6 Cardiac MRI

Late gadolinium enhancement (LGE) cardiac MRI (CMR) is the gold standard for delineating myocardial scar with high resolution, as the superior spatial resolution of

LGE CMR permits differentiation between epicardial, transmural and sub-endocardial infarction. The technique relies on the fact that gadolinium washes out of the blood pool but accumulates in the extracellular space. Tissues with weak intracellular bonds and high amounts of non-cellular space, including necrotic tissue or fibrous scar, will develop higher concentrations of gadolinium than the surrounding healthy tissues. Scar detected by LGE CMR has been shown to closely match histologically-proven myocardial infarction [57].

3.7 Trans-thoracic echocardiography

Trans-thoracic echocardiography has the potential to identify areas of scarred or fibrotic myocardium. Early work focussed on regional wall thinning [58] and assessment of regional contractile function [59] while more recent work has focussed on the ability of speckle-tracking radial strain [60] and longitudinal strain [61] to better identify areas of regional akinesis. Other techniques include the use of 3D contrast echo [62] and pulse cancellation echocardiography [63] which have both shown some promise as tools to identify areas of scar.

3.8 Cardiac Computed Tomography (CT)

Tissue characterisation using cardiac CT has been used to identify areas of myocardial scarring. After an infarct, myocardial tissue replaced by fibrous scar and eventually, after several months, undergoes significant lipomatous metaplasia [64]. Using unenhanced CT, it is possible to identify the fat in infarcted myocardium. New-generation dual-source CT (DSCT) allows the integration of late-iodine enhancement (LIE) imaging and has been shown to correlate reasonably well (52% sensitivity, 88% specificity) with LGE derived CMR imaging [65].

3.9 Nuclear Imaging

Tracer uptake during Nuclear imaging using either positron emission tomography (PET) or single-photon emission computed tomography (SPECT) relies on adequate myocardial blood flow and myocyte viability. The finding of a fixed perfusion defect can either represent myocardial scar or viable hibernating myocardium. Differentiation between these two states can be further enhanced through an assessment of glucose uptake via Fluorine-18-labeled deoxyglucose (FDG) with hypocontractile regions exhibiting reduced perfusion but normal or increased FDG uptake representing likely hibernating myocardium. During head to head comparison, MIBI has been shown to consistently overestimate areas of myocardial scar tissue whilst FDG lacks the spatial resolution associated with LGE CMR [66].

3.10 Electro-Anatomical Mapping

Whilst LGE CMR has the capacity to directly visualise anatomic myocardial scar, the abnormal electrophysiological substrate extends beyond the dense anatomical scar, into regions of heterogeneous “boarder-zone” tissue [67] and may be optimally identified using electroanatomic mapping (EAM). The ability of EAM to assess myocardial viability on the basis of myocardial voltage has been validated against SPECT [68], PET imaging [69] and latterly LGE CMR [70–73] in both ischaemic and non-ischaemic cardiomyopathies. Furthermore, analysis of electrogram characteristics can also help to predict histologic properties of scar tissue [49].

3.11 Invasive Electroanatomical Mapping

During invasive EAM, intracardiac electrical activation is recorded in relation to

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

Non-contact mapping systems utilise a multi-electrode array (MEA) catheter to simultaneously record endocardial activation over multiple areas [74]. The array is situated on a balloon with 64 electrodes allowing high density mapping from a single heartbeat. Advantages of this system include the ability to acquire multiple endocardial electrograms during a single cardiac cycle however this comes at the cost of greater inaccuracy in electrogram timing and morphology at greater distances from the MEA [75]. Work evaluating this system has already established that non-contact mapping can identify regions of electrically viable myocardium, which could be used to inform lead position, particularly among ischaemic patients [52].

3.12 Electrocardiographic Imaging

Electrocardiographic imaging (ECGI) is a novel, non-invasive 3D epicardial electrophysiology imaging modality. This technique uses 252 ECG electrodes mounted on a wearable vest to reconstruct epicardial potentials from torso potentials, see Figure 1. These are displayed as electrograms and activation sequences (isochrones) on the epicardial surface of the heart [76].

ECGI benefits from a non-invasive approach and is able to measure the activation across the whole heart simultaneously compared to the slower sequential mapping with EAM. Inverse ECG mapping technology is able to identify fibrotic tissue due to the abnormal electrical properties exhibited by scarred myocardium, specifically low-amplitude electrical potentials with broad fractionated electrograms typically in areas exhibiting delayed or slow activation [77–79]. A degree of discrepancy between CMR and EAM is expected as CMR can struggle to detect areas of homogenous microscopic diffuse fibrosis due to the low resolution of the image while inverse ECG EAM can be more sensitive at detecting zones of epicardial and transmural fibrosis but may miss sub-endocardial scar. Despite this, good correlation has been observed between areas of low voltage on ECGI and areas of scar, as identified on LGE CMR [80] with one study quoting an 89% sensitivity and 85% specificity at detecting epicardial scar [81].

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

A paradox exists between the electrical substrate corrected by CRT, specifically dyssynchronous biventricular electrical activation and its mode of action, which is predominately mechanical and aims to enhance cardiac contractility by correcting the mechanical dyssynchrony and restoring the mechano-energetic efficiency of the heart. Intuitively, it would seem sensible to specifically assess the degree of mechanical dyssynchrony present, as this would both help patient selection and aid in the determination of the optimal LV pacing site. Dyssynchrony is the measure of dispersion in the timing of mechanical contraction of the various LV segments [82] and may be measured by a variety of different imaging techniques

4.1 Trans-thoracic echocardiography

Early work assessing the utility of echocardiographic parameters of dyssynchrony to aid patient selection for CRT appeared promising. A systolic dyssynchrony index (SDI), calculated from tissue Doppler imaging (TDI) proved capable of retrospectively predicting enhanced clinical response in single centre work [83]. These benefits were also observed in a multicentre retrospective analysis where the use of baseline TDI imaging predicted not only functional and echocardiographic improvement but also identified patients who yielded prognostic benefit from CRT [84]. Speckle tracking radial strain analysis superseded TDI, as it was less dependent on the angle of incidence of the ultrasound beam and also appeared able to predict echocardiographic response in retrospective analysis [85].

Unfortunately, the utility of mechanical dyssynchrony assessment to identify CRT responders has not been reproduced in larger, prospective, randomised multicentre studies [86] and this has cast some doubt on the reproducibility of the technique. In addition, when all the various echocardiographic measures of mechanical dyssynchrony were analysed in a large, international multi-centre study, no single measure proved capable of improving patient selection for CRT [87]. Promisingly, newer techniques including longitudinal myocardial strain assessment [88] and 3D speckle tracking echo [89] appear more reliable and indicate an encouraging direction for future work.

Given the primary target of CRT is the restoration of coordinated myocardial contraction and those patients exhibiting mechanical dyssynchrony appeared to yield the most benefit from CRT, it seemed logical that the optimal site for LV lead deployment would be at the site of maximal mechanical delay. In a retrospective analysis where TDI

assessment of mechanical activation was performed prior to CRT implantation, patients in whom the LV lead was situated at the site exhibiting the latest activation showed increased functional and echocardiographic improvements [15]. Superior response to CRT was also observed when the site of latest mechanical activation was targeted using tissue synchronization imaging (TSI) [90], 3D echocardiography [91], and speckle tracking [92]. The TARGET [13] and STARTER [16] trials prospectively assessed the utility of echocardiographic speckle-tracking 2-dimensional radial strain imaging to inform LV lead deployment. Echo guided lead implantation was associated with echocardiographic response rates (>15% reduction in ESV) of 70% & 57% respectively. Both studies showed increased rates of event free survival over empirical lead placement.

4.2 Cardiac MRI

CMR has several potential advantages when looking to characterise mechanical activation. These include greater reproducibility, less artefact secondary to patient habitus, detailed assessment of myocardial tissue characterisation as well as chamber size and volumes and greater spatial resolution. CMR can also assess strain in multiple planes allowing the assessment of both radial and longitudinal strain. A recent prospective, single-centre randomised study (CMR-CRT) showed the feasibility of performing an assessment of circumferential strain in order to identify the latest mechanically activated viable segment [93]. Several dyssynchrony assessment metrics have been proposed including myocardial tagging, displacement encoding with stimulated echoes (DENSE) and phase contrast tissue velocity mapping (TVM). Whilst myocardial tag data has been shown to predict functional improvement following CRT implantation [94], tag decay remains an issue and this led to the development of 3D

volumetric change as a means of assessing both global LV dyssynchrony and assessing mechanical activation [95]. When compared to other mechanical dyssynchrony measures, volume change systolic dyssynchrony index (SDI) proved the sole predictor of chronic reverse remodelling [18].

4.3 Cardiac Computed Tomography (CT)

Cardiac computed tomography (CT) offers a potential benefit over CMR due to the fact that approximately 28% of patients undergoing CRT implantation have already received an implantable cardiac device rendering them unsuitable to undergo CMR scanning [96]. Cardiac CT is associated with submillimetre spatial resolution and can assess regional and global LV dyssynchrony by calculating the stretch of the endocardial surface throughout the cardiac cycle (stretch quantifier for endocardial engraved zones [SQUEEZ]) [97]. When assessed in patients undergoing an upgrade to a CRT pacing system, CT-SQUEEZ targets were associated with a similar improvement in AHR as the best achievable ($20.4\% \pm 13.7\%$ vs $24.9\% \pm 11.1\%$; $P=0.36$) [98]. In addition, delivering LV stimulation at a site identified using CT-SQUEEZ resulted in greater clinical response vs non-target segments (90% vs 60%, $P < 0.001$).

5.0 IDENTIFYING THE SITE OF LATEST ELECTRICAL ACTIVATION (LEA)

The primary substrate targeted during CRT is delayed electrical activation, typically manifest by a left bundle branch block pattern on the surface ECG. Detailed analysis of ventricular activation confirms a myriad of differing underlying conduction disturbances amongst even this group, with ischaemic patients displaying a particularly high degree

of variability in activation [99]. The standard 12 lead ECG is therefore of limited use when looking to define the optimal site for LV stimulation and focus has shifted to more detailed methods of visualising electrical latency. In the context of LBBB, ventricular activation is initiated at the distal branching of the right bundle, with activation of the left endocardium occurring after a significant delay, as a result of slow conduction through the interventricular septum. Theoretically, the site of latest activation should exhibit the most dyssynchrony and as such would represent an ideal pacing site. Whilst some work appears to confirm the site of LEA is synonymous with the optimal pacing site [21], more recent analysis has shown optimal site exhibits late but not supremely delayed activation [100]. Sites demonstrating excessively delayed activity may in fact merely represent distal activation occurring within islands of non-viable tissue. A variety of different methods of identifying the site of latest activation have been described, as outlined below.

5.1 Q-LV & LV Lead Electrical Delay

An advantage of assessing electrical delay is that it can be performed both intra-procedurally and without the need for any additional mapping equipment. Singh et al, devised a measure of electrical latency called the Left Ventricular Lead Electrical Delay (LVLED) [20]. This marker of electrical delay was calculated during LV lead implantation by determining the onset of the surface ECG QRS complex to the onset of the sensed electrogram on the LV lead, and expressing the value (the Q-LV time) as a percentage of the baseline QRS interval. They identified that LVLED correlated with greater haemodynamic improvements (derived using transthoracic echo).

When dichotomised, patients with an LVLED of > 50% exhibited greater event free survival and reduced rates of hospitalisation. In a sub-study of the SMART AV Trial

[101], patients were again dichotomised, although this time according to the median Q-LV value (95ms). Gold et al showed that implanting the LV lead at a site with a favourable Q-LV was independently associated with symptomatic improvement and greater reverse remodelling at 6 months [19].

Both of these studies retrospectively analysed the degree of electrical latency at the site of LV lead deployment however, Zanon et al evaluated whether Q-LV might be used to identify the optimal site in an individual patient by systematically screening all of the suitable coronary sinus veins [21]. A strong correlation was observed between Q-LV prolongation and improvements in acute haemodynamic response. Again a Q-LV value of greater than 95ms appeared significant, yielding an improvement in AHR of >10%, a finding which has been associated with predicting long term remodelling [34]. Crucially, in 96.8% of patients, the optimal haemodynamic performance was associated with delivering pacing therapy at the site exhibiting the latest electrical activation. A similar figure (85%) was observed by van Gelder et al in their evaluation of the effects of LV endocardial pacing amongst a cohort of non-responders to epicardial CRT [102]. The small discrepancy may be attributed to the larger cohort of ischaemic patients in this study.

5.2 Narrowing of the Paced QRS

Reductions in the paced QRSd during biventricular pacing may also aid identification of late activating tissue. Widening of the QRS after CRT implantation has been found to be an independent predictor of mortality or progression to heart transplantation [103] and achieving a reduction in the paced QRS has been shown to predict response in several studies [104] including via multi-variate logistic regression [105]. In other work, a reduction in paced QRS duration was found to be the only predictor of response [106].

However, this finding is disputed in other studies [107]. There is also no consensus as to whether delivering biventricular pacing at a site which achieves a narrowing of the paced QRS is associated with improvements in haemodynamics. Whilst some work has shown a correlation between narrowing of the QRS and improvements in AHR [100], this finding has not been consistently replicated [21].

5.3 Invasive Electro-Anatomical Mapping

Electroanatomical mapping has also been used to evaluate electrical activation and locate the site of LEA. Analysis of contact and non-contact mapping first data identified a “U shaped” pattern of activation during LBBB with depolarisation originating at a single septal breakthrough site [99]. Activation could not proceed directly from the anterior to the lateral wall, due to the presence of lines of block, forcing the depolarisation wave front to pass inferiorly around the apex. Crucially, even amongst patients who presented with LBBB on their surface ECG, the location of this line of block varied between patients, exposing the heterogeneity of this complex conduction disorder and the difficulty in establishing a universal site of LEA.

More detailed analysis of LV activation revealed heterogeneity in conduction velocities in both non-ischaemic and ischaemic patients at the site of LV stimulation in the lateral and postero-lateral walls [52]. The location of these areas of slow conduction influenced the pattern and direction of wave front propagation. Whilst it was possible to mitigate the effects of positioning the lead in an area of slow conduction by altering the timing between LV and RV stimulation during CRT; locating and stimulating healthy, late

activating tissue was consistently associated with superior haemodynamic improvements.

The anatomical constraints of transvenous, epicardial CRT mean that LV stimulation can only occur at a site accessible via a tributary of the coronary sinus. Coronary venous electroanatomical mapping allows the assessment of electrical latency exclusively within the coronary sinus [23]. A high degree of variability in the location of the site of LEA was observed between patients. Intra-procedural assessment of latency utilising this technique is feasible and whilst of practical value to the implanting physician, is limited to only those sites accessible via the available coronary venous system.

5.4 Non-Invasive Electro-anatomical mapping of Electrical Activation

The heterogeneous nature of LV activation in patients with LBBB has also been described using ECGi. A key advantage of this technique is the ability to non-invasively identify the area of LEA and this approach has already been shown to allow peri-procedural guidance of the LV lead to the target site. ECGi can also compute an LV electrical dyssynchrony index and this metric appears may predict patients likely to respond to CRT and aid in identifying the optimal site during LV lead deployment [108,109].

5.5 Correlation between the site of LMA and LEA

One hypothesis advanced to explain the persistent issue of non-response to CRT is the existence of uncoupling of mechanical and electrical synchronicity. Whilst these two

substrates can be assessed individually, performing an assessment of both may be preferable. Early work appeared to suggest that the site of LEA was synonymous with the area of LMA, when evaluated using non-contact EAM and TTE TDI [110]. Similar findings were observed when the LMA was assessed using CMR [111]. One explanation for this uniformity may be the crucial role played by aetiology and the disruptive effects of tissue heterogeneity. The impact of aetiology was better assessed by Fujiwara et al who included patients with both ischaemic and non-ischaemic cardiomyopathy in their study and identified a clear discrepancy between the site of LMA and LEA [112], see Figure 2. Unanimity between the LMA and the LEA site was only observed in 19% of patients.

5.6 Electrical Activation During RV Pacing & LBBB

Current class 1 indications for CRT include evidence of dyssynchronous electrical activation, manifest on the surface ECG by LBBB. Whilst there has been a great deal of focus on characterising the precise nature of LV depolarization which occurs during LBBB, activation during CRT occurs as a result of paced stimulation at the LV and typically, the RV apex. Whilst an RV paced event appears morphologically similar on the surface ECG to conduction resulting from LBBB, Eschalier et al set out to perform a more detailed examination. Non-invasive body surface mapping demonstrated clear differences in the depolarisation pattern of both the RV and LV during RV pacing and LBBB activation. Apical pacing resulted in slower RV conduction with lines of conduction detected around the pacing site [113]. LV depolarisation was also observed to be prolonged by RV pacing although lines of slow conduction were fewer and shorter in size in comparison to those observed during LBBB activation. **The LV site of LEA was**

similar during both RV apical pacing and LBBB activation and was consistently located at the LV base.

5.7 Electrical Activation & RV Pacing Site Selection

RV pacing appears to result in delayed LV depolarisation and the deleterious effects of RV apical pacing have been widely acknowledged [114,115]. Positioning the RV lead in a septal position has been associated with beneficial haemodynamic effects [116]. Early work evaluating non-apical RV pacing conducted by Khan et al [117] showed that LV remodelling rates were unaffected by RV lead position while Kutuyifa et al [118] also highlighted a higher risk of ventricular arrhythmias. The SEPTAL CRT study randomly assigned patients to receive either an septal or apical RV lead and demonstrated no significant difference in clinical outcome [119].

It is worth noting that there is little consensus on a universal optimal site of LV lead deployment and instead an individualised approach which takes into account aetiology, tissue characterisation and the underlying electrical substrate appears to yield the greatest benefit [120]. Similarly, patient specific RV lead placement may represent a superior strategy, particularly when faced with limited viable LV pacing sites due to the anatomical constraints associated with transvenous, epicardial CRT. In a pilot study of seven patients, Kumar et al observed that patient specific RV lead placement guided by real time assessment of the cardiac output resulted in significant acute haemodynamic improvements [121].

Electrical latency appears a useful marker when looking to identify the optimal LV pacing site [19,20] and a similar approach can also be used when looking to optimise RV lead position. In the INTER-V study, the measurement of paced RV-LV interlead electrical delay predicted mid-term CRT response [122]. In a blinded, randomised controlled trial which prospectively allocated patients to receive CRT with either RV apical pacing or RV pacing at a site guided by maximal electrical separation (MES), individualised RV lead placement was associated with increased rates of echocardiographic response [123].

6.0 SITE SELECTION DURING LV ONLY PACING

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

6.1 LV Only Epicardial Pacing

Several comparative studies assessing LV only epicardial (LV_{EPI}) pacing timed to coincide with intrinsic RV activation have been performed. LV_{EPI} pacing has been shown to be associated with non-inferior outcomes [124–126], with some studies showing trends towards superior LV remodelling [127] and improvements in LVEF [128]. In all these studies, the LV lead was empirically placed in a lateral or posterolateral target vein and as such it is impossible to predict the implications of delivering LV_{EPI} pacing at an alternative site.

6.2 LV Only Endocardial Pacing

LV only endocardial (LV_{ENDO}) pacing has also been investigated. Activation of the LV endocardium during CRT is associated with a reduction in both LV and biventricular (BiV) activation time [129]. This is in part explained by the shorter activation path length but also earlier activation of fast-conducting endocardial tissue, which possess a higher conduction velocity. LV_{ENDO} pacing was associated with greater improvements in AHR than could be achieved using conventional, transvenous CRT (BiV_{EPI}) [130]. Only biventricular endocardial CRT (BiV_{ENDO}) proved capable of yielding a similar haemodynamic improvement.

Much attention has been traditionally focussed on correcting the underlying electromechanical delay associated with LBBB by delivering LV stimulation at the site of latest activation, typically identified in the postero-lateral wall. An alternative approach is to try and replicate the activation sequence observed during normal sinus rhythm, where activation occurs initially at the left mid-septal endocardium [131,132]. When assessed, activation at this site results in an almost identical temporospatial activation envelope to that observed during normal sinus rhythm, especially when compared to BiV_{EPI}, LV_{EPI} and RV_{ENDO} pacing [133]. This can be achieved via a transvenous approach, using a bespoke delivery mechanism incorporating a custom pacing lead which is introduced transvenously into the RV and positioned against the RV septum, before being deployed through the interventricular septum until the left ventricular septum is reached but without perforating the LV septum [134]. One major benefit of this approach is it negates the need for long-term anti-coagulation, typically associated with lead based LV_{ENDO} pacing.

LV_{ENDO} septal pacing can achieve a haemodynamic performance similar to that observed during normal sinus rhythm in patients with preserved LV function [134]. The

effects of LV_{ENDO} septal pacing have also been assessed in a small series of patients who fulfil current criteria for CRT implantation. A combination of RV_{ENDO} and LV_{ENDO} septal pacing achieved the greatest improvement in cardiac stroke work, suggesting that whilst the septum may represent a potential location to deliver stimulation in patients with impaired LV function, LV_{ENDO} septal pacing alone may not be sufficient to achieve optimal resynchronisation [135].

7.0 MULTI-MODALITY IMAGING & IMAGE FUSION TECHNOLOGY

7.1 Multi-Modality Imaging

A novel approach to site selection incorporates the fusion of two differing imaging modalities via multi-modality imaging in order to maximise the reliability of the acquisition. Bertini et al describe an excellent approach aimed at targeting late mechanically activating, viable tissue [136]. Patients first underwent a CMR scan where areas the myocardial wall displaying of > 75% LGE were excluded. The next stage of the “CRT Team” approach involved the use of 2D speckle tracking echocardiography which assessed global LV longitudinal strain in order to highlight the most delayed area between non-fibrotic segments. The highest frequency of reverse remodelling at six months (93.1%) was observed in the 58% of patients where the final lead position was concordant with the prespecified optimal site [136].

Another novel approach employs the fusion of pre-procedural CMR imaging with computer modelling to predict the optimal pacing site. In this series, a 3D navigation model was designed to rank the available sites for LV and RV lead deployment. Sites were graded to ensure the LV lead was directed into the segment with the lowest scar burden which exhibited the greatest mechanical delay whilst also maximising the geographic distance between the LV and RV pacing sites. The RC lead tip was directed

to the area with lowest scar burden. The optimal location for the RV lead tip was assigned first followed by the preferential LV pacing site. At follow up, 74% of patients met the predefined echocardiographic criteria of a responder despite the fact that lead implantation was informed purely by fluoroscopy and visual assessment of the 3D models, and real time guidance was used [137].

7.2 Image Fusion and Guidance Technology

Optimal site selection can only be achieved when used in conjunction with a targeting system which can identify and inform pacing electrode deployment in real time during implantation. The use of fluoroscopy alone to facilitate targeted electrode deployment is challenging given the radiolucency of the cardiac silhouette and high variability in the rotation of the left and right sided chambers relative to one another. When previously evaluated, concordance between final fluoroscopic LV lead position & CT images was only observed in 35% of patients [138]. In over half of the cases studied, LV lead deployment had actually occurred in an adjacent segment, although this is hardly surprising given the relatively small size of an individual myocardial segment (order of magnitude, cms). As such, site selection and X-Ray co-registration are essential in order to ensure optimal electrode deployment.

7.3 Image Fusion with Fluoroscopic Coronary Sinus Balloon Venography

Both the TARGET and STARTER studies showed the benefits of targeting lead deployment at the site of latest mechanical activation, defined using TTE [13,16]. Unfortunately, in the STARTER study, it was only possible to deploy the lead at the target segment in 30% of patients due to issues with coronary venous anatomy and

lead stability. Even in recent work where CMR was used to define the optimal pacing site, concordant LV lead positioning was only achieved in 52% of cases [93]. One approach to facilitate site selection at an achievable location subtended by a tributary of the coronary sinus is to evaluate both mechanical activation and coronary sinus anatomy. This can be achieved by fusing TTE derived 3D echo data with fluoroscopic coronary sinus balloon venography [14]. Use of this image guidance tool resulted in an LV reverse remodelling rate of 81% of patients, where concordance between final LV lead position and the site of LMA was confirmed. Whilst the use of coronary venous anatomy helps pre-procedural planning, this data was acquired via an additional invasive catheter study.

A more streamlined approach fusing peri-procedural fluoroscopic coronary sinus balloon venography with CMR imaging has also been developed [139], see Figure 3A. A major benefit of this system is the integrated nature of the GuideCRT platform (Siemens Healthineers, Erlangen, Germany). Image processing is automatic with manual verification. A quantitative analysis of late gadolinium enhancement is exported including information on scar location, burden and transmural. In addition, regional motion analysis of volume vs. time is plotted via endocardial tracking for each of the 16 myocardial segments, allowing identification of the latest activating region, see Figure 3B. Image processing has now been accelerated to the stage (25 ± 8 mins) that the patient can undergo a CMR immediately prior to their CRT implant and by the time CS venography has been performed, image co-registration can be performed without delay.

Nuclear perfusion imaging can also usefully delineate areas of viable (non-scared) myocardium which display late activation [140]. Again as coronary venous anatomy is not delineated on SPECT imaging, geometric alignment, landmark-based registration

and vessel-surface overlay were used to fuse the 3D venous anatomy with the epicardial mesh derived from the SPECT images [141], see Figure 4.

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

Whilst it is possible to visualise the coronary sinus using CMR [142], direct imaging of the sub-branches can be difficult to consistently achieve. CT however is capable of accurately delineating the coronary venous tree with submillimetre spatial resolution via rapid acquisition, 3D, isotropic, whole heart data sets [143]. Co-registration between pre-procedural CT derived volumetric datasets and intra-operative 2D image acquisitions is more straight forward and can be performed using both a feature-based and an intensity-based methods [144]. Work evaluating the use of dual-source CT to both inform site selection and identify an overlying tributary of the coronary sinus subtending this area is currently ongoing [145], see Figure 5.

8. EXPERT COMMENTARY

Transvenous, epicardial CRT remains the optimal therapy for those patients who exhibit a remediable underlying substrate and whose anatomy is amenable to allow adequate correction. The constraints of the CS anatomy have forced the exploration of novel means or performing resynchronisation pacing and of these endocardial CRT holds the most promise. Endocardial LV pacing results in a more physiological, endocardial to epicardial activation pattern, a greater reduction in total LV activation time (LV_{TAT}) and an improved haemodynamic performance (greater increases in $LV\ dP/dt_{max}$) in both the LV [129,146] and RV [147]. It is also associated with a higher implant success rates, less phrenic nerve stimulation and far greater access to different pacing sites. The

optimal LV endocardial pacing site displays marked inter and intra-patient variability and whilst some argue that any endocardial pacing site will invariably prove superior to epicardial stimulation, research has shown that sub-optimal BiV_{ENDO} CRT can achieve haemodynamic improvements inferior to those associated with empirically positioned BiV_{EPI} CRT [100]. As such, whilst endocardial pacing affords the freedom to perform LV stimulation at a customisable location, site selection is even more critical in order to maximise the potential benefits associated with this technique.

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

Assessing mechanical dyssynchrony can also be achieved through a variety of modalities however, the prospective evidence proving dyssynchrony assessments can improve patient selection for CRT is lacking [86,87]. The use of CMR based dyssynchrony indexes may offer a more reliable solution [18], however larger scale, prospective, randomised validation of these techniques is required before they can be comprehensively endorsed. In the mean-time, mechanical dyssynchrony assessments aimed at identifying viable sites exhibiting late mechanical activation do appear to aid LV site selection. It's not clear whether this approach is superior to targeting sites of electrical latency or even whether these two sites are synonymous [112]. Both Q-LV [19] and LVLED [20] appear particularly useful markers to aid site selection. Neither technique requires sophisticated electro-anatomical mapping or additional pre-

procedural image processing and instead can be calculated by the operator at the time of LV lead deployment. A more integrated approach is likely to be necessary however, than simply targeting the site of latest electrical activation, particularly in ischaemic patients. Instead, the focus should be on targeting a site which displays late activation in the absence of myocardial scar. Narrowing of the paced QRS during pacing appears a less reliable marker of the optimal pacing site and we would urge caution with this approach given the potential for electro-mechanical uncoupling. Optimising the RV pacing site by identifying electrical delay also appears to be beneficial [123], especially when revising a previously implanted system where the position of the LV lead is relatively fixed.

Another novel approach to CRT involves attempting to selectively capture the His-Purkinji network of fast conducting fibres via LV only pacing. Rather than trying to correct underlying electro-mechanical dyssynchrony, this approach aims to replicate healthy intrinsic biventricular depolarisation. New delivery mechanisms allow stimulation of the LV septum via trans-venous access [134] meaning this approach may well become increasingly widespread. Whether similar results can be achieved through selective His capture in the RV remains to be seen, although initial studies of this promising pacing modality appear promising [148].

Site selection remains only as good as the adjunctive guidance system given the technical limitations of spatial orientation using conventional fluoroscopy [138]. Co-registration between 2D and 3D modalities is challenging with the simplest solution integrating pre-implant imaging data with peri-procedural coronary sinus balloon venography. However, these systems are unable to determine whether a suitable tributary of the coronary sinus subtends the target segment until the procedure has begun highlighting a limitation of the transvenous, epicardial CRT. Guidance systems

which can accurately visualise the entire coronary sinus network pre-procedurally, allow decisions to be made regarding not just the most appropriate target but also the most suitable means of targeting this area.

9. FIVE YEAR VIEW

Transvenous epicardial CRT will continue to function as the default strategy for the delivery of CRT. Pre-procedural imaging and modelling [149] will however, allow physicians to identify those patients who may benefit from an alternative pacing strategy; either due to a lack of suitable targets or recognition that the target area cannot be accessed via the epicardial coronary venous system. More widespread recognition of cases where this is the case will result in greater use of endocardial pacing, and in particular leadless endocardial pacing systems such as the WiSE-CRT system (WiSE-CRT System, EBR Systems, Sunnyvale, California) which have proved safe and effective and do not require long-term anticoagulation [150]. Growth in endocardial pacing will mandate increasing use of site selection and guidance given the optimal LV endocardial pacing displays such a high degree of variability.

The WiSE-CRT system has been developed with trans-femoral arterial access in mind, however, arterial access complications remain an issue and given the EP community's familiarity with trans-septal access, trans-venous access [151] will become increasingly de rigour. In addition, entire pacing systems will likely become leadless with atrial and right ventricular activation coordinated via communication between the various components.

CMR remains the pre-eminent imaging modality for assessing both tissue characterisation and mechanical activation and increasing experience with ultrahigh field CMR will inevitably result in improved image quality [152,153]. Greater spatial

resolution will allow detailed visualisation of the entire coronary venous tree allowing pre-procedural planning to be performed entirely from one, non-ionising imaging modality.

Other non-invasive imaging techniques which may become increasingly adopted are electrocardiographic imaging & Holographic imaging systems. ECGi allows an assessment of tissue characterisation and can be used to locate areas exhibiting late electrical activation. Refinement of body surface mapping systems now means that instead of multiple electrode vests, a more straightforward ECG belt [154] can derive information on local electrical delay in order to guide LV lead implantation. Holographic imaging systems like the Hologscope (Real View Imaging, Yokneam, Israel) allow users to interact directly with a live 3D digital hologram. Physicians can manipulate the image (rotating, slicing, measuring and marking) [155] fostering a greater understanding of the patients own unique anatomy.

10. KEY ISSUES

- Transvenous, epicardial CRT remains an excellent therapy for those patients with right substrate and the right anatomy allowing this substrate to be corrected.
- The constraints of CS anatomy have forced the exploration of novel means of performing CRT and of these endocardial CRT holds the most promise.
- Endocardial CRT has several advantages over epicardial CRT, but the optimal endocardial site displays marked variability and in order to maximise benefits, site selection is critical.
- Assessment of tissue characterisation is essential as viable myocardium should always be targeted. This can be achieved in a number of different ways.

- There is conflicting evidence as to whether an assessment of mechanical dyssynchrony can aid in patient selection for CRT over and above current guideline indications however, targeting sites exhibiting late mechanical activation appears useful.
- Targeting late electrical activation also appears a promising strategy. Q-LV and LVLED appear very useful when looking to identify the optimal site. The site of latest activation is not consistently associated with the optimal haemodynamic improvement. Instead a position which displays late but not excessively late activation appears the most beneficial.
- Narrowing of the QRS during pacing appears a less reliable marker of the optimal pacing site.
- Optimising the RV pacing site may be of benefit, especially when revising a previously implanted system where the position of the LV lead is relatively fixed.
- LV only pacing appears promising, particularly in those with preserved LV function. New delivery technology means both of these systems can be implanted transvenously.
- Site selection is only as good as the adjunctive guidance system. Guidance systems which integrate pre-procedural imaging with peri-procedural coronary sinus balloon venography are unable to determine whether a suitable tributary of the CS subtends the target segment until the procedure has begun. This is a limitation of the transvenous epicardial approach. Systems which can directly visualise the CS during pre-procedural planning allow decisions to be made regarding the most suitable method of targeting this area.

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FIGURE TITLES AND LEGENDS:

Figure 1. The 252-lead vest records torso surface electrograms. Reproduced with permission from MEDTRONIC.

Figure 2. Comparison of sites of LEA (A) and LMA (B). The circled numbers refer to the patient numbers. Reproduced with permission from Pacing and Clinical Electrophysiology

Figure 3A. (Top left) Anteroposterior venogram with overlay of CMR-derived epicardial/endocardial shell with 16-segment American Heart Association model showing an anterior interventricular vein. The 3D CMR-derived shell has the same colours as displayed in the guidance platform as shown in Figures 2 and 3. Infero-septal, antero-septal, and anterior segments are coloured in yellow, green, and blue, respectively. (Top right) left anterior oblique (LAO) 20 venogram with automated rotation and alignment of the 16-segment model with the x-ray. Inferolateral veins are demonstrated. (Bottom left) LAO 40 projection. Positioning of a quadripolar left ventricular lead into a preselected target segment (green). (Bottom right) LAO 40 projection, alternate view with CMR-derived scar distribution (red). Attempted positioning and pacing using left ventricular poles out of regions of scar. [139] Reproduced with permission due to the creative commons license.

Figure 3B. This display screen is seen following the processing of the CMR dataset and is mimicked on the large screen in the catheter laboratory. Total scar burden calculated as a mean of all myocardial segments. (Top middle) Scar distribution denoted in grey upon an American Heart Association 16-segment model. (Top right) Scar burden (% scar per myocardial segment volume), displayed in 5% ranges. (Bottom right) Scar transmural demonstrating the mean transmural from endocardium to epicardium. Those segments >50% transmural myocardial fibrosis are also denoted in red. (Bottom left) Mechanical activation curves for the 16 segments, corresponding to the colours shown in the middle panels. Endocardial tracking of the left ventricle provides absolute changes in the volume per segment (ml, y axis) over the cardiac cycle (0% end diastole, 30% to 50% end systole, 100% end diastole). Because these

are absolute volume changes, the apical segments are always at the bottom because they have a smaller start and end volume. When the user hovers over a segment in the top middle panel, the associated volume time curve appears in bold; in this case, the target posterolateral segment is shown. (Bottom middle) Target selection panel. Upon reviewing the scar location, burden, transmural, and mechanical activation curves, target segments are chosen (seen here in white; basal anterior, mid-posterolateral). EDV 1/4 end-diastolic volume; EF 1/4 ejection fraction; ESV 1/4 end-systolic volume; SDI 1/4 systolic dyssynchrony using endocardial tracking of CMR cine images in short and long axis; Reproduced with permission due to the creative commons license. [139].

Figure 4. (A) Target venous site for LV lead placement. Major LV veins were drawn on fluoroscopic venograms, reconstructed to a 3D structure, and fused with SPECT LV epicardial surface. The mid part of AV (blue line) was aligned with the optimal segment (white segment) and so was targeted for lead placement. (B) Post-implant fluoroscopy. The LV lead was placed using the guidance in (A). The post-implant images show that the LV lead (red arrows) was on target. (C) Post-implant electrocardiogram. The QRS duration decreased from 168 to 140 ms immediately after the cardiac resynchronization therapy (CRT) device was turned on. RAO 1/4 right anterior oblique. Reproduced with permission from JACC: Cardiovascular Imaging [141]

Figure 5. Series of DECCT-derived scar and image overlay of the coronary sinus and optimal target segment derived from CT strain measurements from one patient: Retrospective CCT demonstrating calcification in a Left Anterior Descending (LAD) and circumflex territory infarct (A). Dual energy CCT demonstrating subtle ventricular scar in the LAD and circumflex territory (B). Late iodinated enhancement plotted on American

Heart Association (AHA) 17 segment bull's-eye plot suggesting scar in the LAD and circumflex territory but also artefact from an existing RV pacing lead in the basal to mid antero-septum (C). First pass iodine uptake plotted on an AHA 17 segment bull's-eye plot showing what we believe to be residual iodine predominately in the LAD and circumflex territory (D). CCT-derived dyssynchrony curves calculated by myocardial strain (E). Cardiac magnetic resonance short axis image of the mid LV showing late gadolinium enhancement of the same patient taken two years prior to any device implantation for comparison purposes (F). Pre-procedure DECCT-derived coronary sinus segmentation fused with latest mechanical activating segments determined from DECCT-derived strain (G) co-registered and overlaid onto live fluoroscopy using fusion software (H).[145]

TABLE TITLES AND LEGENDS:

Table 1 Techniques for assessment of viability and scar