Use of myocardial scar characterization to predict ventricular arrhythmia in cardiac resynchronization therapy

Juan Fernández-Armenta, Antonio Berruezo*, Lluís Mont, Marta Sitges, David Andreu, Etelvino Silva, Jose Tomás Ortiz-Pérez, Jose María Tolosana, Teresa M de Caralt, Rosario Jesús Perea, Naiara Calvo, Emilce Trucco, Roger Borràs, María Matas, and Josep Brugada

1 Arrhythmia Section, Cardiology Department, Thorax Institute, Hospital Clinic, Universitat de Barcelona; and 2 Cardiac Imaging, Radiology Department, Center for Diagnostic Imaging, Hospital Clinic, Universitat de Barcelona, C/ Villarroel 170, 08036 Barcelona, Catalonia, Spain

Received 8 January 2012; accepted after revision 28 March 2012; online publish-ahead-of-print 4 May 2012

Aims

There is insufficient evidence to implant a combined cardiac resynchronization therapy (CRT) device with defibrillation capabilities (CRT-D) in all CRT candidates. The aim of the study was to assess myocardial scar size and its heterogeneity as predictors of sudden cardiac death (SCD) in CRT candidates.

Methods and results

A cohort of 78 consecutive patients with dilated cardiomyopathy and class I indication for CRT-D were prospectively enrolled. Before CRT-D implantation, a contrast-enhanced cardiac magnetic resonance (ce-CMR) was performed. The core and border zone (BZ) of the myocardial scar were characterized and quantified with a customized post-processing software. The first appropriate implantable cardioverter defibrillator (ICD) therapy was considered as a surrogate of SCD. During a mean follow-up of 25 months (25–75th percentiles, 15–34), appropriate ICD therapy occurred in 11.5% of patients. In a multivariate Cox proportional hazards regression model for clinical and ce-CMR variables, the scar mass percentage [hazard ratio (HR) per 1% increase 1.1 (1.06–1.15), P<0.01], the BZ mass [HR per 1 g increase 1.06 (1.04–1.09), P<0.01], and the BZ percentage of the scar [HR per 1% increase 1.06 (1.02–1.11), P<0.01], were the only independent predictors of appropriate ICD therapy. Receiver-operating characteristic curve analysis showed that a scar mass <16% and a BZ <9.5 g had a negative predictive value of 100%.

Conclusions

The presence, size, and heterogeneity of myocardial scar independently predict appropriate ICD therapies in CRT candidates. The ce-CMR-based scar analysis might help identify a subgroup of patients at relatively low risk of SCD.

Keywords

Magnetic resonance imaging • Cardiac resynchronization therapy • Ventricular tachycardia • Sudden death • Cardiomyopathy • Myocardial infarction

Introduction

A cardiac resynchronization therapy pacemaker (CRT-P), alone or combined with defibrillation capabilities (CRT-D), will induce left ventricular (LV) reverse remodelling, and improve symptoms and survival in patients with heart failure (HF), LV dysfunction, and prolonged QRS duration. Both therapies are a class I recommendation under current guidelines. As many of the candidates for CRT also meet implantable cardioverter defibrillator (ICD) criteria, a high CRT-D implantation rate (70–80%) occurs in clinical practice. However, the survival benefit of CRT-D over CRT-P is not well established. It is well known that CRT-P reduces the burden of ventricular arrhythmia (VA), risk of sudden cardiac death (SCD), and total mortality. As a result, the rate of appropriate ICD therapies is relatively low in this subset of patients. Furthermore, ICD therapy is costly and CRT-D is less cost-effective than CRT-P, especially in patients over the age of 65. In addition, the incidence of relevant complications related to defibrillator technology (lead dysfunction, inappropriate shocks) is significantly high. In the COMPANION study, 38% of shock therapies were...
inappropriate, whether due to supraventricular tachycardia, oversensing, or other causes. The impact of inappropriate therapy on quality of life is remarkable. Therefore, it is warranted to develop algorithms or new diagnostic tools to identify patients who are at risk of SCD and likely to benefit from an ICD.

Myocardial scar tissue provides the structural substrate for arrhythmogenicity. Identification of fibrosis by contrast-enhanced cardiac magnetic resonance (ce-CMR) has been associated with the occurrence of VA in ischaemic and non-ischaemic cardiomyopathies. It has been recently suggested that a precise characterization of infarcted or fibrotic tissue by means of ce-CMR may have a role in stratifying arrhythmogenic risk after acute myocardial infarction. The identification and measurement of the scar border zone (BZ) (areas with intermediate degrees of fibrosis) in ischaemic patients have been associated with inducibility of ventricular tachycardia (VT) and prediction of mortality and spontaneous VA. However, no studies have examined the prognostic value of scar identification and characterization in patients referred for CRT.

We hypothesized that the presence, extent, and/or characteristics of scar tissue could identify increased risk of spontaneous VA in CRT candidates of any aetiology.

**Methods**

**Patient population**

Consecutive ($n = 78$) HF patients with dilated cardiomyopathy and severe LV dysfunction [left ventricular ejection fraction (LVEF) $<35\%$] who were referred for primary prevention CRT-D implantation were prospectively enrolled. A wide QRS complex and/or LV dyssynchrony was present in all patients. The aetiology was considered to be ischaemic if there was $>70\%$ stenosis of a coronary artery on angiography, a history of proven myocardial infarction, or evidence of ischaemia on image stress testing. A ce-CMR was performed before device implantation to assess LV function and identify and characterize scar tissue. Patients with contraindications to ce-CMR examination were excluded. After implantation, all patients had a two-zone detection programmed: fast VT zone (180–230 b.p.m.) and VF zone ($>230$ b.p.m.). Supraventricular tachycardia discrimination algorithms were programmed for the VT zone. Antitachycardia pacing, burst at 91 and 81% of tachycardia cycle length with 10 ms scan, and shock were programmed on VT zone and shock (plus antitachycardia pacing during charging) in the VF zone.

**Contrast-enhanced cardiac magnetic resonance protocol**

All ce-CMR studies were performed using a 1.5 T scanner (HDX-t Signa, General Electric, Milwaukee, WI, USA). All images were acquired during repeated breath-holds and synchronized with the electrocardiogram. The LV function was evaluated using the two-, three-, and four-chamber view and a standard steady-state free precession cine sequence applied on 10 mm-thick, sequential short axis slices, from LV base to apex. The number of cardiac cycle phases varied according to the heart rate, with an average of 35 phases per cycle, yielding a temporal resolution of 35–45 ms. Ten minutes after administration of 0.2 mmol/kg gadodiamide-diethylenetriamine pentaacetic

---

**Figure 1** Analysis of myocardial scar. A contrast-enhanced cardiac magnetic resonance with lateral delayed enhancement is shown in the upper panels. Endocardial and epicardial borders are outlined in the short axis. The area of late enhancement is roughly delineated manually (red). A region of interest is selected within the healthy myocardium (blue). The automatic algorithm is then applied. The scar tissue is divided into core (red) and border zone (green). The core is defined as tissue with signal intensity $>50\%$ of the maximum signal intensity of the scar. The threshold between healthy tissue and border zone is defined by SI $>2$ standard deviations of the region of interest. The cut-off points are reflected in the bottom panel, showing signal intensity for histograms of the region of interest (blue) and scar (black). ROA, region of interest; SD, standard deviation.
Sequential short-axis slices were totalled and then divided by the total LV myocardial volume to calculate the scar size as a percentage of LV myocardial volume.

To characterize the scar, a half-maximum-intensity approach was used to define the BZ and core areas. The algorithm uses the maximum pixel signal intensity (MSI) of the scar region to define the threshold between the core and the BZ. The core was established as a region with signal intensity >50% of MSI in the scar area. The BZ was defined as the region between signal intensity >2 SDs of the ROI as the lower limit and 50% of the MSI of the scar as the upper limit (Figure 1).

**Follow-up and endpoints**

Clinical and echocardiographic evaluation was performed before device implantation and every 6 months thereafter. End-systolic and end-diastolic LV volumes and LVEF were calculated by echo from the apical two- and four-chamber views using the biplane Simpson technique. Positive response to CRT was defined as a combined endpoint of (i) relative reduction of 15% in LV end systolic volume compared with baseline and (ii) 12-month survival without cardiac transplantation.

Device interrogation was performed at 1 month after implantation and every 6 months thereafter. Appropriate ICD therapy was the primary endpoint and was counted and classified as

**Table 1 Baseline characteristics of patients**

<table>
<thead>
<tr>
<th></th>
<th>All (n = 78)</th>
<th>No appropriate ICD therapy (n = 69)</th>
<th>Appropriate ICD therapy (n = 9)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>64 ± 11</td>
<td>65 ± 10</td>
<td>63 ± 14</td>
<td>0.97 (0.92–1.04)</td>
<td>0.46</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>65 (83%)</td>
<td>58 (84%)</td>
<td>7 (78%)</td>
<td>1.55 (0.32–7.55)</td>
<td>0.59</td>
</tr>
<tr>
<td>Ischaemic cardiomyopathy, n (%)</td>
<td>41 (53%)</td>
<td>39 (57%)</td>
<td>2 (22%)</td>
<td>0.22 (0.04–1.05)</td>
<td>0.06</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>21 (27%)</td>
<td>18 (26%)</td>
<td>3 (33%)</td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>III</td>
<td>53 (68%)</td>
<td>47 (68%)</td>
<td>6 (67%)</td>
<td>0.71 (0.18–2.86)</td>
<td>0.63</td>
</tr>
<tr>
<td>IV</td>
<td>4 (5%)</td>
<td>4 (6%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration, ms&lt;sup&gt;a&lt;/sup&gt;</td>
<td>159 ± 33</td>
<td>160 ± 34</td>
<td>156 ± 25</td>
<td>1 (0.98–1.02)</td>
<td>0.86</td>
</tr>
<tr>
<td>LBBB, n (%)</td>
<td>49 (63%)</td>
<td>42 (61%)</td>
<td>7 (78%)</td>
<td>2.5 (0.51–12.18)</td>
<td>0.26</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>17 (22%)</td>
<td>14 (20%)</td>
<td>3 (33%)</td>
<td>1.85 (0.46–7.41)</td>
<td>0.38</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.2 ± 0.42</td>
<td>1.2 ± 0.45</td>
<td>1.14 ± 0.59</td>
<td>0.7 (0.14–3.29)</td>
<td>0.61</td>
</tr>
<tr>
<td>Invasive cardiac procedure&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21 (27%)</td>
<td>18 (26%)</td>
<td>6 (67%)</td>
<td>1.6 (0.39–6.51)</td>
<td>0.51</td>
</tr>
<tr>
<td>LVEF, %&lt;sup&gt;abc&lt;/sup&gt;</td>
<td>22 ± 7</td>
<td>22 ± 7</td>
<td>23 ± 8</td>
<td>1 (0.91–1.1)</td>
<td>0.97</td>
</tr>
<tr>
<td>LVESV, mL&lt;sup&gt;abc&lt;/sup&gt;</td>
<td>202.7 ± 92.9</td>
<td>204.7 ± 94.4</td>
<td>188.2 ± 84.7</td>
<td>1 (0.99–1.01)</td>
<td>0.65</td>
</tr>
<tr>
<td>QoL (MLHFQ)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>43 ± 18</td>
<td>42 ± 18</td>
<td>50 ± 21</td>
<td>1.02 (0.98–1.06)</td>
<td>0.25</td>
</tr>
<tr>
<td>6MWT, m&lt;sup&gt;a&lt;/sup&gt;</td>
<td>283 ± 133</td>
<td>278 ± 138</td>
<td>323 ± 81</td>
<td>1 (0.99–1.01)</td>
<td>0.38</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>64 (82%)</td>
<td>57 (83%)</td>
<td>7 (78%)</td>
<td>0.76 (0.16–3.68)</td>
<td>0.73</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>69 (89%)</td>
<td>62 (90%)</td>
<td>7 (78%)</td>
<td>0.76 (0.16–3.68)</td>
<td>0.73</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>29 (37%)</td>
<td>26 (38%)</td>
<td>3 (33%)</td>
<td>0.9 (0.23–3.61)</td>
<td>0.88</td>
</tr>
<tr>
<td>Diuretic</td>
<td>59 (76%)</td>
<td>53 (77%)</td>
<td>6 (67%)</td>
<td>0.54 (0.13–2.19)</td>
<td>0.39</td>
</tr>
<tr>
<td>Digoxin</td>
<td>11 (14%)</td>
<td>10 (15%)</td>
<td>1 (11%)</td>
<td>0.75 (0.09–6.02)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Univariable analysis for association to appropriate implantable cardioverter defibrillator therapy. LBBB, left bundle branch block; MLHFQ, Minnesota Living with Heart Failure Questionnaire; 6MWT, 6 min walk test; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker.

<sup>a</sup>Mean ± SD.

<sup>b</sup>Cardiac catheterization, myocardial revascularization, cardiac surgery, electrophysiology study, radiofrequency ablation performed the year before device implantation.

<sup>c</sup>Basal echocardiographic measurements.
Use of myocardial scar characterization to predict SCD

antitachycardia pacing or shock. Inappropriate ICD therapy (secondary to supraventricular tachycardia, oversensing, or electrode dysfunction) was recorded. Echocardiographic and clinical parameters, including LVEF, LV diameters, New York Heart Association (NYHA) class, quality-of-life score, and 6 min walking distance were reassessed at 12-month follow-up. Furthermore, total mortality and cardiac mortality were analysed. The composite of cardiac mortality and appropriate ICD therapy was considered as a secondary endpoint.

Statistical analysis
Continuous data are reported as mean ± SD and comparisons between groups were performed by using Student’s t-test or Mann–Whitney U test, as appropriate. Categorical variables are presented as frequencies (percentages) and compared with the χ² test or Fisher’s exact method. Receiver-operating characteristic (ROC) curves were performed to estimate the predictive value of scar variables and to identify cut-off points of interest.

Variables selected in the univariable analyses (P < 0.05) and those considered clinically relevant (LVEF and NYHA class, because of its established prognostic value) were entered into multivariable Cox proportional hazards regression models to estimate the independent effect of the scar tissue characteristics on event-free survival. Scar-related variables were included separately in the multivariable analysis because they were strongly related and therefore different multivariate models were needed.

Kaplan–Meier curves and log-rank tests were used to evaluate the time to first appropriate ICD therapy. For all tests, a P value <0.05 was considered statistically significant. Analysis was performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA).

Results
Patient characteristics
Seventy-eight consecutive patients were included in the study. The baseline characteristics of the patients are summarized in Table 1. Appropriate ICD therapy was documented in nine patients (11.5%) during follow-up [median 25 months (25–75th percentiles, 15–34 months)]. There were no differences in systolic function or clinical severity of HF (NYHA class, 6 min walking test, or QoL score) between the two groups. Drug treatment was similar in both groups. The proportion of patients with non-ischaemic cardiomyopathy tended to be higher among those receiving appropriate ICD therapy.

Magnetic resonance imaging data
Data extracted from the ce-CMR analysis are summarized in Table 2. Areas of late enhancement were present in 54 patients (69.2%) (Figure 2). The proportion of patients with scar was higher in the group with VA during follow-up (100 vs. 65.2%, P = 0.03). None of the patients without late enhancement had appropriate ICD therapies during follow-up. The scar mass was greater in the group receiving appropriate ICD therapies during follow-up. Scar mass expressed as a percentage of total LV myocardium (scar mass percentage) was also greater in the group with appropriate ICD therapies. Moreover, the BZ mass and the core scar mass were greater in patients with VA (Table 2 and Figure 3).

Table 2 Scar analysis by contrast-enhanced cardiac magnetic resonance

<table>
<thead>
<tr>
<th></th>
<th>All (n = 78)</th>
<th>No appropriate ICD therapy (n = 69)</th>
<th>Appropriate ICD therapy (n = 9)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scar mass (g)</td>
<td>25 ± 33.1</td>
<td>16.9 ± 20.3</td>
<td>86.9 ± 46.3</td>
<td>1.04 (1.02–1.06)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Scar as percentage of LV myocardium (%)</td>
<td>11.2 ± 13.8</td>
<td>8.1 ± 9.3</td>
<td>35.5 ± 18.6</td>
<td>1.09 (1.05–1.14)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Core mass (g)</td>
<td>12.1 ± 13.2</td>
<td>9.7 ± 10.6</td>
<td>30.8 ± 16.6</td>
<td>1.09 (1.05–1.14)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Border zone mass (g)</td>
<td>10.3 ± 18.5</td>
<td>5.8 ± 9.9</td>
<td>44.9 ± 30.6</td>
<td>1.06 (1.03–1.08)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Multivariate: Model I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scar % of myocardium</td>
<td>1.1 (1.06–1.15)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEFc</td>
<td>0.99 (0.90–1.09)</td>
<td>0.77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF class (I–II vs. III–IV)</td>
<td>0.41 (0.08–2.13)</td>
<td>0.29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate: Model II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Border zone massd</td>
<td>1.06 (1.04–1.09)</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEFc</td>
<td>1.01 (0.92–1.1)</td>
<td>0.89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF class (I–II vs. III–IV)</td>
<td>0.35 (0.07–1.76)</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Univariable and multivariable analysis for association to appropriate implantable cardioverter defibrillator therapy.
LV, left ventricle; LVEF, left ventricular ejection fraction; HF, heart failure.
*Mean ± SD.
*HR per 1% of total scar increase.
*HR per 1% of LVEF increase.
*HR per 1 g of border zone increase.
Prediction of appropriate implantable cardioverter defibrillator therapy

The univariable analysis showed that the scar mass was related to ICD therapy [HR 1.04 per 1 g increase (1.02–1.06), P < 0.001]. Similarly, a higher scar mass percentage was associated with appropriate ICD therapy [HR per 1% increase 1.09 (1.05–1.14), P < 0.001]. The BZ mass was also related to appropriate ICD therapy [HR 1.06 per 1 g increase (1.02–1.1), P < 0.001], as shown in Table 2.

Two Cox regression models were created for BZ mass and scar mass percentage (Table 2). Model 1 was adjusted for LVEF and NYHA class. The scar mass percentage was the only independent predictor of appropriate therapies, with a 10% increased risk per 1% increase. Model 2 was adjusted for the same variables, and the only independent predictor of appropriate therapies was the BZ mass, with a 6% increased risk for each gram.

In the group of patients in whom late enhancement was identified, scar characteristics were also related to appropriate ICD therapy during follow-up. The higher the BZ percentage of the scar (heterogeneous scars), the higher the risk of VA during follow-up. In contrast, the higher the core percentage of the scar (homogeneous scars), the lower the risk of VA during follow-up (Figure 3). Again, Cox regression models (adjusted for LVEF and NYHA class) were created for scar-related variables in this group (Table 3). The scar mass and its heterogeneity (BZ percentage of the scar) were the only independent predictors of events. In contrast, the scar homogeneity (core percentage of the scar) showed a protective effect for appropriate ICD therapies.

In the whole cohort, the area under the ROC curve (AUC) was 0.94 for scar mass percentage. A scar mass percentage >16% had 100% sensitivity, 81% specificity, and 39% positive predictive value for appropriate ICD therapy. The negative predictive value of a small scar (<16% of LV mass) was 100%. Fifty-five (70.5%) patients had a scar mass under 16%.

The AUC was 0.95 for the BZ mass. A BZ mass >9.5 g showed a sensitivity and specificity of 100 and 93%, respectively, with a 43% positive predictive value and 100% negative predictive value. The presence of a BZ mass <9.5 g identified patients at low risk of...
Figure 3  Comparison of scar characteristics based on the appropriate implantable cardioverter defibrillator therapy. As shown in the three upper panels, the scar mass, as well as the border zone mass and core mass, were higher in patients with appropriate implantable cardioverter defibrillator therapy. The heterogeneity of the scar, quantified as the percentage of border zone of scar, was significantly higher in the group of patients with appropriate implantable cardioverter defibrillator therapy. In contrast, the percentage of core of scar was lower in this group. ICD, implantable cardioverter defibrillator.

Table 3  Contrast-enhanced cardiac magnetic resonance data for patients with evidence of late enhancement

<table>
<thead>
<tr>
<th></th>
<th>No appropriate ICD therapy (n = 46)</th>
<th>Appropriate ICD therapy (n = 9)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scar as percentage of LV myocardium (%)</td>
<td>11.69 ± 9.73</td>
<td>35.5 ± 18.6</td>
<td>1.09 (1.05–1.14)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Core mass (g)</td>
<td>14.69 ± 9.73</td>
<td>30.8 ± 16.6</td>
<td>1.09 (1.04–1.13)</td>
<td>0.02</td>
</tr>
<tr>
<td>Core as percentage of scar (%)</td>
<td>69.17 ± 18.63</td>
<td>44.14 ± 16.22</td>
<td>0.93 (0.89–0.97)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Border zone mass (g)</td>
<td>8.72 ± 11.09</td>
<td>44.9 ± 30.6</td>
<td>1.05 (1.03–1.08)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Border zone as percentage of scar (%)</td>
<td>26.65 ± 15.52</td>
<td>48.42 ± 16.5</td>
<td>1.06 (1.02–1.1)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Multivariate: Model I
- Scar % of myocardiumb  1.1 (1.05–1.15)    <0.01
- LVEFc  0.99 (0.89–1.09)    0.75
- HF class (I–II vs. III–IV)  0.45 (0.09–2.34)    0.35

Multivariate: Model II
- Border zone % of scar d  1.6 (1.02–1.12)    <0.01
- LVEFc  1.04 (0.93–1.15)    0.53
- HF class (I–II vs. III–IV)  0.62 (0.14–2.78)    0.53

Multivariate: Model III
- Core % of scar e  0.93 (0.88–0.97)    <0.01
- LVEFc  1.02 (0.92–1.13)    0.75
- HF class (I–II vs. III–IV)  0.54 (0.11–2.7)    0.46

Scar characteristics in patients with and without appropriate implantable cardioverter defibrillator therapy. Univariable and multivariable analysis for association to appropriate ICD therapy.

LVEF, left ventricular ejection fraction; HF, heart failure.

bMean ± SD.

cHR per 1% of total scar increase.

dHR per 1% of LVEF increase.

eHR per 1% of BZ percentage of the scar increase.

fHR per 1% of core percentage of the scar increase.
SCD, as none of them \( (n = 57.7\%) \) had appropriate ICD therapy during follow-up.

**Mortality and implantable cardioverter defibrillator therapy**

During follow-up, 8 (10%) of 78 patients died. Non-cardiac death was reported in one patient. Cardiac death occurred in seven patients (9%); pump failure was the mode of death in all these cases.

The presence of scar percentage larger than 16% was an independent predictor of the combined endpoint of appropriate ICD therapy and cardiac death \([HR 7.76 (2.49–24.21), P < 0.001]\). Similarly, a BZ mass \( > 9.5 \text{ g} \) was also an independent predictor of the secondary endpoint \([HR 4.61 (1.64–13.0), P = 0.004]\).

The Kaplan–Meier analysis (Figure 4) showed statistically significant differences in event-free survival for primary and secondary endpoints related to scar mass percentage and BZ mass, dichotomized by selected cut-off points.

**Ischaemic vs. non-ischaemic scars**

Areas of delayed enhancement on ce-CMR were identified in 40 (98%) patients with ischaemic and in only 15 (41%) patients with non-ischaemic dilated cardiomyopathy. The overall extent of myocardial scar was lower in non-ischaemic patients (scar mass percentage \( 14.3 \pm 10.9 \text{ vs. } 7.9 \pm 15.8\% \), \( P < 0.01 \)). However, in patients with evidence of HE, there were no significant differences between ischaemic and non-ischaemic patients in scar mass and scar mass percentage (scar mass percentage \( 19.6 \pm 19.9 \text{ vs. } 14.6 \pm 10.8\% \), \( P = 0.71 \)). Post-myocardial infarction scars showed a trend towards a higher proportion of scar core tissue \([\text{core mass/scar mass } \times 100] 63.4 \pm 15.6 \text{ vs. } 52.9 \pm 22.3\% \), \( P = 0.065 \), resulting in less heterogeneous scars.

**Response to cardiac resynchronization therapy**

The percentage of responders tended to be lower among patients with identifiable areas of delayed enhancement on magnetic
Use of myocardial scar characterization to predict SCD

Table 4 Baseline myocardial scar in 1-year cardiac resynchronization therapy responders and non-responders

<table>
<thead>
<tr>
<th>Scar mass (g)</th>
<th>CRT responders (n = 41)</th>
<th>CRT non-responders (n = 34)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scar as percentage of LV myocardium (%)</td>
<td>24.16 ± 36.6</td>
<td>27.61 ± 30.04</td>
<td>0.25</td>
</tr>
<tr>
<td>Core as percentage of LV myocardium (%)</td>
<td>10.35 ± 14.57</td>
<td>12.78 ± 13.03</td>
<td>0.17</td>
</tr>
<tr>
<td>Border zone as percentage of LV myocardium (%)</td>
<td>5.12 ± 5.83</td>
<td>6.5 ± 6.16</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Mean ± SD.

Discussion

The main finding of the study is that the identification and analysis of myocardial scar tissue by ce-CMR in CRT candidates of any aetiology provide useful information in predicting the occurrence of malignant VA during follow-up. Not only the presence and total size of scar, but also its heterogeneity, are independent predictors of appropriate ICD therapies and of the composite endpoint of appropriate ICD therapies and cardiac mortality. The larger and more heterogeneous the scar is, the higher the probability of VA during follow-up. However, the most important aspect is probably the ability to identify a very low-risk subgroup of CRT patients that will not benefit from a back-up defibrillator.

The rate of appropriate ICD therapy was in line with previously published data. Although some clinical variables (i.e. advanced age, NYHA functional class III–IV, renal failure, diabetes, atrial fibrillation, and lack of appropriate HF treatment) have been shown to be related with VA events and mortality in COMPANION and MADIT II substudies, the present study did not find this relationship, probably because it was not powered for this purpose. The only variables having an independent predictive value for VA occurrence during follow-up are those related with the myocardial scar.

Previous reports have shown the usefulness of ce-CMR to identify and characterize myocardial scar in ischaemic and non-ischaemic patients. Recently, various reports have shown that BZ mass predicts VA in patients with remote myocardial infarction. The BZ mass, as a marker of scar heterogeneity, has been associated with cardiovascular events, mortality, and arrhythmia inducibility. However, to the best of our knowledge, no studies on myocardial scar identification and characterization have been conducted in CRT patients, in whom no clear outcome differences have been found between CRT-D and CRT-P groups. The present study shows that myocardial scar analysis permits identification of a group of patients at particularly low risk of VA events: those without scar, with a scar mass percentage <16% or a BZ mass <9.5 g (31, 71, and 73% of patients in this study, respectively). The cut-off point for the scar mass percentage is close to the 15% reported by Bello et al. to predict VA inducibility during electrophysiology study in patients with remote myocardial infarction. In the present study, scar analysis also permitted identification of differences in scar arrhythmogenicity: homogeneous scars (those with a higher percentage of core) were less arrhythmogenic than the heterogeneous ones.

In ischaemic and non-ischaemic patients, late enhancement on ce-CMR indicates the presence of myocardial scar. In the present study, 40% of non-ischaemic patients had late enhancement, which was in the upper range reported by previous studies. The electrophysiological substrate of VA in non-ischaemic cardiomyopathy is related to myocardial scar. The prognostic value of late enhancement on ce-CMR in non-ischaemic patients has also been demonstrated. However, scar characterization in non-ischaemic cardiomyopathies has been limited to assessing the size and transmurality of the late enhancement. In the study by Nazarian et al., the transmural extent of scar identified the substrate for inducible VT in non-ischaemic patients. The present study employed the same methodology for scar analysis in ischaemic and non-ischaemic patients, and the predictive value for VA was independent of the cardiomyopathy aetiology. Furthermore, differences in the degree of scar heterogeneity, which was higher in the non-ischaemic cohort, were striking. This may explain why non-ischaemic patients tended to have more appropriate ICD therapies.

On the other hand, we identified a trend to a lower CRT responder rate in patients with HE, without a significant correlation between scar size and CRT response. The present method of ce-CMR analysis did not take into account the scar distribution on the LV (i.e. post-erolateral scar), which was related to CRT non-response in a previous study. However, the response to CRT was not the primary endpoint of the present study.

Limitations

The main limitation of the study is the sample size, which precludes identification of clinical variables (i.e. male sex, NYHA class IV) already known to influence the occurrence of VA events in similar populations, such as that of the COMPANION study. Another limitation of the study may be the low rate of arrhythmic events, although similar to that in larger studies previously published. Further studies with larger sample sizes are needed to confirm the present results.
Conclusions

The presence, size, and heterogeneity of myocardial scar identified by ce-CMR independently predict appropriate ICD therapies in CRT candidates. The ce-CMR-based scar analysis might help identify a subgroup of patients at relatively low risk of SCD.

Conflict of interest: none declared.

Funding

This study was partially supported by a grant from the ‘Fondo de Investigación Sanitaria’ (FIS 2008–2011, PI080243).

References