Predictors of Spontaneous Reverse Remodeling in Mild Heart Failure Patients With Left Ventricular Dysfunction

Andrew Brenyo, MD; Alon Barsheshet, MD; Valentina Kutyifa, MD; Anne-Christine Ruwald, MD; Mohan Rao, MD; Wojciech Zareba, MD, PhD; Anne-Catherine Pouluer, MD; Dorit Knappe, MD; Scott D. Solomon, MD; Scott McNitt, MS; David T. Huang, MD; Arthur J. Moss, MD; Ilan Goldenberg, MD

Background—There are limited data regarding factors associated with spontaneous left ventricular reverse remodeling (S-LVRR) among mildly symptomatic heart failure (HF) patients and its prognostic implications on clinical outcomes.

Methods and Results—Best subsets logistic regression analysis was used to identify factors associated with S-LVRR (defined as ≥15% reduction in left ventricular end-systolic volume at 1-year of follow-up) among 612 patients treated with internal cardioverter defibrillator–only therapy in Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) and to create a score for the prediction of S-LVRR. Cox proportional hazards regression modeling was used to assess the clinical outcome of all internal cardioverter defibrillator–only patients (n=714) with a high S-LVRR score. S-LVRR occurred in 25% of internal cardioverter defibrillator–only patients. Predictors of S-LVRR included systolic blood pressure ≥140 mm Hg, serum creatinine <1.0 mg/dL, QRS 130 to 160 ms, and nonischemic cardiomyopathy. Multivariate analysis showed that each 1-point increment in S-LVRR score (range, 0–7) was associated with an 11% (P=0.019) reduction in the risk of HF or death. Treatment with cardiac resynchronization therapy was associated with a significant reduction in the risk of death only among internal cardioverter defibrillator–treated patients with a low (Q1–3) S-LVRR score (hazard ratio=0.55; P<0.001), but not among those with a higher (Q4) score (hazard ratio=1.06; P=0.72).

Conclusions—Our data suggest that approximately one quarter of mild HF patients eligible for biventricular pacing experience S-LVRR. Combined assessment of clinical factors associated with S-LVRR can be used to identify mild HF patients with a low risk for clinical events without cardiac resynchronization therapy intervention.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00180271.

Key Words: cardiac resynchronization therapy ■ heart failure

Cardiac resynchronization therapy (CRT-D) has proven beneficial in patients with symptomatic systolic heart failure (HF) and abnormal interventricular conduction.1,2 Data from numerous studies suggest that CRT-D benefit stems from correction of ventricular dyssynchrony and left ventricular reverse remodeling (LVRR).3-9 Such reductions in ventricular volume result in a significant reduction in HF hospitalization, ventricular arrhythmias, and death.10

Clinical Perspective on p 572

Spontaneous LVRR (S-LVRR) as a response to medical HF therapy alone has been identified as a prognostic indicator of improved long-term outcome in patients with abnormal left ventricular (LV) systolic function11-20 and has also been noted in patients with prolonged QRS allocated to the control group of major CRT-D trials.1,2 However, the predictors and prognostic implications of S-LVRR among patients with interventricular conduction delay who are eligible for CRT-D therapy remain unknown.

Accordingly, the present study was designed to: (1) identify predictors of S-LVRR in mild HF patients allocated to the internal cardioverter defibrillator (ICD)–only arm of the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT); (2) create a prediction score for S-LVRR; and (3) assess the clinical outcome of patients with a high likelihood to develop S-LVRR.

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From the Cardiology Division of the Department of Medicine, University of Rochester Medical Center, NY (A. Brenyo, V.K., A.-C.R., M.R., W.Z., D.T.H., A.J.M., L.G., S.M.); Department of Cardiology, Greenville University Health System, SC (A. Brenyo); Department of Cardiology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA (A.-C.P., D.K., S.D.S.); Cardiology Department, Rabin Medical Center, Petah Tikva, Israel (A. Barsheshet); and Department of Cardiology, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel (A. Barsheshet).

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Correspondence to Ilan Goldenberg, MD, Heart Research Follow-up Program, Box 653, University of Rochester Medical Center, Rochester, NY 14642.

E-mail ilan.goldenberg@heart.rochester.edu

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as determined by a high S-LVRR prediction score. We hypothesized that combined assessment of factors associated with S-LVRR can be used to identify mild HF patients eligible for biventricular pacing who experience improved clinical outcome without cardiac resynchronization therapy.

Methods

Study Population

The design and results of MADIT-CRT have been reported previously. Briefly, 1820 patients enrolled at 110 centers in the United States, Canada, and Europe, who had ischemic or nonischemic cardiomyopathy, an ejection fraction of ≤0.30, and abnormal intraventricular conduction with QRS≥130 ms, were randomized to receive CRT-D or ICD therapy in a 3:2 ratio. All patients gave informed consent, and the study was approved by an institutional review committee. Exclusion criteria included an existing indication for CRT-D, New York Heart Association class III/IV in the past 90 days before enrollment, the presence of atrial fibrillation or flutter at enrollment, pacemaker in situ, and coronary artery bypass grafting or percutaneous coronary intervention or myocardial infarction within 90 days before enrollment. The present study population included all subjects enrolled in MADIT-CRT.

Echocardiography

Echocardiograms within the ICD arm were obtained according to a study-specific protocol at baseline, which was prior to device implantation (n=612), and at 1 year (n=612). Echocardiographic parameters were measured in a core laboratory according to established American Society of Echocardiography protocols. LV and left atrial volumes were measured by Simpson’s method of discs in the apical 4- and 2-chamber views and averaged. Left ventricular ejection fraction was calculated through relative changes in these calculated LV volumes. LV mechanical dyssynchrony was measured using B-mode speckle tracking software (TomTec Imaging Systems, Unterschleissheim, Germany) as reported previously. LV dyssynchrony was determined as the standard deviation of regional time-to-peak transverse strain, measured during systole in the 12 segments of the left ventricle (in the septum, lateral, anterior, and inferior walls, and separate in basal, mid, and apical segments). Dyssynchrony values are presented in milliseconds. Percent changes in dyssynchrony values are the change in time to peak strain from baseline at 1-year follow-up echocardiography.

Definitions

Spontaneous Left Ventricular Reverse Remodeling

S-LVRR was defined as ≥15% reduction in left ventricular end-systolic volume (LVESV) at 1-year echocardiographic data. Characteristics of patients categorized by S-LVRR defined as per previous studies (<15% versus ≥15% change in LVESV) were compared with Student t test or χ² test as appropriate. We included 31 potential clinical, electrocardiographic, and laboratory binary predictors of S-LVRR (listed in Table 1). In addition, the number of HF medications patients were receiving at enrollment (1 to >4) was also included as a candidate covariate.

End Points

The primary outcome measures of the current study included the occurrence of an HF event requiring intravenous decongestive therapy as an outpatient or augmented oral or intravenous decongestive therapy as an inpatient or death.

Study Design

The study was conducted in 3 main steps. In the first step, we identified factors associated with S-LVRR in MADIT-CRT patients allocated to ICD-only therapy with paired echocardiograms (n=612); in the second step, we created a prediction score for S-LVRR based on the identified predictors; and in the third step, we assessed the clinical outcome from enrollment of all patients receiving an ICD who did not cross over during follow-up (n=714) by the response score and compared the clinical benefit of CRT-D therapy between ICD patients with a high (upper quartile) versus low S-LVRR score.

Statistical Analysis

Covariates Associated With S-LVRR

The analysis of factors associated with S-LVRR was performed among 612 study patients allocated to ICD-only therapy with paired baseline and 1-year echocardiographic data. Characteristics of patients categorized by S-LVRR defined as per previous studies (<15% versus ≥15% change in LVESV) were compared with Student t test or χ² test as appropriate. We included 31 potential clinical, electrocardiographic, and laboratory binary predictors of S-LVRR (listed in Table 1). In addition, the number of HF medications patients were receiving at enrollment (1 to >4) was also included as a candidate covariate.

Table 1. Baseline Clinical Characteristics for Patients With and Without S-LVRR

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>S-LVRR (N=154)</th>
<th>No LVRR (N=458)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrollment, y</td>
<td>64.9±11.0</td>
<td>64.1±10.6</td>
<td>0.43</td>
</tr>
<tr>
<td>Age&gt;65</td>
<td>54</td>
<td>52</td>
<td>0.64</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
<td>22</td>
<td>0.045</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26</td>
<td>30</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64</td>
<td>64</td>
<td>0.97</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>13</td>
<td>12</td>
<td>0.74</td>
</tr>
<tr>
<td>Ischemic NYHA Class I</td>
<td>14</td>
<td>17</td>
<td>0.35</td>
</tr>
<tr>
<td>Ischemic NYHA Class II</td>
<td>36</td>
<td>38</td>
<td>0.54</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>51</td>
<td>45</td>
<td>0.20</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.10±0.26</td>
<td>1.19±0.35</td>
<td>0.029</td>
</tr>
<tr>
<td>Serum creatinine&lt;1.0 mg/dL</td>
<td>66</td>
<td>74</td>
<td>0.09</td>
</tr>
<tr>
<td>GFR, mL/min/1.73 m²</td>
<td>63.4±16.5</td>
<td>64.8±16.5</td>
<td>0.38</td>
</tr>
<tr>
<td>GFR&lt;50 mL/min/1.73 m²</td>
<td>23</td>
<td>22</td>
<td>0.76</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>21.0±7.7</td>
<td>22.3±10.0</td>
<td>0.32</td>
</tr>
<tr>
<td>BUN&gt;25 mg/dL</td>
<td>23</td>
<td>26</td>
<td>0.37</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>156.3±17.4</td>
<td>160.3±21.2</td>
<td>0.098</td>
</tr>
<tr>
<td>QRS&lt;170 ms</td>
<td>78</td>
<td>70</td>
<td>0.061</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>121.8±17.1</td>
<td>120.5±17.9</td>
<td>0.25</td>
</tr>
<tr>
<td>SBP≥140</td>
<td>21</td>
<td>13</td>
<td>0.038</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>71.4±11.3</td>
<td>70.6±10.2</td>
<td>0.26</td>
</tr>
<tr>
<td>LBBB</td>
<td>70</td>
<td>71</td>
<td>0.81</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>92</td>
<td>93</td>
<td>0.42</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>97</td>
<td>95</td>
<td>0.51</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>32</td>
<td>31</td>
<td>0.65</td>
</tr>
<tr>
<td>Diuretics</td>
<td>65</td>
<td>67</td>
<td>0.90</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>23.9±5.2</td>
<td>23.5±5.2</td>
<td>0.49</td>
</tr>
<tr>
<td>LVESV/BSA, mL</td>
<td>121.7±26.7</td>
<td>126.4±30.9</td>
<td>0.075</td>
</tr>
<tr>
<td>LVESV/BSA, mL</td>
<td>87.2±22.5</td>
<td>90.1±24.7</td>
<td>0.17</td>
</tr>
<tr>
<td>LV/BASA, mL</td>
<td>47.2±10.4</td>
<td>46.4±9.6</td>
<td>0.87</td>
</tr>
<tr>
<td>Baseline dyssynchrony</td>
<td>184±61</td>
<td>188±67</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Data are presented as percentage or mean±SD. Bold indicates statistically significant.

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BUN, blood urea nitrogen; DBP, diastolic blood pressure; GFR, glomerular filtration rate; LV, left atrial volume; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association functional class; SBP, systolic blood pressure; and S-LVRR, spontaneous left ventricular reverse remodeling.
Numeric variables were dichotomized to binary with the goal of finding a simple, clinically relevant scoring method. The cut points for the variables included in the S-LVRR score were determined based on their distribution and independent of variables previously shown to be predictive of CRT response. As the identification of CRT response and patients likely to experience S-LVRR are different, different cut points in the same variables were necessary. Thresholds for categorization of numeric variables provided in Table 1 were prespecified using clinical and laboratory-accepted criteria. Univariate relationships between candidate covariates and S-LVRR (as defined above) in the ICD arm of the trial were assessed by t tests ($\chi^2$ for binary predictors). The covariates with values of $P<0.20$ were further evaluated by performing a best subset regression analysis in the ICD population with paired echocardiograms, examining the models created from all possible combinations of predictor variables, and using a penalty of 3.84 on the likelihood ratio $\chi^2$ value for any additional factor included.

**Prediction Score for S-LVRR**

After selection of binary predictors, each was assigned a numeric value based on the relative value of its regression coefficient in the multivariate regression model. The predictor with the lowest regression coefficient among the 4 variables in the model was assigned a numeric value of 1, and the other 3 factors were assigned numeric values based on the relative values of their regression coefficients to that of the lowest value. The S-LVRR score was constructed in each patient by adding the assigned numeric values for the 4 predictors. The score was subsequently categorized into approximate quartile and defined as a high (upper quartile [score ≥4]) versus low (quartiles 1–3 [score 0–3]) S-LVRR score. We assessed the accuracy of the prediction model through calculation of a c-statistic for survival analysis. Because the development of the S-LVRR score and its application to clinical outcome were performed on the same study population, we performed several cross-validation studies. These are described in detail in the Data Supplement.

A K-fold cross-validation was performed in 2 ways with K=10 to derive an understanding of the consistency of (1) the variable selection for the model predicting the echo change at 1 year and (2) the performance of the echo score in predicting the clinical outcome of HF or death.

The second validation used the same 10 datasets but forced the echo score model to be the 4-variable model chosen in the study on the entire data. This model was scored in each of the ten 10% holdout datasets and again used to predict HF or death.

**S-LVRR and Risk of Primary End Point**

The analyses that evaluated the association between the S-LVRR score and clinical outcome were performed in the total study population, with follow-up time beginning at enrollment.

Kaplan–Meier estimates for HF or death from enrollment, categorized by a high (Q4) versus low (Q1–3) S-LVRR score among all ICD-only patients and in the total CRT-D group, were determined and statistically evaluated with the log-rank test. Cox proportional hazards regression analyses were performed among all ICD-only patients for the assessment of the risk of HF or death by the S-LVRR score (assessed both as a continuous measure and by quartile analysis). Subsequently, Cox proportional hazards regression modeling was performed in the total study population incorporating treatment arm as a 3-level covariate: ICD-only high (Q4) S-LVRR score, ICD-only low (Q1–3) S-LVRR score, and the total CRT-D group. The multivariate model included unbalanced variables between the 2 groups: age≥65, HF hospitalization within year preceding enrollment, diabetes mellitus, and indexed left atrial volume. The findings were further adjusted for time-dependent HF medication change to determine the contribution of medical therapy to the findings.

The statistical software used for the analyses was SAS version 9.3 (SAS Institute, Cary, NC). A 2-sided $P$ value<0.05 was used for declaring statistical significance.

**Results**

**Spontaneous LVRR in ICD-Only Patients and Subsequent Clinical Outcome**

The rate of S-LVRR for ICD patients with paired baseline and 1-year echocardiograms in MADIT-CRT was 25%. The clinical characteristics of ICD-only patients by the occurrence of S-LVRR are presented in Table 1. There was no significant differences between the cohort of patients with paired echocardiograms (n=612) and the entire ICD population minus crossovers during follow-up (n=714). Patients experiencing S-LVRR comprised a higher frequency of women, had higher baseline systolic blood pressure (SBP), lower baseline serum creatinine, milder QRS prolongation, and smaller LV end-diastolic volumes (Table 1). ICD non-LVRR and S-LVRR patients displayed similar average LV dyssynchrony at baseline (184 versus 188 ms, respectively, $P=0.90$; Figure 1, left panel). However, at 1 year, S-LVRR patients significantly decreased the degree of mean LV dyssynchrony compared with ICD non-LVRR patients (166 versus 188 ms, $P=0.019$; Figure 1, right panel), representing a 9% improvement versus no change in LV dyssynchrony in the respective groups.

When outcomes were assessed by LVRR status in the 612 ICD patients with paired echocardiograms, the cumulative probability of HF or death at 3 years of follow-up (landmark analysis: subsequent to the 1-year echocardiography assessment) was shown to be highest in ICD non-LVRR patients (30%). By contrast, ICD-only patients with S-LVRR experienced significantly lower event rates that were similar to those in the CRT-D group (21% and 19%, respectively; Figure 2). Consistent with these findings, multivariate analysis demonstrated the S-LVRR group to be at a significant 38% lower risk of HF or death (hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.41–0.93; $P=0.02$) compared with ICD non-LVRR patients. In addition, the risk of HF or death was not significantly different between S-LVRR patients and those receiving CRT-D (HR, 1.24; 95% CI, 0.82–1.88; $P=0.29$). Furthermore, when S-LVRR patients were compared with CRT-D patients within the same range of LVESV reduction (≥215% to <44%), no significant difference in the risk of HF or death was seen (HR, 1.27; 95% CI, 0.87–2.09; $P=0.18$).

![Figure 1. Dyssynchrony scores at baseline and 1 year by remodeling status. Mean baseline and 1-year dyssynchrony values for patients with (blue bars) and without (red bars) spontaneous left ventricular reverse remodeling (S-LVRR) in the internal cardioverter defibrillator (ICD) arm of Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy. LV dyssynchrony was determined as the standard deviation of regional time-to-peak transverse strain, measured during systole in the 12 segments of the left ventricle with values presented in milliseconds.](image-url)
Predictors of Spontaneous LVRR

A best subset regression analysis in the current ICD-only study population identified 3 factors as being independently associated with S-LVRR. These factors (Table 2) were systolic hypertension (SBP ≥ 140 mm Hg) at baseline, below median serum creatinine (<1.0 mg/dL), and QRS duration below the upper quartile (<170 ms). In addition, nonischemic cardiomyopathy showed a more modest association with S-LVRR (Table 2). Given this modest association and its logical clinical inclusion in the predictive model for S-LVRR, this variable was included as a predictor of S-LVRR even though its statistical association was not as strong as the other three. Individual medical HF therapies and the total number prescribed were not shown to be independently associated with S-LVRR after multivariate adjustment. In addition, echocardiographic parameters including indexed and unindexed LV end-systolic volume, LV end-diastolic volume, and left atrial volume were not predictive of S-LVRR at 1 year.

S-LVRR Prediction Score

To develop a prediction score (S-LVRR score), each of these predictors was assigned a numeric value based on its relative effect in the regression model (derived from the point estimate of each covariate in the 4-variable model). The regression model showed that the contribution was low for nonischemic cardiomyopathy and, similarly, for QRS duration, SBP, and serum creatinine. Accordingly, nonischemic cardiomyopathy was assigned a numeric value of 1 and the remaining 3 factors a value of 2 each. The range of prediction scores was 0 to 7 with an upper quartile of 4, a lower quartile of 2, and a median of 3 (mean of 2.75). When the accuracy of the S-LVRR prediction score was assessed, the c-statistic was 0.75, indicating a reasonable to strong model for the prediction of S-LVRR.

Utility of S-LVRR Score for Risk Assessment in ICD-Only Patients

The rates of spontaneous ventricular remodeling and associated 3-year Kaplan–Meier rates of HF or death for each prediction score are displayed in Figure 3. This analysis demonstrated a significant inverse correlation between the S-LVRR score and 3-year rates of HF or death (P=0.032). Similarly, the rates of S-LVRR dependent on the S-LVRR prediction score among ICD-only patients were also inversely correlated with 3-year rates of clinical events (P=0.006). When the prediction score is applied to all ICD patients minus crossovers during follow-up (n=714), those with a higher (upper quartile) score were shown to experience a significant lower rate of HF or death at 4 years of follow-up from enrollment compared with those possessing a lower score (23% and 39%, respectively). Furthermore, patients with a high S-LVRR score who were treated with ICD-only therapy experienced similar event rates at 4 years of follow-up as those who were treated with cardiac resynchronization therapy (23% for high S-LVRR score and 24% for CRT-D; Figure 4).

Table 2. Predictors of Spontaneous Left Ventricular Remodeling at 1-Year Echocardiogram

<table>
<thead>
<tr>
<th>Remodeling Predictors</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SBP ≥140 mm Hg</td>
<td>1.65</td>
<td>1.02–2.69</td>
<td>0.042</td>
</tr>
<tr>
<td>Creatinine &lt;1.0 mg/dL</td>
<td>1.56</td>
<td>1.03–2.38</td>
<td>0.035</td>
</tr>
<tr>
<td>QRS duration &lt;170 ms</td>
<td>1.47</td>
<td>1.14–1.67</td>
<td>0.011</td>
</tr>
<tr>
<td>Non-Ischemic</td>
<td>1.29</td>
<td>0.94–1.52</td>
<td>0.09</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio; and SBP, systolic blood pressure.
Consistent with the univariate findings, multivariate analysis (Table 3) showed that each 1-point increment in the S-LVRR score was associated with a significant 13% reduction (HR 0.87, \(P=0.005\)) in the risk of HF or death in patients treated with ICD-only therapy. Furthermore, ICD-only patients with an upper quartile S-LVRR score experienced a significant 42% reduction in HF or death (HR 0.58, \(P=0.001\)) compared with ICD patients with a lower S-LVRR score (Table 3).

An additional separate analysis for the risk of ventricular tachycardia/ventricular fibrillation (ICD Shock) or death dependent on an elevated (upper quartile) S-LVRR score was performed in the entire ICD-only population and did not display a significant association (HR, 0.80; 95% CI, 0.56–1.14; \(P=0.22\)). In addition, the S-LVRR score was applied to the CRT-D population without any predictive value for HF or death at the same upper quartile cutoff (HR, 0.90; 95% CI, 0.65–1.23; \(P=0.51\)).

Sensitivity analyses were performed to validate the internal consistency of the findings. The results of the cross-validation analyses are provided in detail in the Data Supplement.

**Discussion**

Our findings from the MADIT-CRT population have several important implications for patients with mildly symptomatic HF and an indication for CRT. We have shown that (1) one quarter of mild HF patients meeting criteria for CRT will exhibit S-LVRR on medical therapy alone, characterized by spontaneous improvements in dyssynchrony and a low risk for clinical events that is similar to those treated with cardiac resynchronization therapy; (2) simple baseline clinical parameters can be used to identify patients who will experience S-LVRR; and (3) combined assessment of S-LVRR predictors can be utilized to identify mild HF patients eligible for biventricular pacing who will experience improved clinical outcome without CRT implantation.

**Predictors of Spontaneous LVRR**

Multiple echocardiographic parameters have been utilized within the literature to identify LVRR. In an effort to remain consistent with existing data,9 and to identify a simple single parameter that identifies S-LVRR, we utilized an unindexed reduction in LVESV of 15%. This simple cutoff allows rapid and straightforward identification of S-LVRR within common clinical practice. With the consistency and strength of the prognostic significance of LVRR defined in this fashion, along with its simplicity, it can be identified as standard in patients with LV dysfunction and mildly symptomatic HF.

Possible mechanism related to predictors of S-LVRR and associated improvements in dyssynchrony seem to be multifactorial. Hypertensive patients were more likely to experience S-LVRR and a favorable prognosis, possibly because (1) the greater LV stroke work required to maintain such SBPs indicates a healthier left ventricle and greater myocardial reserve among patients with LV dysfunction and (2) hypertensive HF patients are more likely to receive and tolerate target doses of evidence-based medical therapy for HF and derive their benefit. In addition, it is possible that in a subset of patients with hypertensive-induced cardiomyopathy, more aggressive treatment of hypertension in the setting of a clinical trial may lead to a greater degree of S-LVRR. The

**Figure 4.** Kaplan–Meier estimates of the cumulative probability of the primary end point from enrollment by upper quartile spontaneous left ventricular reverse remodeling (S-LVRR) prediction score and device received. CRT-D indicates total CRT-D group; Low Pred. Score, S-LVRR score below upper quartile; and High Pred. Score, S-LVRR score above upper quartile.

**Table 3. Multivariate Analysis: Risk of Heart Failure and Death by S-LVRR Score and Device Received**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>HF or Death</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ICD-only patients</td>
<td>S-LVRR score assessed as a continuous measure: each increase in S-LVRR score</td>
<td>0.87</td>
<td>0.80–0.96</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>S-LVRR score dichotomized at upper quartile: high vs low S-LVRR score</td>
<td>0.58</td>
<td>0.41–0.81</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Findings are further adjusted for age>=65, time-dependent heart failure (HF) medication change, prior HF hospitalization within year preceding enrollment, diabetes mellitus, and indexed left atrial volume.

All ICD patients=patients successfully receiving an ICD (n=713) compared with n=612 that the S-LVRR score was derived from. High LVRR Prediction Score=Prediction Score \(<=4\) (upper quartile); Low LVRR Prediction Score=Prediction Score >4 (lower 3 quartiles).

CI indicates confidence interval; HF, heart failure; HR, hazard ratio; ICD, internal cardioverter defibrillator; and S-LVRR, spontaneous left ventricular reverse remodeling.

*All analyses included follow-up time from enrollment in the trial.
paradoxical prognostic implications of hypertension within the HF population have been described previously, and our findings are consistent and supporting.\textsuperscript{12,24,25}

Patients without ischemic cardiovascular disease and a QRS duration that was not extremely (in the range of 130–160 ms) long were also more likely to experience S-LVRR. These findings support LV substrates contribution to the potential for S-LVRR: patients without significant LV scarring (ischemic cardiomyopathy) or profound dyssynchrony (long QRS duration) were more likely to experience S-LVRR without the aid of CRT. Elevated serum creatinine seems to be an indicator of the severity of comorbid illness and not a direct contributor to the prevention of LVRR. It is interesting that serum creatinine and not glomerular filtration rate was associated with S-LVRR and outcome. This finding may be due to the fact that a serum creatinine level of 1.0 mg/dL may be a more sensitive marker for S-LVRR compared with the Modification of Diet in Renal Disease thresholds used to categorize glomerular filtration rate. It is also possible that patients with higher serum creatinine and muscle mass but preserved renal function may have not received aggressive HF therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and thus less likely to experience S-LVRR. In addition, lower blood pressure leading to decreased renal perfusion with an increase in serum creatinine may be acting as a surrogate for the health of the LV and reversibility of its dysfunction.

It is important to note that all of the predictors seem to either influence or be influenced by the aggressiveness of medical therapy and stress its early application prior to irreversible adverse LV remodeling. Of note, individual HF agent classes (\(\beta\)-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aldosterone antagonists, etc) and the cumulative number of them being received by the patients at device implant were not shown to be predictive of S-LVRR after multivariate adjustment. This may relate to the inability of patients with lower blood pressure or impaired renal function to tolerate multiple classes of HF therapeutic agents.

Limiting medical therapy as a possible explanation for the development of S-LVRR and subsequent clinical benefit is the consistency of the findings when they are adjusted for change in medical HF therapy (\(\beta\)-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, etc) and the cumulative number of them being received by the patients at device implant were not shown to be predictive of S-LVRR after multivariate adjustment. However, MADIT-CRT was not designed to assess the efficacy of medical HF therapy on outcome and any conclusions regarding its role as a mechanism for S-LVRR are difficult.

**Spontaneous LVRR and Subsequent Outcome**

To our knowledge, this is the first study in the modern CHF therapy era to compare the prognostic significance of S-LVRR among mild HF patients who are eligible for cardiac resynchronization therapy. The present findings suggest that the prognosis of patients who experience S-LVRR is favorable and comparable to those who are treated with cardiac resynchronization therapy. The primary difference between CRT and S-LVRR is the incidence of LVRR within each group. Ninety percent of CRT-D patients experienced LVRR, which is dramatically more frequent than the rate of spontaneous remodeling seen in the ICD arm (25%). It is interesting that S-LVRR was associated with improvements in echocardiographic dyssynchrony, as this is presumed to be a predominantly electric (and subsequently mechanical) phenomenon addressed only by CRT. This finding is consistent with other studies examining dyssynchrony change within the ICD arm of MADIT-CRT.\textsuperscript{22,26}

Several studies have examined the incidence and prognostic significance of spontaneous or medical therapy–associated LVRR,\textsuperscript{11–20} and extend prior data to patients who are currently eligible for CRT implantation. Most recently, Merlo et al\textsuperscript{12} examined S-LVRR defined utilizing several echocardiographic parameters (improvement in left ventricular ejection fraction and reductions in left ventricular end-diastolic volume) in a cohort of 242 idiopathic dilated cardiomyopathy patients finding an S-LVRR incidence of 37%. In similar fashion to this study, S-LVRR was associated with significant reductions in HF, death, or heart transplant through a follow-up of almost 10 years. Consistent with our findings, increasing baseline SBP (each 10 mmHg increase) was associated with S-LVRR at echocardiographic follow-up. This provides further evidence that systolic hypertension is a good prognostic sign in patients with mild HF due to impaired systolic function.\textsuperscript{25}

In an effort to predict S-LVRR within our ICD-only (medically treated) population, we developed a prediction score based on the identified independent predictors of S-LVRR. The primary application of this score seems to be the identification of patients who are most likely to experience S-LVRR and, therefore, may possibly be managed with optimal medical therapy and defibrillator therapy alone, with clinical and echocardiographic follow-up prior to a decision regarding the need for upgrade to a CRT-D device. By contrast, the present findings also support an important role for early CRT-D intervention in mild HF patients who are unlikely to experience S-LVRR.

**Study Limitations**

The primary limitation of this study is that it is a post hoc analysis of a randomized clinical trial that was not designed to identify factors associated with S-LVRR. In addition, independent validation of this score in a similar CRT-D eligible population is required prior to widespread application and is lacking here. However, as this study involves the entire arm of a randomized trial with complete echocardiographic and follow-up data, this limitation portends a relatively minor bias. Moreover, after adjustment for baseline differences, the findings regarding the prognostic significance of S-LVRR were unchanged and emphasize their strength.

The predictors of S-LVRR and the resulting prediction score include several variables that have been shown to carry a good prognosis in the HF population. Therefore, it is possible that the predictive value of the S-LVRR model may be somewhat independent of S-LVRR. In addition, it should be noted only 3 variables out of the 30 tested show a P value below the 0.05 level. Therefore, if multiple comparisons were accounted for, none of the predictors would be likely to show a significant correlation with S-LVRR. This study is only applicable to patients with mild congestive HF eligible for CRT-D although currently there is little data regarding factors affecting spontaneous LVRR and subsequent outcomes among CRT-eligible patients with more advanced HF symptoms.
The thresholds used to categorize predictors of S-LVRR in the present study were prespecified based on their frequency among study patients. These variable thresholds may vary from those previously identified as predictive of CRT response (such as a QRS>150 ms) because the latter cutoffs may not be applicable to patients who are not treated with cardiac resynchronization therapy. In addition, as real-world patients are not truly binary, it is often the discretion of the bedside clinician to determine what side of the binary definition they fit better, which may limit the real-world clinical applicability of the S-LVRR prediction score.

Conclusions and Clinical Implications

Our findings suggest that baseline factors that are associated with S-LVRR can be used to identify patients who are at increased likelihood of experiencing S-LVRR and may therefore not derive benefit from CRT. Furthermore, we have shown that the prognosis of ICD patients meeting MADIT-CRT entry criteria is directly related to the number of factors associated with S-LVRR present in an individual patient. These findings, if appropriately validated in similar populations of ICD recipients, may be used for improved selection of patients unlike to experience spontaneous LVRR, thereby requiring early CRT intervention, or those in whom a more conservative approach may be attempted prior to CRT implantation.

Disclosures

The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy study was supported by a research grant from Boston Scientific, St. Paul, Minnesota, to the University of Rochester School of Medicine and Dentistry. Dr Alon Barsheshet is a Mirowski-Moss Career Development Awardee in Cardiology.

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There are limited data regarding factors associated with spontaneous left ventricular reverse remodeling (S-LVRR) among mildly symptomatic heart failure patients and its prognostic implications on clinical outcomes. We utilized best subsets regression analysis to identify factors associated with S-LVRR (defined as ≥15% reduction in left ventricular end-systolic volume at 1-year of follow-up) among 612 patients treated with internal cardioverter defibrillator–only therapy in Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) and to create a score for the prediction of S-LVRR. Of the internal cardioverter defibrillator population, 25% experienced S-LVRR. Predictors of S-LVRR included systolic blood pressure ≥140 mm Hg, serum creatinine <1.0 mg/dL, QRS 130 to 160 ms, and nonischemic cardiomyopathy. Based on their predictive strength for S-LVRR, systolic blood pressure, creatinine, and QRS were given a value of 2 in the S-LVRR prediction score and nonischemic cardiomyopathy a value of 1. Multivariate analysis showed that each 1-point increment in S-LVRR score (range, 0–7) was associated with an 11% (P=0.019) reduction in the risk of heart failure or death. Treatment with cardiac resynchronization therapy was associated with a significant reduction in the risk of heart failure or death only among internal cardioverter defibrillator–treated patients with a low (<4, Q1–3) S-LVRR score (hazard ratio=0.55; P<0.001), but not among those with a higher (Q4) score (≥4, hazard ratio=1.06; P=0.72). These data suggest that combined assessment of clinical factors associated with S-LVRR can be used to identify mild heart failure patients with a low risk for clinical events without cardiac resynchronization therapy intervention.
Predictors of Spontaneous Reverse Remodeling in Mild Heart Failure Patients With Left Ventricular Dysfunction

Andrew Brenyo, Alon Barsheshet, Valentina Kütyifa, Anne-Christine Ruwald, Mohan Rao, Wojciech Zareba, Anne-Catherine Pouleur, Dorit Knappe, Scott D. Solomon, Scott McNitt, David T. Huang, Arthur J. Moss and Ilan Goldenberg

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SUPPLEMENTAL MATERIAL

K-fold cross validation for echo response score

Methodology

A K-fold cross validation was performed in two ways with K=10 in order to derive an understanding of the consistency of 1) the variable selection for the model predicting the echo change at 1 year and 2) the performance of the echo score in predicting the clinical outcome of heart failure or death. This type of approach was used as opposed to a more straightforward model validation process because it was felt that there were not enough study data to create reasonably large datasets with sufficient endpoints for both model development and validation.

In the first validation, the data were randomly parsed into 10 mutually exclusive groups, from which there were 10 sets of model development data made of 90% of the data with a different 10% held out for validation in each case. A logistic regression model using a stepwise selection process with a significance level of 0.10 was used for each version of the echo response predictive model development data thus allowing the models to be different from the one chosen in the original analysis. Next, each of the 10 hold-out datasets was scored with its replication-specific model and these scores were then used to predict clinical outcome of Heart Failure or Death using both a continuous echo-score predictor and the upper quartile, as was reported in Table 3 of the manuscript.

The second validation used the same 10 datasets but forced the echo score model to be the 4 variable model chosen in the manuscript on the entire data. This model was scored in each of the ten 10% hold-out datasets and again used to predict Heart Failure or Death.

Results – Variable selection

Not surprisingly, as each model was derived on 90% of the data, in the first validation the covariates chosen were fairly consistent with the original four. Specifically, three of the original four variables (SBP> 140 mmHg, Creatinine<1.0 mg/dl and QRS<170 ms) were chosen between 70% and 90% of the time and ischemic status chosen 40% of the time. A few other variables were added in 10%-20% of the replications.

Results – Score performance in predicting clinical outcome

In the first validation, across the 10 separate holdout samples for the continuous score the median hazard ratio was 0.82, with an interquartile range (IQR) of 0.17 (25%ile=0.74, 75%ile=0.91). The echo score dichotomized at the 3rd quartile had a median hazard ratio of 0.23, IQR of 0.50 (25%ile=0.10, 75%ile=0.60).

In the second validation, across the 10 separate holdout samples for the continuous score the median hazard ratio was 0.81, with an IQR of 0.24 (25%ile=0.74, 75%ile=0.98). The echo score
dichotomized at the 3rd quartile had a median hazard ratio of 0.36, IQR of 0.58 (25%ile=0.21, 75%ile=0.80).

It should be understood that the percent of data above the Q3 dichotomization in the hold out samples varied substantially which is not surprisingly given they were based on 10% of the data and therefore fairly coarse.

To review, the main findings were that the continuous echo-score had a hazard ratio of 0.87 (95% CI: 0.80-0.96) and the upper-quartile dichotomized score had a hazard ratio of 0.58 (95% CI: 0.41-0.81). We believe the median validation hazard ratios shown above demonstrate sufficient consistency, especially in the case of the continuous echo-score, with the main findings to warrant confidence in the estimates reported in the manuscript.