Systolic heart failure is the leading cause of cardiovascular morbidity and mortality in North America, consuming $20 billion per year of global healthcare expenditures.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).2 Although CRT has been shown to reduce symptoms and mortality in select patients with heart failure,2–9 up to 30% to 40% of candidates may not respond.10,11 Reasons for response failure seem multifactorial, with 3 dominant variables implicated to date: (1) lack of LV dyssynchrony,12,13 (2) geographic placement of the LV lead,14–19 and (3) scar within the LV pacing region.20–22 Preliminary evidence similarly suggests absence of RV pacing region (ie, septal wall) scar to be of importance for achieving response.23,24 However, the relative and combined influence of these variables on response to CRT has not been well studied.

Methods

Study Population

Ninety-three consecutive patients referred for CRT between January 2008 and March 2011 at the London Health Sciences Center were screened for study eligibility. Inclusion criteria were the following:
age ≥18 years, LV ejection fraction ≤35%, QRS duration ≥120 ms, New York Heart Association (NYHA) class ≥2, and on maximal tolerated medical therapy for ≥6 weeks. Exclusion criteria were the following: myocardial infarction or revascularization procedure ≤3 months, standard contraindications to MRI, and a glomerular filtration rate ≤30 mL/min per 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 system (16), and severe claustrophobia (2). Patients were classified according to cardiomyopathy pathogenesis. Ischemic cardiomyopathy (ICM) was defined as those with previous myocardial infarction (admission for chest pain with cardiac marker elevation and development of new Q waves on ECG) or an invasive coronary angiogram with obstructive coronary artery disease (≥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 were performed at 3 and 6 months. Clinical evaluations, each performed by an experienced research nurse, included a 12-lead ECG, New York Heart Association (NYHA) class determination, 6-minute walk test, and a quality of life assessment using the Minnesota Living With Heart Failure (MLWH) questionnaire. All imaging studies were blindly analyzed using the same 16-segment cardiac model with the use of standardized anatomic markers (RV insertion site) to provide consistent segmental assignment. Using this model, 2 geographic regions were predefined: 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 adjacentely located border. For example, if the LV paced segment was segment 11 (midinferolateral wall), then the LV pacing region was defined by segments 5, 10, 11, 12, 15, and 16.

The study protocol was approved by the Ethics Review Board of the University of Western Ontario, 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 atrioventricular node to the apex in addition to 2, 3, and 4-chamber views. Typical pulse sequence parameters were the following: slice thickness=6 mm, gap=2 mm, echo time (TE)=1.8 ms, flip angle=50°, matrix 256×213, temporal resolution=30 to 35 ms, and integrated Parallel Acquisition Techniques (iPAT)=2. LGE imaging was performed using a standard inversion-recovery gradient pulse sequence in matched slice orientations 10 to 15 minutes after 0.2 mmol/kg gadolinium chelate (Gadovist, Bayer Inc, Canada) administration. The inversion time was manually adjusted to provide optimal nulling of the normal myocardium, as previously described. Typical pulse sequence parameters were the following: slice thickness=6 mm, gap=2 mm, temporal resolution=800 ms, TE=3.9 ms, flip angle=20°, matrix 256×205, 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 (CMR42, Circle Cardiovascular Inc, Calgary, Canada). Semi-automated endocardial and epicardial contour tracing was performed throughout the cardiac cycle (all phases) with the time to maximal wall thickness determined for each myocardial segment, as previously described. 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 was used to provide a mean wall thickness at each of the cardiac phases. Time to maximal wall thickness of the LV paced segment was defined as the time in milliseconds 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 attributable to image artifact. Quantitative assessment of myocardial scar was performed by trained core-laboratory personnel using a signal-threshold-based analysis, and reported for the entire LV (total percentage scar) and for each myocardial segment. This was performed using a Signal Threshold versus Reference Myocardium approach, as previously described, where a signal threshold of ≥5 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 to 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) using standard acquisition protocols. As part of an expanded study protocol (although not required for lead localization), contrast enhancement was used with 80 to 100 mL of iodinated contrast agent (Visipaque [iodixanol], Amersham Health, Princeton, NJ) administered. Typical imaging parameters were the following: slice thickness=0.625 mm, tube voltage=120 kV, and tube current=550 mA, followed by a 40-mL 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 0.5 mm and image matrix of 512×512 pixels. Segmental assignment of the LV and RV lead tips was performed by a blinded interpreter using a 3-dimensional (3D) multiplanar 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 2.5-mm slice thickness and displayed this data set using 3D multiplanar reconstruction, averaging signal of 4 consecutive slices (maximum intensity projection thickness=10 mm). The tips of the LV and RV lead were separately localized on axial images, and orthogonal short- and long-axis projections were 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 middle, and 4 apical), the segmental positions of the LV and RV leads were determined. The corresponding long-axis view was used to determine its basal, middle, 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 (SS-1, Philips, Bothell, WA) on commercially available equipment (iE33, Philips, Eindhoven, The Netherlands). Digitally captured images were stored for offline analysis using the Xcelera software suite version 3.1 (Philips, Eindhoven, The Netherlands). All imaging was performed at end-expiration. The LV end-diastolic volume and LV end-systolic volume were determined using the biplane method of discs method (modified Simpson’s technique)\(^\text{31}\) 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 conventional practice of the site. V-V intervals were set to 0 ms with A-V intervals programmed to the manufacturer 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 LV end-systolic volume ≥15% at 6 months postimplantation. Predefined thresholds for the following clinical variables were used to define secondary clinical end points: NYHA functional class improvement by ≥1 class, 6-minute walk test ≥30 m or by 10%, and quality of life score improvement ≥10.

Interobserver and Intraobserver Reproducibility
Interobserver and intraobserver reproducibility measures for scar analysis in this population have been reported separately from our laboratory.\(^\text{32}\) 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, whereas 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 nonresponders to CRT was performed using the Mann–Whitney U test for continuous variables and the Fisher Exact Test for categorical variables. Similar analyses were performed for improvement in NYHA, 6-minute walk test, and quality of life. All end points 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 the occurrence of nonresponse to CRT using backward stepwise selection (P<0.10 for entry and P>0.05 for removal). Because of the number of events, we limited covariates to comply with the general rule that 10 events should be available for each variable tested.\(^\text{33,34}\) Reproducibility analyses were performed using both linear regression analysis and Bland and Altman analysis. Sample size calculations were performed a priori based on available literature,\(^\text{20,25}\) and adequate power was ensured for the selected primary outcome. All statistical tests were 2-tailed, and P value <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 months) follow-up; 2 dying—one because of heart failure and the other because of device-unrelated sepsis—and 1 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 (interquartile range, 3–3). Referral pathogenesis was ICM in 25 patients (42%) and DCM in 35 patients (58%).

Baseline non-LGE MRI findings revealed a mean LV ejection fraction 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 time to maximal wall thickness values for all 16 myocardial segments are graphically shown in Figure 3. Univariate analysis showed the following to be associated with nonresponse to CRT: lower glomerular filtration rate (P=0.04), higher NYHA class (P=0.04), ICM (P=0.01), and right bundle-branch block (P=0.02). No dyssynchrony measure was predictive of CRT response.

Echocardiographic and Clinical Response to CRT
The primary end point was met in 42 patients (70%) at 6 months. Secondary end points were achieved as follows: improvement ≥1 NYHA class in 37 patients (62%), increase in 6-minute walk test ≥30 m 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 middle) 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 placements 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 pathogenesis.

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 nonischemic cohorts.

The results of segmental scar analysis among responders and nonresponders are shown in Table 2. The mean scar volume of the LV pacing region was significantly lower in responders versus nonresponders (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 nonresponse (ie, response rate 55%). Eight patients had significant scar in the LV pacing region with 75% having nonresponse (ie, response rate 25%). Among these patients, 4 had significant scar in both the LV and RV pacing regions, 100% having nonresponse 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 nonresponse after adjustment for cardiomyopathy pathogenesis with an odds ratio of 7.2 (95% confidence interval, 1.2–43.8; P=0.03).** By multivariate analysis,
when LV and RV pacing region scars were entered into the same model, only LV pacing region scar remained predictive with an odds ratio of 7.7 (95% confidence interval, 1.3–46.3; \(P = 0.03\)).

Secondary end points were achieved with high frequency among those with no scarring of LV or RV pacing regions. Among these patients, a reduction of NYHA class \(\geq 1\) was achieved in 82% of patients, an increase in 6MHW \(\geq 10\) m in 82%, and a reduction in MLWH score \(\geq 10\) in 96% of patients. Although a trend toward reduction in these outcomes was seen among those with scarring of LV and RV pacing regions, these differences were not statistically significant.

**Interobserver and Intraobserver Reproducibility**

Good interobserver reproducibility was seen for the measurement of dyssynchrony by SD16-time to maximal wall thickness (TmWT) for all patients, ischemic cardiomyopathy (ICM), and dilated cardiomyopathy (DCM) patients. Shown using the AHA 16-segment model divided into septal and nonseptal segments relevant to the right ventricular and left ventricular pacing leads, respectively.

The potential relevance of RV pacing region scar was highlighted in a recent study by Duckett et al.\textsuperscript{24} that evaluated the feasibility of achieving a midseptal RV pacing position among 50 consecutive patients receiving CRT. In this study, a more conventional apical position was conceded to 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 dyssynchrony, 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 nonscarred 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 left bundle-branch block when irreversible injury is realized in the LAD-territory (ie, septal wall). Similarly, patients with DCM preferentially demonstrate nonischemic fibrosis of the septum in advanced stages of disease, a finding associated with worse prognosis.\textsuperscript{38} Irrespective of pathogenesis, mechanisms relating septal scar to nonresponse 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.
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 electromechanical dispersion can, therefore, be theorized. This latter concept presents 1 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 midseptal or RV outflow tract pacing has been shown to be both feasible\cite{39–42} and potentially of clinical value.\cite{24,42} In a study by Haghjoo et al,\cite{40} 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% versus 30%; \( P = 0.01 \)). Furthermore, Duckett et al\cite{24} showed that midseptal pacing was associated with improved response rate compared with apical pacing (70% versus 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\cite{21,36,37,43–45} and support that lead delivery to viable targets may be a prerequisite 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. Although 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, although not the focus of the current article, the MRI-derived measure of mechanical dyssynchrony used in this study, adopted from Marsan et al,\cite{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 on user-selected regions for referencing of normal myocardium. In this study, we used a Signal Threshold versus

### Table 2. Baseline MRI Characteristics of the Study Population and for Those With and Without Response to CRT, Stratified According to Cardiomyopathy Pathogenesis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Population (n=60)</th>
<th>ICM (n=25)</th>
<th>DCM (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Response (n=42)</td>
<td>No Response (n=18)</td>
<td>P Value</td>
</tr>
<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>0.48</td>
</tr>
<tr>
<td>LV EDV, mL</td>
<td>275±78</td>
<td>320±68</td>
<td>0.02*</td>
</tr>
<tr>
<td>LV ESV, mL</td>
<td>206±71</td>
<td>245±64</td>
<td>0.03*</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>191±41</td>
<td>229±66</td>
<td>0.03*</td>
</tr>
<tr>
<td>LV mass–indexed, g/m²</td>
<td>96±20</td>
<td>105±27</td>
<td>0.28</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>0.88</td>
</tr>
<tr>
<td>Septal to LVp segment delay, ms</td>
<td>323±159</td>
<td>303±192</td>
<td>0.54</td>
</tr>
<tr>
<td>Septal to LVp segment ≥130 ms</td>
<td>34 (81%)</td>
<td>17 (79%)</td>
<td>0.52</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>0.24</td>
</tr>
<tr>
<td>Total LV scar volume, %</td>
<td>13±16</td>
<td>17±11</td>
<td>0.08</td>
</tr>
<tr>
<td>Total LV pacing region scar, %</td>
<td>8±14</td>
<td>23±23</td>
<td>0.01*</td>
</tr>
<tr>
<td>Total RV pacing region scar, %</td>
<td>24±30</td>
<td>40±32</td>
<td>0.04*</td>
</tr>
<tr>
<td>LVp segment ≥50% scar</td>
<td>1 (2%)</td>
<td>3 (17%)</td>
<td>0.08</td>
</tr>
<tr>
<td>LVp region ≥25% scar</td>
<td>2 (5%)</td>
<td>6 (33%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>RVp segment ≥50% scar</td>
<td>8 (19%)</td>
<td>5 (28%)</td>
<td>0.33</td>
</tr>
<tr>
<td>RVp region ≥25% scar</td>
<td>12 (29%)</td>
<td>10 (56%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Data expressed as mean±SD. CRT indicates cardiac resynchronization therapy; DCM, dilated cardiomyopathy; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; ICM, ischemic cardiomyopathy; LV, left ventricular; LVpD, left ventricular paced segment delay; RV, right ventricular; RVp, right ventricular paced; and SD16-TmWT, standard deviation of the time to maximal radial wall thickening obtained from all 16 segments.

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

*Statistically significant.
technique, limited analysis to a Signal Threshold versus Reference Myocardium–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 nonscarred myocardial targets seem justified.

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References


Myocardial scar is recognized to predict clinical response to cardiac resynchronization therapy (CRT), with an emerging paradigm of image-guided CRT lead delivery to nonscarred myocardial targets. For such a paradigm to evolve, a more detailed understanding of how the spatial distribution of scar within the left ventricle (LV) and its relationship to lead electrode placement must be established. Such explorations require consideration of scar surrounding the LV pacing region and the right ventricular pacing region because the latter may provide unique obstacles to improvements in LV remodeling. In this study, we spatially registered findings of late gadolinium enhancement scar imaging and cardiac computed tomography lead imaging to characterize geographic influences of scar on the achievement of LV remodeling in patients receiving standard CRT lead placement. We identified that patients without significant scar in targeted LV or right ventricular pacing regions achieved LV remodeling criteria (≥15% reduction in LV end-systolic volume) by 6 months in 81% of cases. When scar was present in the right ventricular pacing region, this response rate was significantly reduced to 55%, and when present in the LV pacing region reduced further to 25%. If scar was present in both pacing regions, no patient responded to CRT. These findings support that myocardial scar has a graded influence on LV remodeling that is weighted on its geographic distribution. Accordingly, targeted CRT lead delivery seems justified if also considering scar beyond the LV pacing region when anticipating clinical response.
Influence of Pacing Site Characteristics on Response to Cardiac Resynchronization Therapy

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