Influence of Pacing Site Characteristics on Response to Cardiac Resynchronization Therapy

Wong et al: Pacing Site Scar and CRT Response

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Abstract

**Background**—Transmural scar occupying left ventricular pacing regions has been associated with reduced response to cardiac resynchronization therapy (CRT). However, spatial influences of lead tip delivery relative to scar at both pacing sites remains poorly explored. This study evaluated scar distribution relative to left ventricular (LV) and right ventricular (RV) lead tip placement through co-registration of Late Gadolinium Enhancement (LGE) MRI and cardiac computed tomography (CT) findings. Influences on CRT response were assessed by serial echocardiography.

**Methods and Results**—Sixty patients receiving CRT underwent pre-implant LGE-MRI, post-implant cardiac CT and serial echocardiography. Blinded segmental evaluations of mechanical delay, percent scar burden, and lead tip location were performed. Response to CRT was defined as a reduction in LVESV ≥15% at 6 months. The mean age and LVEF were 64±9 years and 25±7%, respectively. Mean scar volume was higher among CRT non-responders for both the LV [23±23 vs. 8±14% (p=0.01)] and RV pacing regions [40±32 vs. 24±30% (p=0.04)]. Significant pacing region scar was identified in 13% of LV pacing regions and 37% of RV pacing regions. Absence of scar in both regions was associated with an 81% response rate, compared to 55%, 25% and 0%, respectively when the RV, LV or both pacing regions contained scar. LV pacing region dysynchrony was not predictive of response.

**Conclusions**—Myocardial scar occupying the LV pacing region is associated with non-response to CRT. Scar occupying the RV pacing region is encountered at higher frequency and appears to provide a more intermediate influence on CRT response.

**Key Words:** cardiac resynchronization therapy, cardiac magnetic resonance imaging, late gadolinium enhancement, dyssynchrony, cardiac computed tomography, scar, response
Abbreviations:
LV = Left Ventricle
RV = Right Ventricle
EF = Ejection Fraction
CRT = Cardiac Resynchronization Therapy
NYHA = New York Heart Association
CAD = Coronary Artery Disease
ICM = Ischemic Cardiomyopathy
DCM = Dilated Cardiomyopathy
QOL = Quality of Life
6-MWT = 6 minute walk test
MLWH = Minnesota Living with Heart Failure
DE-MRI = Delayed Enhancement Magnetic Resonance Imaging
EDV = End Diastolic Volume
ESV = End Systolic Volume
LBBB = Left Bundle Branch Block
RBBB = Right Bundle Branch Block
Systolic heart failure is the leading cause of cardiovascular morbidity and mortality in North America, consuming over $20 billion per year of global health care expenditures\textsuperscript{1}. Therapeutic strategies currently include cardiac resynchronization therapy (CRT), a permanent pacing therapy aimed at correcting dysynchronous mechanical activation of the left ventricle (LV) through simultaneous pacing of the right ventricular (RV) septum and the lateral wall (via a coronary sinus lead).\textsuperscript{2} While CRT has been shown to reduce symptoms and mortality in select heart failure patients\textsuperscript{2-9} up to 30-40\% of candidates may not respond.\textsuperscript{10, 11} Reasons for response failure appear multi-factorial, with 3 dominant variables implicated to date: i) lack of LV dyssynchrony\textsuperscript{12, 13}, ii) geographic placement of the LV lead\textsuperscript{14-19}, and iii) scar within the LV pacing region.\textsuperscript{20-22} Preliminary evidence similarly suggests absence of RV pacing region (ie: septal wall) scar to be of importance for achieving response.\textsuperscript{23, 24} However, the relative and combined influence of these variables on response to CRT has not been well studied.

In this prospective cohort study we combine findings from Late Gadolinium Enhancement (LGE) Magnetic Resonance Imaging (MRI) and Cardiac-gated Computerized Tomography (CCT) to achieve accurate geographic registration of myocardial scar and lead tip location for both the LV and RV pacing leads. These findings are correlated to CRT response, as assessed by serial echocardiography.

**Methods**

**Study Population**

Ninety-three consecutive patients referred for CRT between January 2008 and March 2011 at the London Health Sciences Centre were screened for study eligibility. Inclusion criteria were: age ≥18 years, LV ejection fraction (EF) ≤35\%, QRS duration ≥120 ms, NYHA class ≥II and on maximal tolerated medical therapy for ≥6 weeks. Exclusion criteria were: myocardial infarction
or revascularization procedure ≤3 months, standard contraindications to MRI, and a GFR ≤ 30ml/min/1.73 m².

Of all screened patients 63 satisfied study entry criteria and successfully completed baseline evaluations. Screened patients were excluded for the following reasons; renal insufficiency (12), existing pacemaker or implantable cardiac defibrillator (ICD) system (16), and severe claustrophobia (2). Patients were classified according to cardiomyopathy etiology. Ischemic cardiomyopathy (ICM) was defined as those with prior myocardial infarction (admission for chest pain with cardiac marker elevation and/or development of new Q waves on ECG) or an invasive coronary angiogram with obstructive coronary artery disease (CAD) (≥1 coronary artery with ≥70% stenosis). Those patients not meeting these criteria were classified as dilated cardiomyopathy (DCM).

**Study Protocol**

All patients received baseline clinical evaluations followed by LGE-MRI and a baseline echocardiogram within 4 weeks of device implantation. An ECG-gated CCT was performed at the 3-month device interrogation visit to establish lead tip location. A repeat echocardiogram and clinical evaluation was performed at 3 and 6-months. Clinical evaluations, each performed by an experienced research nurse, included a 12-lead ECG, NYHA class determination, 6-minute walk test (6-MWT)²⁵ and a quality of life (QOL) assessment using the Minnesota Living With Heart Failure (MLWH) questionnaire.²⁶ All imaging studies were blindly analyzed using to the same 16-segment cardiac model²⁷ with the use of standardized anatomic markers (RV insertion site) to provide consistent segmental assignment. Using this model 2 geographic regions were pre-defined: “Paced segment”; the segment below the pacing portion of the LV or RV lead tip,
and: “Pacing region”; the paced segment plus corresponding segments sharing ≥50% of an
adjacently located border. For example, if the LV paced segment was segment 11 (mid
inferolateral wall) the LV pacing region was defined by segments 5, 10, 11, 12, 15 and 16.

The study protocol was approved by the University of Western Ontario’s ethics review board,
and all patients provided informed consent.

**LGE-MRI Protocol and Image Analysis**

LGE-MRI was performed using a 3.0 Tesla scanner (Trio or Verio, Siemens Medical Solutions,
Germany) equipped with a 32-channel cardiac coil. Retrospectively gated, breath-held cine
imaging was performed in serial short axis planes from the atrio-ventricular annulus to apex in
addition to 2, 3 and 4-chamber views. Typical pulse sequence parameters were: slice thickness 6
mm, gap 2 mm, TE 1.8 ms, flip angle 50, matrix 256 x 213, temporal resolution 30-35 ms, iPAT
= 2. Ten to fifteen minutes following 0.2 mmol/kg gadolinium chelate (Gadovist, Bayer Inc.
Canada) administration, LGE imaging was performed using a standard inversion-recovery
gradient pulse sequence in matched slice orientations. The inversion time was manually adjusted
to provide optimal nulling of the normal myocardium, as previously described. Typical pulse
sequence parameters were: slice thickness = 6 mm, gap = 2 mm, TR = 800 ms, TE = 3.9 ms, flip
angle = 20 degrees, matrix 256 x 205, iPAT = 2.

CMR images were analyzed using commercially available visualization and analysis software
(CMR42, Circle Cardiovascular Imaging, Calgary, Canada). Short axis cine images were
analyzed to determine segmental measures of time to maximal wall thickening using FDA-
approved commercial software (CMR, Circle Cardiovascular Inc., Calgary). Semi-automated
endocardial and epicardial contour tracing was performed throughout the cardiac cycle (all
phases) with the time to maximal wall thickness (TmWT) determined for each myocardial
segment, as previously described.\textsuperscript{21} As shown in Figure 1, 90 radial spokes (15 per segment) were projected from the center of the LV with wall thickness calculated as the linear difference in length from its intersection of the endocardial and epicardial borders. For each segment the mean of 15 radial measurements were used to provide a mean wall thickness at each of the cardiac phases. TmWT of the LV paced segment was defined as the time in milliseconds (ms) required to reach maximal wall thickness for this segment, identified by CCT analysis.

An experienced investigator, blinded to patient identity, visually scored each myocardial segment to identify those with “any myocardial scar”, defined as unequivocal signal enhancement of the myocardium not felt to be due to image artifact. Quantitative assessment of myocardial scar was performed by trained core-lab personnel using a signal-threshold based analysis, and reported for the entire LV (total percent scar) and for each myocardial segment. This was done using a Signal Threshold versus Reference Myocardium (STRM) approach, as previously described\textsuperscript{29, 30}, where a signal threshold of \( \geq 5\text{SD} \) above the mean signal of normal myocardium was used to define scar. With respect to the referenced myocardial region; careful attention was paid to avoid tissue-blood and tissue-fat interfaces, and select only homogeneous regions of signal-nulled tissue.

**CCT Imaging Protocol and Image Analysis**

Cardiac CT imaging was performed using a 64-slice CT scanner (Lightspeed VCT, GE Medical Systems, USA) using standard acquisition protocols.\textsuperscript{31} As part of an expanded study protocol (although not required for lead localization) contrast enhancement was employed with 80-100 cc of iodinated contrast agent (Visipaque\textsuperscript{TM} (iodixanol), Amersham Health, Princeton, NJ) administered. Typical imaging parameters were: slice thickness 0.625 mm, tube voltage 120 kV, and tube current 550 mA, followed by a 40 cc saline flush. Image reconstruction was performed...
using retrospective ECG-gating to obtain the optimal phase for lead visualization with overlapping 0.75 mm cross-sectional images reconstructed at 0.5mm and image matrix of 512 x 512 pixels.

Segmental assignment of the LV and RV lead tips were performed by a blinded interpreter using a 3D multi-planar reconstruction (OsiriX, Version 3.7.1), as shown in Figure 2. To minimize artifact related to the CRT lead system we reconstructed images using a 2.5mm slice thickness and displayed this dataset using 3D multi-planar reconstruction (MPR), averaging signal of 4 consecutive slices (MIP thickness 10mm). The tips of the LV and RV lead were separately localized on axial images and orthogonal short and long-axis projections generated. Using a radial grid manually overlaid on the short axis view to mark standard segmental assignments according to the AHA 16-segment model (6 basal, 6 mid and 4 apical) the segmental position of the LV and RV leads were determined. The corresponding long axis view was used to determine its basal, mid or apical position (equal division of the LV into 3 zones). For the LV lead, pacing lead polarity (ie: ring to tip versus tip to ring) was incrementally considered to ensure that the pacing portion of the lead was scored.

**Echocardiography Imaging Protocol and Image Analysis**

Standard 2D echocardiography was performed at baseline, 3 and 6 months using a 3.5 MHz transducer (S5-1, Philips, Bothell, WA, USA) on commercially available equipment (iE33, Philips, Eindhoven, Netherlands). Digitally captured images were stored for offline analysis using the Xcelera software suite version 3.1 (Philips, Eindhoven, Netherlands). All imaging was performed at end-expiration. The LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were determined using the biplane method of discs method (modified Simpson’s technique) by an experienced, blinded echocardiographer.
**CRT device implantation**

CRT devices with defibrillator capability were implanted in the standard fashion in all patients. The LV pacing lead was inserted transvenously into the coronary sinus and positioned according to standard clinical practice. The RV septal lead was routinely placed to the apical septal segment in accordance with the site’s conventional practice. V-V intervals were set to 0 ms with A-V intervals programmed to the manufacturer’s nominal settings. These settings were not adjusted during the first 6-months of therapy.

**Definition of Response to CRT**

The primary outcome, echocardiographic response to CRT, was defined as a reduction in the LVESV ≥15% at 6-months post implantation. Pre-defined thresholds for the following clinical variables were used to define secondary clinical endpoints: NYHA functional class improvement by ≥1 class, 6-MWT increase by ≥30m or 10%, and QOL score improvement (reduction) by ≥10 points.

**Inter-observer and Intra-observer Reproducibility**

Inter-observer and intra-observer reproducibility measures for scar analysis in this population have been reported separately from our laboratory. To assess reproducibility of dysynchrony measurement 10 randomly selected cases underwent blinded evaluations by 2 investigators followed by a repeat evaluation by the first investigator on a separate day.

**Statistical Methods**

Continuous variables are expressed as the mean ± SD, while medians with 25th and 75th percentiles are provided for non-normally distributed data. Categorical variables are expressed as simple proportions. Univariate analysis to test for differences between responders and non-
responders to CRT was performed using the Mann-Whitney U test for continuous variables and Fisher’s Exact Test for categorical variables. Similar analyses were performed for improvement in NYHA, 6-minute walk test and QOL. All endpoints were assessed at 6 months post CRT device implantation. We constructed a multivariate logistic regression model to assess the incremental association of MRI and baseline clinical variables to predict to occurrence of non-response to CRT using backward stepwise selection (p<0.10 for entry and p>0.05 for removal). Due to the number of events we limited covariates to comply with the general rule that 10 events should be available for each variable tested.33,34 Reproducibility analyses were performed using both linear regression analysis and Bland and Altman analysis. Sample size calculations were performed a-priori based upon available literature20,23 and adequate power was ensured for the selected primary outcome. All statistical tests were two-tailed and p value of <0.05 was regarded as significant. S-Plus (version 8.0, Insightful Software, Seattle, WA) was used to perform the statistical analyses.

Results

Baseline Patient Characteristics

Sixty of the 63 enrolled patients (95%) completed study follow-up and were included in final analysis. Three patients did not complete initial (3-month) follow-up; two dying - one due to heart failure and one due to device-unrelated sepsis - and one patient voluntarily withdrawing from the study. Baseline patient characteristics are summarized in Table 1. The mean age was 64±9 years with 16 (27%) being female. The median baseline NYHA was 3 (IQR 3, 3). Referral etiology was ICM in 25 patients (42%) and DCM in 35 (58%).

Baseline non-LGE MRI findings revealed a mean LVEF of 25.3±7.1%. No significant
differences in septal to LV paced segment mechanical delay was identified between ICM and DCM cohorts (p=0.22). Mean segmental TmWT values for all 16 myocardial segments are graphically shown in Figure 3. Univariate analysis showed the following to be associated with non-response to CRT; lower GFR (p=0.04), higher NYHA class (p=0.04), ischemic cardiomyopathy (p=0.01) and right bundle branch block (RBBB) (p=0.02). No dysynchrony measure was predictive of CRT response.

**Echocardiographic and Clinical Response to CRT**

The primary endpoint was met in 42 patients (70%) at 6-months. Secondary endpoints were achieved as follows; Improvement ≥ 1 NYHA class in 37 patients (62%), increase in 6-MWT ≥30m or by 10% in 37 patients (62%), and a reduction in MLWH score ≥10 in 39 patients (65%).

**CRT Lead Tip Locations by CCT**

The RV lead tip was delivered to the apical septal segment in 100% of patients. The LV lead tip was delivered to a posterolateral wall segment (basal or mid) in the majority of patients (59.0%), a finding that was consistent between ICM and DCM cohorts (58.6% and 59.1%, respectively). A graphical illustration of RV and LV lead placement for the population is shown in Figure 3. Patients achieving the primary outcome were more likely to have had the LV lead placed on a posterolateral wall segment (83%) versus those without response (50%).

**Scar Burden and Distribution by LGE-MRI**

Analysis of LGE imaging confirmed a higher prevalence and total burden of myocardial scar in those with ICM versus those with DCM (Table 2). Overall, 25 patients with ICM (100%) and 27 patients with DCM (77%) showed any visible scar by LGE-MRI. Similarly, the mean total
scar burden was significantly higher among those with ICM versus DCM (26.2±14.5% versus 5.9±7.2, p<0.001). Segmental scar analysis, shown in Figure 3, revealed the burden of scar to be highest among the septal wall segments, irrespective of cardiomyopathy etiology.

The prevalence of transmural scar (≥50% wall thickness) within the LV paced segment was 7%, with a prevalence of 22% for the RV paced segment. The prevalence of significant pacing region (paced segment plus adjacent segments) scar, defined as ≥25% scar by volume, was 13% for the LV pacing region and 37% for the RV pacing region. Patient examples are shown in Figure 4.

**Pacing Site Scar and Response to CRT**

Total scar burden was not statistically different between those achieving and not achieving the primary outcome (Table 2). This finding was consistent for both ischemic and non-ischemic cohorts.

The results of segmental scar analysis among responders and non-responders are shown in Table 2. The mean scar volume of the LV pacing region was significantly lower in responders versus non-responders (p=0.01) with a similar finding identified for the RV pacing region (p=0.04). Thirty-four patients had no significant scar (<25%) in either the LV or RV pacing regions. Of these patients 19% failed to achieve CRT response at 6-months (ie: response rate 81%). Twenty-two patients had significant scar in the RV pacing region with 45% of this group having non-response (ie: response rate 55%). Eight patients had significant scar in the LV pacing region with 75% having non-response (ie: response rate 25%). Among these patients 4 had significant scar in both the LV and RV pacing regions, 100% having non-response to CRT at 6-months. The relationship between pacing region scar and CRT response is graphically shown in Figure 5.
LV pacing region scar ≥ 25% was the strongest independent predictor of CRT non-response following adjustment for cardiomyopathy etiology with an odds ratio of 7.2 (95% CI 1.2 to 43.8, p=0.03). By multivariate analysis, when LV and RV pacing region scar were entered into the same model only LV pacing region scar remained predictive with an odds ratio of 7.7 (95% CI 1.3 to 46.3, p=0.03).

Secondary endpoints were achieved with high frequency among those with no scarring of LV or RV pacing regions. Among these patients a reduction of NYHA class ≥1 was achieved in 82%, an increase in 6MHW ≥30m in 82%, and a reduction in MLWH score ≥10 in 96% of patients. While a trend towards reduction in these outcomes was seen among those with scarring of LV and/or RV pacing regions, these differences were not statistically significant.

**Inter-observer and Intra-observer Reproducibility**

Good inter-observer reproducibility was seen for the measurement of dysynchrony by SD16-TmWT. The Pearson correlation coefficients for intra- and inter-observer measurements were 0.87 and 0.85, respectively. Corresponding Bland and Altman analyses showed non-significant bias of -3.4 ms (-45.6 to 38.7 ms) and 19.4 (-22.9 to 61.7 ms), respectively.

**Discussion**

In this prospective, multimodality imaging study analyzing the effects of regional scar in relation to lead tip localization on CRT response, the primary findings were as follows: 1. Scar in the LV pacing region was observed in a minority of patients but was associated with a low CRT response; 2. Scar occupying the RV pacing region was seen more commonly and was associated
with intermediate CRT response; 3. Presence of scar in both pacing regions was associated with no response, whereas absence of scar in these regions was associated with the highest response rate.

The over-arching goal of CRT is to advance electro-mechanical activation of the lateral wall such that it becomes physiologically synchronous with the septal wall. If accomplished this therapy can realize substantial improvement in stroke volume and cardiac performance. Studies to date evaluating optimal patient selection and CRT delivery have focused primarily on characteristics of the posterolateral wall, suggesting scar in this region to be associated with lower rates of LV remodeling. Such findings led to the recent reporting of the first randomized control trial of targeted LV lead placement in CRT. In this study, a reported 15% improvement in CRT response was observed when LV leads were targeted to dysynchronous but non-scarred myocardial segments, the latter defined by surrogate echocardiographic markers of viability. Our current study presents the most comprehensive evaluation of scar burden relative to lead tip delivery to date and confirms that scar within the LV pacing region, encountered in approximately 1 out of 8 cases, is an important impediment to CRT response. Scar within the RV pacing region is more common, being encountered in 1 out of 3 cases. This finding did not provide an independent influence on CRT response among those also having LV pacing region scar. However, a reduction in CRT response was appreciated among the whole population when significant RV pacing region scar was present.

The potential relevance of RV pacing region scar was highlighted in a recent study by Duckett, et al. that evaluated the feasibility of achieving a mid-septal RV pacing position among 50 consecutive patients receiving CRT. In this study a more conventional apical position was conceded to in those patients with poor R-wave pacing amplitudes (≤5 mV) and identified that
these patients had a 67% prevalence of septal scar by LGE imaging versus 33% in those where adequate voltages were achieved. Septal wall scar by LGE imaging was associated with a lower rate of LV remodeling at 6-months (20% versus 56%, p=0.02) within the context of this lead placement strategy. Segmental characterization of LV lead position, LV dysynchrony or LV pacing region scar were not evaluated. By comparison, our current study shows that the delivery of both LV and RV pacing leads to non-scarred myocardium provides a robust 81% response rate to CRT, versus 55% when significant scar is present in the RV pacing region, 25% when in the LV pacing region, and 0% when present in both pacing regions.

The septal-predominant distribution of myocardial injury found among this referral population is not unexpected. ICM patients are anticipated to be at higher likelihood of both heart failure and LBBB when irreversible injury is realized in the LAD-territory (ie: septal wall). Similarly, patients with DCM preferentially demonstrate non-ischemic fibrosis of the septum in advanced stages of disease, a finding associated with worse prognosis. Irrespective of etiology, mechanisms relating septal scar to non-response in CRT can be envisioned. First, electromechanical advancement of the lateral wall is aimed at reducing afterload effects on the septum, and re-engaging its contribution to stroke volume. Such contribution may not be enlisted if the septum is substantially injured, limiting its capacity to augment stroke volume. Second, the aim of RV paced stimulation to activate the LV myocardium simultaneous to paced stimulation of the lateral wall may be violated by interposed scar. An introduction of electro-mechanical dispersion can therefore be theorized. This latter concept presents one plausible role for directing RV lead tips to alternate and viable geographic targets - similar to that proposed for the LV lead. Indeed, the concept of mid-septal or RV outflow tract pacing has been shown to be both feasible and potentially of clinical value. In a study by Haghjoo, et al. patients
otherwise receiving optimal LV pacing (ie: those with LV leads delivered to the posterolateral wall) had significantly higher CRT response rates when the RV lead was placed to the high (basal) septum compared with conventional apical placement (70% vs. 30%, $p=0.01$). Further, Duckett, et al., showed that mid-septal pacing was associated with improved response rate compared with apical pacing (70% vs. 30%, $p=0.01$). However, whether the selective placement of the RV lead to viable myocardial targets improves outcomes in this population remains to be evaluated.

**Clinical Implications**

Our findings add justification for lead navigation approaches to optimal myocardial targets in CRT. Several studies to date, inclusive of the current study, demonstrate that characteristics of the LV pacing region strongly influence response to CRT and support that lead delivery to viable targets may be a pre-requisite for response to occur. We found that without image-guidance the delivery of this lead to a scarred myocardial region occurs in 13% of cases with 75% of these patients failing to respond. Navigation strategies to guide the LV lead to viable targets is therefore of potential importance for this cohort. While the role of RV lead navigation to optimal septal targets remains uncertain, recognition that scar within this region may contribute to response failure justifies expanded exploration within larger cohort studies.

**Study Limitations**

This study must be considered in recognition of several limitations. First, this was a single-center cohort study and was not sufficiently sized to evaluate clinical outcomes beyond the surrogate of LV remodeling at 6-months. Second, while not the focus of the current paper, the MRI-derived measure of mechanical dyssynchrony used in this study, adopted from Marsan, et
al.\textsuperscript{21} has not undergone rigorous clinical validation versus other measures of dyssynchrony, such as tissue Doppler or strain imaging. Finally, signal-threshold based scar quantification is inherently dependent upon user-selected regions for referencing of “normal” myocardium. In this study we employed an STRM-based technique with careful attention to the selection of the reference region. We also selected a higher signal threshold (≥5SD) to maximize reproducibility, as previously described.\textsuperscript{30, 46} These technical factors must always be considered when comparing values of scar burden between otherwise comparable studies. Alternate techniques, such as the Full-Width Half of Maximum, may offer slightly superior reproducibility in those with ischemic cardiomyopathy.\textsuperscript{30, 46} However, the inclusion of patients with dilated cardiomyopathy in this study, a cohort recognized to have inconsistent results using this technique\textsuperscript{30}, limited analysis to an STRM-based approach.

Conclusions

Scar within the LV and RV pacing regions is associated with a lower response rate to CRT at 6-months. Strategies aimed at the selective placement of pacing leads to non-scarred myocardial targets appear justified.

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Disclosures

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References


Table 1. Non-MRI baseline patient characteristics, presented for the total population and for those with and without response to CRT (defined as a ≥15% reduction in LVESV at 3 or 6 months).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Population (N=60)</th>
<th>ICM (N=25)</th>
<th>DCM (N=35)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64±9</td>
<td>63±10</td>
<td>66±8</td>
<td>.35</td>
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<tr>
<td>Female sex</td>
<td>16(27%)</td>
<td>14(33%)</td>
<td>2(11%)</td>
<td>.07</td>
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<td>Hypertension</td>
<td>34(57%)</td>
<td>25(59%)</td>
<td>9(50%)</td>
<td>.34</td>
</tr>
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<td>Diabetes mellitus</td>
<td>19(32%)</td>
<td>13(31%)</td>
<td>6(33%)</td>
<td>.54</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>37(62%)</td>
<td>25(59%)</td>
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<td>.41</td>
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<td>Smoking</td>
<td>22(37%)</td>
<td>14(33%)</td>
<td>8(44%)</td>
<td>.30</td>
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<tr>
<td>Any prior revascularization</td>
<td>14(23%)</td>
<td>9(21%)</td>
<td>5(28%)</td>
<td>.41</td>
</tr>
<tr>
<td>GFR (ml/min/1.73m²)</td>
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<td>71±17</td>
<td>61±12</td>
<td>.04*</td>
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<tr>
<td>Atrial fibrillation</td>
<td>9(15%)</td>
<td>5(12%)</td>
<td>4(24%)</td>
<td>.25</td>
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<td>QRS duration (ms)</td>
<td>159±21</td>
<td>162±20</td>
<td>151±23</td>
<td>.08</td>
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<td>LBBB</td>
<td>48(81%)</td>
<td>36(86%)</td>
<td>12(71%)</td>
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<tr>
<td>RBBB</td>
<td>5(8%)</td>
<td>1(2%)</td>
<td>4(24%)</td>
<td>.02*</td>
</tr>
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<td>Non-specific delay</td>
<td>6(10%)</td>
<td>5(12%)</td>
<td>1(6%)</td>
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<td>1(6%)</td>
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<tr>
<td>Class III</td>
<td>39(65%)</td>
<td>22(52%)</td>
<td>17(94%)</td>
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<tr>
<td>Class IV</td>
<td>3(5%)</td>
<td>3(7%)</td>
<td>0(0%)</td>
<td>.44</td>
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<td>Medications</td>
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<td></td>
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<tr>
<td>ACE inhibitor</td>
<td>43(72%)</td>
<td>31(74%)</td>
<td>12(67%)</td>
<td>.40</td>
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<tr>
<td>ARB</td>
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<td>13(31%)</td>
<td>7(39%)</td>
<td>.38</td>
</tr>
<tr>
<td>ACE inhibitor or</td>
<td>57(95%)</td>
<td>40(95%)</td>
<td>17(94%)</td>
<td>.66</td>
</tr>
<tr>
<td></td>
<td>ARB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>54(90%)</td>
<td>38(90%)</td>
<td>16(89%)</td>
<td>.59</td>
</tr>
<tr>
<td>Diuretic</td>
<td>50(83%)</td>
<td>34(81%)</td>
<td>16(89%)</td>
<td>.36</td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean ±SD, categorical data as n (%). ICM = Ischemic cardiomyopathy; DCM = Dilated cardiomyopathy; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; MI = Myocardial infarction, GFR = Glomerular Filtration Rate; LBBB, left bundle-branch block; NYHA = New York Heart Association; CRT = Cardiac resynchronization therapy; ACE = angiotensin-converting enzyme.
Table 2. Baseline MRI characteristics of the study population and for those with and without response to CRT, stratified according to cardiomyopathy Etiology.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Population (N=60)</th>
<th>ICM (N=25)</th>
<th>DCM (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV volumes / mass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>26±6</td>
<td>24±9</td>
<td>.48</td>
</tr>
<tr>
<td>LV EDV (mL)</td>
<td>275±78</td>
<td>320±68</td>
<td>.02*</td>
</tr>
<tr>
<td>LV ESV (mL)</td>
<td>206±71</td>
<td>245±64</td>
<td>.03*</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>191±41</td>
<td>229±66</td>
<td>.03*</td>
</tr>
<tr>
<td>LV mass – indexed (g/m²)</td>
<td>96±20</td>
<td>105±27</td>
<td>.28</td>
</tr>
<tr>
<td>Dyssynchrony</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD16 TmWT (ms)</td>
<td>151±48</td>
<td>144±51</td>
<td>.88</td>
</tr>
<tr>
<td>Septal to LVp segment delay (ms)</td>
<td>323±159</td>
<td>303±192</td>
<td>.54</td>
</tr>
<tr>
<td>Septal to LVp segment ≥130ms</td>
<td>34(81%)</td>
<td>14(78%)</td>
<td>.52</td>
</tr>
<tr>
<td>Scar Analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any myocardial scar*</td>
<td>35(83%)</td>
<td>17(94%)</td>
<td>.24</td>
</tr>
<tr>
<td>Total LV scar volume (%)</td>
<td>13±16</td>
<td>17±11</td>
<td>.08</td>
</tr>
<tr>
<td>Total LV pacing region scar (%)</td>
<td>8±14</td>
<td>23±23</td>
<td>.01*</td>
</tr>
<tr>
<td>Total RV pacing region scar (%)</td>
<td>24±30</td>
<td>40±32</td>
<td>.04*</td>
</tr>
<tr>
<td>LVp segment ≥50% scar</td>
<td>1(2%)</td>
<td>3(17%)</td>
<td>.08</td>
</tr>
<tr>
<td>LVp region ≥25% scar</td>
<td>2(5%)</td>
<td>6(33%)</td>
<td>.01*</td>
</tr>
<tr>
<td>RVp segment ≥50% scar</td>
<td>8(19%)</td>
<td>5(28%)</td>
<td>.33</td>
</tr>
<tr>
<td>RVp region ≥25% scar</td>
<td>12(29%)</td>
<td>10(56%)</td>
<td>.05</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD. ICM = Ischemic cardiomyopathy; DCM = Dilated cardiomyopathy; LV = left ventricular; EDV = end-diastolic volume; ESV = end-systolic volume; EF= ejection fraction; SD16 TmWT = Standard Deviation of the Time to Maximal Radial Wall Thickening obtained from all 16 segments; LVpD = Left Ventricular Paced Segment Delay

*Defined as the presence of ≥1 myocardial segment with unequivocal scar, as determined by an experienced, blinded investigator.
Figure Legends

**Figure 1.** Example of quantitative wall motion analysis applied to a mid-ventricular short axis cine image. End-systolic and end-diastolic phases shown to illustrate changes in radial “spokes” representing wall thickening. The mean length of 15 spokes per myocardial segment were used to determine the mean wall thickness at each phase of the cardiac cycle.

**Figure 2.** Example of cardiac-gated CT lead mapping. Left: 3D maximum intensity projection (MIP) showing the RV lead (open arrow) in the typical apical segment location and the LV lead (solid arrow) positioned within the anterior interventricular vein. Middle: 3D multi-planar reconstruction (MPR) in short axis showing both the RV and LV leads relative to the myocardial soft tissues (dashed lines) with standard chamber segmentation. Right: 3D volume rendering in the same patient (AP view) showing the LV lead is positioned distant from a calcified inferolateral transmural scar (inset: corresponding short axis DE-MRI image showing enhancing scar in white against the normal black myocardium).

**Figure 3.** Results of segmental analysis showing the segmental prevalence of CRT lead tip delivery, any myocardial scar, and mean time to maximal wall thickness (SD16-TmWT) for all patients, ICM, and DCM patients. Shown using the AHA 16-segment model divided into septal and non-septal segments relevant to the RV and LV pacing leads, respectively.

**Figure 4.** Late gadolinium enhancement (LGE) images of patients found to have significant scar (bright signal within myocardium) within the left ventricular pacing region scar (A) and right
ventricular pacing region (B). Examples provided for both ischemic and non-ischemic patterns of injury. Left column shows the 4-chamber view (highlighted in red). Middle column shows a representative short axis view. Right column shows the corresponding signal threshold-based scar analysis with division into the AHA segment model. Red line corresponds to approximate position of the 4-chamber view.

Figure 5. Six-month response rate to cardiac resynchronization therapy (CRT) among patients with i) both leads delivered non-scarred pacing regions, ii) only the right ventricular (RV) lead delivered to a scarred pacing region, iii) only the left ventricular (LV) lead delivered to a scarred pacing region, or iv) both the LV and RV lead delivered to scarred pacing regions. CRT response was defined as a reduction in LV end diastolic volume (LVEDV) by ≥15% by serial echocardiography. RVPR = right ventricular pacing region; LVPR = left ventricular pacing region.
Figure 2
Figure 3
Figure 4
Figure 5
Influence of Pacing Site Characteristics on Response to Cardiac Resynchronization Therapy
Jorge A. Wong, Raymond Yee, John Stirrat, David Scholl, Andrew D. Krahn, Lorne J. Gula, Allan C. Skanes, Peter Leong-Sit, George J. Klein, David McCarty, Nowell Fine, Aashish Goela, Ali Islam, Terry Thompson, Maria Drangova and James A. White

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