Impact of scar burden by single-photon emission computed tomography myocardial perfusion imaging on patient outcomes following cardiac resynchronization therapy

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Aims
Ischaemic heart disease negatively impacts response to cardiac resynchronization therapy (CRT), yet the impact of infarct scar burden on clinical outcomes and its interaction with mechanical dyssynchrony have not been well described.

Methods and results
We studied 620 NYHA classes III–IV heart failure patients with ejection fraction (EF) ≤ 35% and QRS duration ≥ 120 ms referred for CRT. Included were 190 ischaemic cardiomyopathy (ICM) CRT recipients with scar burden quantified by rest–redistribution Tl201 myocardial perfusion imaging using a 17-segment (0 = normal to 4 = absence of uptake) summed rest score (SRS). Non-ICM (NICM) CRT recipients (n = 380) and 50 patients referred for CRT with unsuccessful LV lead implant comprised the comparison groups. Echocardiographic dyssynchrony analysis was performed in a subgroup of 150 patients. Follow-up left ventricular EF (LVEF) and volumes were examined at 7 ± 3 months in 143 patients. The outcome of death, cardiac transplant, or mechanical circulatory support was assessed in all. Over 2.1 ± 1.6 years, ICM patients had significantly worse survival and less LVEF improvement than NICM patients (P < 0.01). Ischaemic cardiomyopathy patients with low scar burden (SRS < 27) had favourable survival and LVEF improvement, similar to NICM patients. A high scar burden (SRS ≥ 27) was associated with reduced survival and lack of LV functional improvement (P ≤ 0.01), similar to those with unsuccessful LV lead implant, whereas baseline dyssynchrony was not predictive of outcome in these patients.

Conclusion
Extensive scar burden in ICM patients unfavourably affected clinical and LV functional outcomes after CRT, regardless of baseline dyssynchrony measures. Patients with ICM and lower scar burden had significantly better outcomes, similar to NICM patients.

Keywords
Heart failure • Pacing • Imaging • Nuclear medicine • Echocardiography

Introduction
Cardiac resynchronization therapy (CRT) has been shown to improve symptoms and prognosis in selected patients with refractory New York Heart Association classes III–IV heart failure (HF), left ventricular (LV) ejection fraction (EF) ≤ 35%, and a QRS duration ≥ 120 ms, regardless of HF aetiology.1–3 However, approximately 30% of patients do not respond favourably to CRT, and much attention has been focused on prospective predictors of response.14–10 Although previous studies have suggested that CRT provides greater morbidity and mortality benefits to patients with non-ischaemic cardiomyopathy (NICM) when compared with those with ischaemic cardiomyopathy (ICM), conflicting data have been reported.13,11–16 Further evidence suggests that
among patients with ICM, significant scar burden related to lead position is also associated with lack of response.\textsuperscript{17–19} Although quantification of scar by magnetic resonance imaging is a promising method, resting single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is more commonly utilized in mainstream clinical practice and is safe in patients with previously implanted devices. Accordingly, the objective of this study was to test the hypothesis that scar burden from prior myocardial infarction, as quantified by MPI, is an important determinant of patient outcomes following CRT.

**Methods**

**Patient population**

This study examined consecutive patients (n = 620) referred to our institution for CRT-defibrillator (CRT-D) implantation between 1998 and 2008 who satisfied one of the following criteria: (i) ICM with a pre-CRT SPECT MPI study, (ii) NICM, or (iii) attempted but unsuccessful LV lead implantation regardless of HF aetiology. The Institutional Review Board approved all research activities, and all subjects provided informed consent. All patients had New York Heart Association classes III–IV HF symptoms refractory to optimal medical therapy, LVEF ≤ 35%, and QRS duration ≥ 120 ms (Table 1). There were 190 CRT patients characterized as ICM based upon the angiographic finding of >70% stenosis of at least one major epicardial coronary artery or a documented ST-elevation myocardial infarction. A group of 380 CRT recipients were classified as NICM by having major epicardial coronary disease excluded by coronary angiography and included idiopathic, inflammatory, and post-partum aetiologies of chronic HF. Patients with unsuccessful LV lead implant were similarly categorized as ICM (n = 27) and NICM (n = 23), and all received a standard defibrillator. All patients were managed with optimal tolerated medical therapy, including β-adrenergic antagonists and inhibitors of the renin–angiotensin–aldosterone axis.

**Myocardial perfusion imaging**

Myocardial scar burden was assessed by Tl\textsuperscript{201} SPECT MPI using a rest–24 h redistribution protocol.\textsuperscript{20,21} Patients were injected at rest with 3 mCi of Tl\textsuperscript{201}, with weight-based dosing for patients ≥ 110 kg. Single-photon emission computed tomography imaging was commenced 5 min after radiotracer injection on a dual-headed system (Philips Medical Systems, Andover, MA, USA) using a 180° circular orbit (45° right anterior oblique to 45° left posterior oblique) and a step-and-shoot format with 30 s of imaging at each of 64 total stops. When a perfusion abnormality was present on this early image, a redistribution image was acquired 24 h later using the same acquisition parameters but with 45 s of imaging per stop. Scar burden analysis was performed on the 24 h redistribution image using a standard 17-segment LV model and a five-point, semi-quantitative, visual perfusion score (0 = normal to 4 = absent perfusion; Figure 1). A summed rest score (SRS) was calculated as the sum of individual segment scores, which was indicative of the extent and severity of

**Table 1** Baseline demographic and clinical characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (n = 620)</th>
<th>CRT NICM (n = 380)</th>
<th>CRT ICM (n = 190)</th>
<th>Unsuccessful LV lead implant (n = 50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age (years)</td>
<td>64 ± 13</td>
<td>62 ± 13</td>
<td>68 ± 10</td>
<td>65 ± 15</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Men</td>
<td>438 (70.2%)</td>
<td>242 (63.4%)</td>
<td>164 (85.0%)</td>
<td>32 (65.3%)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>35 (5.6%)</td>
<td>18 (4.7%)</td>
<td>15 (7.8%)</td>
<td>2 (4.1%)</td>
<td>0.266</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>209 (33.5%)</td>
<td>104 (27.2%)</td>
<td>84 (43.5%)</td>
<td>21 (42.9%)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Atrial fibrillation history</td>
<td>306 (49.0%)</td>
<td>166 (43.5%)</td>
<td>115 (59.6%)</td>
<td>25 (51.0%)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Serum creatinine (mg/DL)</td>
<td>1.4 ± 0.8</td>
<td>1.3 ± 0.7</td>
<td>1.5 ± 0.7</td>
<td>1.6 ± 1.1</td>
<td>&lt;0.001†</td>
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<tr>
<td><strong>ECG characteristics</strong></td>
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<tr>
<td>QRS duration (ms)</td>
<td>169 ± 33</td>
<td>171 ± 34</td>
<td>166 ± 33</td>
<td>170 ± 31</td>
<td>0.472</td>
</tr>
<tr>
<td>Native RBBB</td>
<td>53 (8.6%)</td>
<td>24 (6.4%)</td>
<td>24 (12.5%)</td>
<td>5 (10.4%)</td>
<td>0.063</td>
</tr>
<tr>
<td><strong>HF medical therapy</strong></td>
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<tr>
<td>β-Blocker</td>
<td>496 (79.6%)</td>
<td>308 (80.8%)</td>
<td>151 (78.2%)</td>
<td>37 (75.5%)</td>
<td>0.597</td>
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<tr>
<td>ACE-I or ARB</td>
<td>527 (84.7%)</td>
<td>331 (87.1%)</td>
<td>158 (81.9%)</td>
<td>38 (77.6%)</td>
<td>0.05†</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>151 (24.4%)</td>
<td>102 (26.9%)</td>
<td>38 (19.8%)</td>
<td>11 (22.4%)</td>
<td>0.176</td>
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<tr>
<td><strong>Baseline echocardiography</strong></td>
<td></td>
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<tr>
<td>LVEF (%)</td>
<td>24 ± 6</td>
<td>23 ± 7</td>
<td>25 ± 6</td>
<td>25 ± 5</td>
<td>0.178</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>210 ± 82</td>
<td>204 ± 83</td>
<td>213 ± 80</td>
<td>228 ± 84</td>
<td>0.520</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>162 ± 71</td>
<td>167 ± 78</td>
<td>159 ± 67</td>
<td>169 ± 71</td>
<td>0.723</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; RBBB, right bundle-branch block; ACE-I, angiotensin-converting enzyme-inhibitor; ARB, angiotensin receptor-blocker; EDV, end-diastolic volume; ESV, end-systolic volume; NS, not significant. \( P \)-values reflect a three-way comparison of NICM, ICM, and unsuccessful LV lead implant groups.

Significant differences (\( P \leq 0.05 \)) in two-way comparisons are annotated as follows.

\(^*\)NICM vs. ICM.

\(^†\)NICM vs. unsuccessful LV lead implant.

\(^‡\)ICM vs. unsuccessful LV lead implant.
myocardial infarction. Interobserver variability of SRS was prospectively tested in a sample of 54 randomly selected studies and found to be 10% (Spearman’s correlation coefficient 0.901).

**Echocardiography**

Echocardiographic studies were performed with commercially available imaging systems (VIVID 7, GE-Vingmed, Horten, Norway; Sequoia, Siemens Medical Solutions, Mountain View, CA, USA; or Apio SSA-770A, Toshiba Medical Systems Corp., Tokyo, Japan). All patients were studied before CRT, and 143 patients had follow-up echocardiograms available for quantitative analysis 7±3 months after CRT. Left ventricular volumes and EF were assessed by biplane Simpson’s rule using manual tracing of digital images. A subset of 150 patients had baseline dyssynchrony analysis, including tissue Doppler imaging (TDI) and/or speckle tracking, as previously described in detail (EchoPAC BT08 GE-Vingmed or Research Arena Siemens Medical Solutions). Briefly, frame rates were 30–100 Hz (mean 65±15 Hz) for grayscale imaging used for speckle tracking and 72–154 Hz for TDI. Longitudinal velocity was determined from digitally stored apical four-chamber, two-chamber, and long-axis views. Ejection intervals were indicated from the LV outflow tract spectral Doppler signal. Colour-coded TDI analysis was performed using regions of interest (7 mm × 15 mm) placed in the basal and mid-segments and adjusted manually to optimize time–velocity curves with the most reproducible peak velocities during ejection. Speckle tracking was performed on routine grayscale images as previously described in detail. Longitudinal time–velocity curves were determined towards the LV apex from all three apical views. Longitudinal dyssynchrony was defined as the maximal difference in peak velocity at basal and mid-segments in opposing walls. Significant longitudinal dyssynchrony was defined as the maximal time difference between opposing walls in one view ≥65 ms, using the same cut-off by either software approach. For radial strain, an end-systolic circular region of interest was traced on the endocardial cavity with a second larger circle automatically generated and adjusted near the epicardium. Time–strain curves from each of six standard segments were generated from the short-axis image. Significant radial dyssynchrony was defined as the time difference between the anteroventricular to posterior wall peak strain ≥130 ms. No corrections for heart rate were performed; heart rates were in the range of 50–100 b.p.m.

**Device implantation**

Patients undergoing CRT implant received a standard active-fixation pacing lead in the right atrium, a high-voltage lead in or near the right ventricular apex, and an LV pacing lead in the coronary venous system, preferentially targeting lateral or posterolateral cardiac veins. In the event that a lead could not be placed transvenously because of anatomic constraints, excessively elevated LV thresholds, and/or low phrenic nerve capture thresholds, epicardial LV leads were surgically implanted via mini-thoracotomy in selected patients (n=29). A group of patients who met standard CRT implant criteria but in whom transvenous LV lead implantation was unsuccessful and no epicardial LV leads were implanted comprised the control group (n=50). The decision to forgo surgical epicardial lead implantation was primarily based on patient refusal. The unsuccessful LV lead implant patients reflected the overall CRT population at our institution with respect to HF aetiology, consisting of 23 patients with NICM and 27 with ICM. All CRT patients received CRT-D, and all unsuccessful LV lead implant patients received a standard cardioverter-defibrillator.

**Outcome analysis**

The pre-defined principal outcome variable was the combined endpoint of death, cardiac transplant, or the need for mechanical circulatory support (i.e. ventricular assist device). This endpoint was pre-determined because only patients with end-stage HF undergo transplant or ventricular assist device implantation. Follow-up echocardiograms were available in a subset of 143 patients for LVEF as a measure of LV function and LV end-systolic volume as a marker of...
reverse remodelling. Left ventricular volume and EF response were pre-specified as a relative ≥ 15% improvement from baseline values, as utilized in previous studies.\(^7,8,25\)

Statistical analysis
Categorical variables were compared using the \(\chi^2\) square test. Continuous variables were observed to approximate a normal distribution and were therefore compared using ANOVA and are reported as means ± 1 SD. The cut-off point for high vs. low scar burden was previously obtained by receiver operating curve analysis when performing logistic regression of LV functional response on the scar burden score.\(^17\) Kaplan–Meier and the multivariate Cox proportional hazard regression were used for time-dependent outcomes. Multivariate analysis of binary discrete endpoints was performed with logistic regression. A combination of forward and backward selection procedures was used to aid in determining the best model of independent predictors. This was followed by forcing potential confounders into the models and determining their effect on the relationship of interest. A \(P\)-value of ≤ 0.05 was considered statistically significant, and all tests were two-sided. All statistical calculations were performed using SPSS 16.0 (SPSS, Inc., Chicago, IL, USA) and SAS 9.2 (SAS Institute, Cary, NC, USA). The authors had full access to the data and take responsibility for its integrity.

Results

Demographic and clinical characteristics
Baseline characteristics of the study population are shown in Table 1. Variables differing (\(P \leq 0.05\)) among the ICM, NICM, and unsuccessful LV lead implant groups included age, gender, prevalence of diabetes and atrial fibrillation, baseline serum creatinine concentration, and the use of angiotensin-converting enzyme-inhibitors or angiotensin receptor-blockers.

Survival according to heart failure aetiology
The overall follow-up duration was 2.1 ± 1.6 years (median 1.9 years, range 2 days to 10 years) for survival free from transplant or assist device. Follow-up data were 100% complete for the primary endpoint of death, transplant, or assist device implantation, with a total of 155 events overall. There were primary endpoint events in 73 (19%) NICM patients, 65 (34%) ICM patients, and 17 (35%) unsuccessful LV lead implant patients. Survival free from transplant or mechanical circulatory support was significantly longer in NICM patients than in both ICM patients (hazard ratio 1.8, 1.3–2.5, \(P < 0.001\); Figure 2) and unsuccessful LV lead implant patients (hazard ratio 2.4, 1.4–4.2, \(P = 0.001\); Figure 2). The significant difference in survival between ICM and NICM patients was retained after adjusting for differences in baseline clinical characteristics detailed in Table 1 (i.e. age, gender, diabetes, atrial fibrillation, serum creatinine concentration, and use of angiotensin-converting-enzyme-inhibitors or angiotensin receptor-blockers). Both ICM (hazard ratio 0.68, 0.48–0.96, \(P = 0.03\)) and unsuccessful LV lead implant (hazard ratio 0.51, 0.29–0.88, \(P = 0.02\)) were also significantly associated with increased mortality, transplant, or need for circulatory support in a multivariate model that also included those baseline characteristics individually predictive of this primary endpoint (i.e. NYHA class IV HF, serum creatinine concentration, baseline right bundle-branch block, and use of \(\beta\)-blockers).

Figure 2 Kaplan–Meier curves depicting survival free from cardiac transplant or mechanical circulatory support in heart failure patients after cardiac resynchronization therapy-defibrillator implantation, stratified according to ischaemic cardiomyopathy or non-ischaemic cardiomyopathy. A third group of patients with attempted but unsuccessful left ventricular lead implant who received a standard cardioverter-defibrillator was included for comparison. Patients with non-ischaemic cardiomyopathy had significantly more favourable event-free survival than the other groups.
Association of survival with scar burden
The ICM cohort was divided according to the extent of MPI scar burden using a pre-defined cut-off SRS value of ≥27, which has previously been shown to delineate LV functional response to CRT among ICM recipients.17 There were no other baseline differences between the two groups of ICM patients (Table 2). Receiver operator characteristic curve analysis using death, heart transplant, or mechanical circulatory support at 1 year as the outcome variable and SRS as the continuous variable confirmed that SRS ≥ 27 has the best predictive value (AUC 0.66, P = 0.008). Ischaemic cardiomyopathy patients with SRS < 27 demonstrated better survival free from transplant or assist device than ICM patients with SRS ≥ 27, with similar outcomes as NICM patients (Figure 3), even after controlling for potential confounding variables of age, gender, prevalence of atrial fibrillation and diabetes, and baseline serum creatinine concentration (hazard ratio 2.38, 1.44–3.94, P = 0.02). Multivariate analysis using individual baseline characteristics associated with the primary endpoint (i.e. NYHA class IV HF, serum creatinine concentration, baseline right bundle-branch block, and β-blocker use) also confirmed that among ICM patients, SRS < 27 is a significant predictor of favourable survival free from transplant or assist device (hazard ratio 2.19, 1.32–3.62, P = 0.002).

The cohort with ICM and SRS ≥ 27 was compared separately with unsuccessful LV lead implant patients with ICM. These groups were similar at baseline, differing only in age and serum creatinine concentration (Table 2). Survival free from transplant or mechanical circulatory support did not differ (Figure 3), even after controlling for age and baseline renal function.

Left ventricular reverse remodelling response
Follow-up LV volume and EF data were available to assess reverse remodelling in a subgroup of 143 patients at an interval of 7 ± 3 months after CRT. These included 62 CRT recipients with ICM, 63 CRT recipients with NICM, and 18 with unsuccessful LV lead implant. Overall, CRT resulted in significant improvements in LV end-systolic volume from 163 ± 73 to 137 ± 80 mL (P < 0.001) and LVEF from 24 ± 6 to 33 ± 12% (P < 0.001). When examined by HF aetiology, NICM patients had significantly greater reduction in LV end-systolic volumes than ICM patients, decreasing from 167 ± 78 to 130 ± 87 vs. 159 ± 67 to 144 ± 71 mL in the ICM group (P < 0.001), and had greater improvement in LVEF, increasing from 23 ± 7 to 34 ± 14 vs. 25 ± 6 to 31 ± 11% in the ICM group (P < 0.005; Figure 4). Patients with unsuccessful LV lead implant had non-statistically significant changes in both LV end-systolic volume (169 ± 71 mL at baseline vs. 166 ± 56 mL at follow-up) and LVEF (25 ± 5% at baseline vs. 23 ± 9% at follow-up), as expected. Among CRT recipients, ICM patients with SRS ≥ 27 had the least LV reverse remodelling with CRT; group mean LV end-systolic volume increased from 180 ± 86 mL at baseline to 183 ± 84 mL and group mean LVEF changed from 23 ± 5 to 25 ± 9% (Figure 5). Although individual variability in reverse remodelling response was observed, this was similar to the unsuccessful LV lead implant patients.

### Table 2 Baseline demographic and clinical characteristics of the subjects with ischaemic cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>CRT recipients</th>
<th>Unsuccessful LV lead implant with ICM (n = 27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICM, SRS &lt; 27 (n = 123)</td>
<td>ICM, SRS ≥ 27 (n = 67)</td>
<td></td>
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<tr>
<td><strong>Demographics</strong></td>
<td></td>
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</tr>
<tr>
<td>Age (years)</td>
<td>68 ± 10</td>
<td>66 ± 10</td>
<td>72 ± 9</td>
</tr>
<tr>
<td>Men</td>
<td>105 (85.4%)</td>
<td>57 (85.1%)</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>7 (5.7%)</td>
<td>8 (11.9%)</td>
<td>7 (2.7%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>55 (44.7%)</td>
<td>28 (41.8%)</td>
<td>11 (40.7%)</td>
</tr>
<tr>
<td>Atrial fibrillation history</td>
<td>78 (63.4%)</td>
<td>35 (52.2%)</td>
<td>15 (55.6%)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.5 ± 0.7</td>
<td>1.4 ± 0.5</td>
<td>1.9 ± 1.4</td>
</tr>
<tr>
<td><strong>ECG characteristics</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>166 ± 33</td>
<td>169 ± 34</td>
<td>172 ± 32</td>
</tr>
<tr>
<td>Native RBBB</td>
<td>12 (9.8%)</td>
<td>11 (16.4%)</td>
<td>2 (7.7%)</td>
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<tr>
<td><strong>HF medical therapy</strong></td>
<td></td>
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<tr>
<td>β-Blocker</td>
<td>98 (79.7%)</td>
<td>50 (74.6%)</td>
<td>21 (77.8%)</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>98 (79.7%)</td>
<td>57 (85.1%)</td>
<td>20 (74.1%)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>20 (16.4%)</td>
<td>18 (26.9%)</td>
<td>7 (25.9%)</td>
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<tr>
<td><strong>Baseline echocardiography</strong></td>
<td></td>
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<tr>
<td>LVEF (%)</td>
<td>26 ± 6</td>
<td>24 ± 6</td>
<td>26 ± 6</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>209 ± 65</td>
<td>227 ± 97</td>
<td>215 ± 84</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>156 ± 55</td>
<td>174 ± 81</td>
<td>161 ± 72</td>
</tr>
</tbody>
</table>

See Table 1 for abbreviations. P-value reflects three-way comparison of ICM SRS ≥ 27, ICM SRS < 27, and unsuccessful LV lead implant with ICM groups. No differences were seen between the two CRT groups.

*P < 0.05 between ICM SRS ≥ 27 CRT group and unsuccessful LV lead implant ICM group
†P < 0.01 between ICM SRS ≥ 27 CRT group and unsuccessful LV lead implant ICM group.
Relative influence of scar burden and dyssynchrony on echocardiographic response

Of the 150 study patients with available baseline dyssynchrony analysis, 66 were ICM CRT recipients, 80 were NICM CRT recipients, and 4 were unsuccessful LV lead patients. Among CRT recipients, dyssynchrony was more predictive of improvements in LVEF and reverse remodelling in NICM than ICM patients. Defining response as a relative ≥15% improvement in LVEF or end-systolic volume, the pre-defined cut-off of ≥65 ms for longitudinal velocity opposing wall delay had a sensitivity of 79% and specificity of 89% for NICM patients, in contrast to a lower sensitivity of 67% and lower specificity of 55% for ICM patients. Similarly, the pre-defined cut-off of ≥130 ms for radial strain septal to posterior wall delay had a higher sensitivity of 84% and higher specificity of 78% for NICM patients, compared with a sensitivity of 66% and specificity of 65% for ICM patients. One hundred and forty-two (97%) had paired longitudinal and radial dyssynchrony data available, which have been shown previously to predict EF response after CRT.25 Using the same definition of response as above, significant combined longitudinal and radial dyssynchrony data available, which have been shown previously to predict EF response after CRT.25 Using the same definition of response as above, significant combined longitudinal and radial dyssynchrony had a sensitivity of 77% and specificity of 89% for NICM patients and both a lower sensitivity of 62% and lower specificity of 65% for ICM patients. Among the 66 ICM patients with complete dyssynchrony analysis, high scar burden (SRS ≥27) was associated with poor survival free from transplant or assist device, whereas combined dyssynchrony did not predict this primary endpoint (Figure 6). Multivariate analysis also demonstrated that high scar burden, not combined dyssynchrony, correlated with lack of echocardiographic response (odds ratio 0.28, 0.09–0.91, P = 0.03).

Discussion

This is the first study of a large series of consecutive patients undergoing CRT to demonstrate the important association of scar burden by SPECT MPI with survival, LV functional response, and reverse remodelling. A differential response to CRT was observed with respect to HF aetiology, with NICM patients having better survival and improvement in LVEF and end-systolic volume than ICM patients. Among ICM patients, lesser scar burden by SPECT MPI (SRS ≤27) was associated with more favourable survival and reverse remodelling following CRT, with outcomes similar to NICM patients. High scar burden (SRS ≥27) was associated with the lack of LV functional improvement, absence of reverse remodelling, and worse survival. Furthermore, baseline echocardiographic dyssynchrony, previously associated with LV functional improvement and reverse remodelling following CRT, did not correlate with response in ICM patients with high scar burden. High scar burden by SPECT was the most powerful independent predictor of outcome in these patients.

Multi-centre, randomized trials of CRT have demonstrated significant morbidity and mortality benefit in patients with and without coronary artery disease.1–3 However, multiple smaller studies have shown that NICM patients derive significantly greater benefit...
than their ICM counterparts, in terms of both symptomatic and ventricular functional improvement.\textsuperscript{11–15} No post-CRT survival analysis has differentiated ICM patients based upon scar burden severity, which may be a key determinant of CRT response among those with ICM.\textsuperscript{17} Our large single-centre experience using SPECT MPI, which may be more representative of mainstream clinical practice, confirms that ICM portends a less favourable prognosis following CRT compared with NICM. Ischaemic cardiomyopathy alone did not dictate lack of response, but myocardial scar burden by SPECT MPI appeared to differentiate LV reverse remodelling responders from non-responders and survivors from non-survivors.

The present analysis adds to a growing body of data implicating myocardial scar from prior infarction as an impediment to CRT response, whether defined by improvement in functional capacity, cardiac function, or reverse remodelling.\textsuperscript{9,29,30} Scar defined by SPECT MPI, in terms of both overall scar burden and scar localized near the LV lead, has been shown previously in smaller studies to predict the lack of clinical response and failure to improve ventricular function after CRT with follow-up limited to 6 months.\textsuperscript{17,31} The present study extends these observations to a larger series of CRT patients with longer survival follow-up and corroborates the SRS cut-off value of $\geq 27$ described in an earlier work by our group.\textsuperscript{17} Myocardial scar delineated by delayed enhancement cardiac magnetic resonance has also been shown to impact CRT outcomes. Bleeker et al.\textsuperscript{30} first described the effect of scar localized to the posterolateral left ventricle on clinical and echocardiographic parameters in a relatively small series of CRT recipients, concluding that a scar in this region, which corresponded to both the site of the LV lead and the area of latest LV mechanical activation, is associated with lack of functional improvement and reverse remodelling. They observed that posterolateral scar was as predictive of poor outcomes as lack of dyssynchrony. Similar

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Dot plots of ejection fractions and end-systolic volumes before and after cardiac resynchronization therapy in patients grouped according to ischaemic cardiomyopathy or non-ischaemic cardiomyopathy. A third group of patients with attempted but unsuccessful left ventricular lead implant who received a standard cardioverter-defibrillator was included for comparison. Significant improvements in ventricular function and reverse remodelling were observed in patient groups who received cardiac resynchronization therapy.}
\end{figure}
findings have been subsequently described with longer clinical follow-up. A study by White et al. utilizing cardiac magnetic resonance imaging demonstrated that ≥ 15% total scar burden predicted lack of CRT response, defined broadly as an improvement in symptoms or LVEF. Bilchick et al. more recently used cardiac magnetic resonance imaging to combine the assessment of dyssynchrony and scar burden to predict outcome in CRT patients. Although quantification of scar by magnetic resonance imaging continues to evolve, it is presently less clinically available than SPECT MPI, and incompatibility with previously implanted hardware, such as cardioverter-defibrillators or pacemakers, remains a concern. Accordingly, scar quantification by SPECT MPI remains a practical and realistic approach for current clinical practice and is well validated in the literature.

The negative impact of scar on CRT outcomes may relate mechanistically to overall scar burden, localized scar near the region of LV pre-excitation, and/or persistent increased risk of future ischaemic events. Large amounts of scar may directly prevent CRT-induced reverse remodelling, which has been shown to predict improved survival with CRT. After an acute myocardial infarction, remodelling occurs both within and remote from the affected infarct territory. Densely infarcted areas are replaced by fibrous tissue, forming relatively inert areas of scar. In contrast, non-infarcted segments undergo adverse remodelling in response to the imposed alteration in workload. These regions of myocardium should be susceptible to CRT-induced reverse remodelling, as they are also the target of other life-prolonging HF therapies (e.g. angiotensin-converting enzyme-inhibitors). A large scar burden may be a marker of a greater propensity towards future ischaemic insults or non-arrhythmogenic sudden death (e.g. pulseless electrical activity) that cannot be treated by a defibrillator. Localized non-contractile scar near the LV lead site may directly preclude mechanical resynchronization with the septum or may excessively slow conduction from the stimulation site, diminishing the amount of myocardium preexcited by the LV lead.
An interesting finding in the present study was that measures of dyssynchrony were less predictive of outcomes in ICM patients compared with those with NICM and did not appear to be predictive in those with high scar burden. Although a large body of literature supports the value of echocardiographic dyssynchrony indices to predict response to CRT, their ability to predict response is not clear. The PROSPECT study examined M-mode, routine Doppler, and tissue Doppler dyssynchrony indices, but was inconclusive for convincingly predicting response to CRT at 6 months. However, speckle-tracking deformation analysis was not evaluated in PROSPECT, nor were patients studied with respect to aetiology of HF or scar burden. Our present study, in contrast to PROSPECT, supports tissue Doppler and speckle tracking dyssynchrony analysis as being predictive of CRT response but less predictive in patients with ischaemic disease when compared with patients with NICM. Furthermore, our findings indicated that patients with high scar burden appear to have an unfavourable outcome after CRT and that scar burden appears to be more importantly associated with outcome than dyssynchrony in this subset of patients.

**Study limitations**

A limitation of this study was that SPECT MPI studies were performed as the clinical standard of care and not uniformly in all consecutive patients. Although this may represent selection bias, the amount of scar burden was widely distributed within the ICM patient cohort, and baseline LVEF and other important baseline characteristics were similar between the groups. Automated quantitative scoring of scar burden was not used because of the lack of availability of a normal database for 24 h Tl(201) redistribution studies. Furthermore, semi-quantitative visual scoring has heretofore been most frequently used to provide prognostic data in the literature. Another limitation is the comparatively lower spatial resolution of scar quantification by SPECT MPI compared with cardiac magnetic resonance imaging methods. However, our findings would also suggest that the identification of small amounts of scar tissue is unlikely to improve prognostication following CRT. We acknowledge that follow-up LVEF and volume data were only available in a subset of patients who were referred to our institution for CRT implant; many returned to satellite facilities or their remote primary healthcare providers for follow-up echocardiography. Our sample of 143 patients was appropriately distributed among the study groups and statistically powered to demonstrate significant results. Dyssynchrony data were not available on all patients because electrical dyssynchrony (i.e. QRS duration ≥ 120 ms) not mechanical dyssynchrony is one of the current criteria for considering CRT. Although recent criticism has emerged regarding dyssynchrony analysis for the prediction of response to CRT, the present investigation focuses on differences between NICM and ICM patients and scar burden, and it extends these observations to the use of speckle tracking, which was not tested in the PROSPECT study. Another limitation is that the subgroup of patients with high scar burden was relatively small and possibly insufficiently powered in comparison to the overall study group. Accordingly, future study of dyssynchrony on a larger group of patients with high scar burden would be of interest to confirm these findings.

**Conclusions**

In conclusion, higher scar burden quantified by SPECT MPI negatively impacts survival free from transplant or mechanical circulatory support and LV functional outcomes following CRT-D among ICM patients. Although the benefits of CRT appeared greater in NICM patients overall, ICM itself is not necessarily predictive of adverse outcomes. Ischaemic cardiomyopathy patients with low scar burden experience similar favourable outcomes as those with NICM. In contrast, ICM patients with high scar burden appear to have an unfavourable prognosis following CRT, regardless of baseline dyssynchrony. These findings merit further prospective study.

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