Echocardiographic Predictors of Reverse Remodeling After Cardiac Resynchronization Therapy and Subsequent Events

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Background—Studies of echocardiographic predictors of response after cardiac resynchronization therapy (CRT) have largely involved single parameters. We hypothesized that combining parameters would be more robust and sought to develop a multiparametric echocardiographic score for predicting CRT response.

Methods and Results—Global longitudinal strain of left ventricle was added to standard echocardiographic measurements in 334 consecutive patients (224 men; mean, 65±12 years) who underwent baseline echocardiography before CRT and underwent follow-up echocardiograms at 1 year. Regression analysis was performed to create an echocardiographic score for prediction of LV reverse remodeling (defined as ≥15% reduction in the LV end-systolic volume). Cox proportional hazards models were used to identify the association of the score with death, transplantation or LV assist device implantation, and heart failure hospitalization during 57±22 months of follow-up. LV reverse remodeling (n=161; 48%) was associated with pre-CRT LV end-diastolic dimension index <3.1 cm/m², global longitudinal strain of left ventricle <-7%, left atrial area <26 cm², right ventricular end-diastolic area index <10.0 cm²/m², right atrial area <20 cm², and right ventricular fractional area change ≥35%. Combination of these into an echocardiographic score allowed prediction of LV reverse remodeling with a sensitivity of 84% and a specificity of 79%. During follow-up, there were 134 deaths, 18 heart transplantations/LV assist device implantations, and 93 heart failure admissions. The score was associated with heart failure admission, heart transplantation/LV assist device, or death (hazard ratio, 0.97; 95% confidence interval, 0.95–0.98; \(P<0.001\)) and all-cause death (hazard ratio, 0.97; 95% confidence interval, 0.96–0.98; \(P<0.001\)), independent of age, sex, ischemic cause, and initial functional class.

Conclusions—A multiparametric echocardiographic score is helpful in selecting patients likely to undergo reverse remodeling after CRT and predicts clinical outcomes. (Circ Cardiovasc Imaging. 2013;6:864-872.)

Key Words: cardiac resynchronization therapy ■ echocardiography ■ heart failure ■ ventricular remodeling

Cardiac resynchronization therapy (CRT) is an established treatment option for improving morbidity, quality of life, and survival in patients with heart failure (HF) with reduced left ventricular ejection fraction (LVEF), HF symptoms, and wide QRS complex.1-3 Recent studies have shown the beneficial effects of CRT on LV morphology, HF symptoms, and mortality in patients with mild HF.4-7 Although prognostic benefit occurs across populations, approximately one third of patients undergoing CRT fail to experience symptomatic benefit,1,3,7 and LV reverse remodeling has been proposed as a surrogate for CRT response.1-3,6 The occurrence of LV reverse remodeling has recently been associated with survival benefit after CRT.3-10

Clinical Perspective on p 872

Several previous studies of LV synchrony markers have sought to predict reverse remodeling but have been constrained by variability in these measurements and variation in the response parameter.11 The use of multiple parameters may overcome the limitations caused by error in individual measurements, and follow-up is an effective means of verifying the response of surrogate markers. A recent substudy of the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) demonstrated that a score based on previous hospitalization of HF, female sex, nonischemic cause, left bundle branch block, QRS duration, LV end-diastolic volume, and left atrial (LA) volume could predict response albeit limited to the MADIT-CRT population with mild HF.12 However, keeping in mind the routine performance of baseline 2-dimensional echocardiography, it is possible that additional echocardiographic parameters could be used to predict LV reverse remodeling after CRT. More sophisticated echocardiographic parameters are now available, including 2-dimensional strain imaging, which may identify global and regional LV function,13 LV scar burden, and
available echocardiographic scoring system with conventional and strain echocardiographic parameters could predict LV reverse remodeling and subsequent clinical outcomes after CRT.

Methods

Study Population
The records of all patients with HF who underwent CRT device implantation at the Cleveland Clinic between February 2005 and August 2007 were reviewed for this study. The criteria applied for CRT implantation were recent New York Heart Association functional class ≥II symptoms despite optimal medical therapy, QRS width ≥120 ms, and LVEF ≤35%. From this population, we included patients who had longitudinal follow-up at our institution. Patients were excluded if no baseline transthoracic echocardiographic study was performed at our institution before the implantation. Patients with insufficient echocardiographic image quality for the 2-dimensional strain measurement were excluded. Patients with a device implanted before 2005 undergoing exchange of their battery during the specified period for any reason (end of life or previous removal of a device because of endocarditis) were also excluded. The study protocol was approved by the Cleveland Clinic Institutional Review Board.

Clinical Variables
These patients were evaluated for clinical (cause of HF, symptom status and medication, heart rate, and blood pressure) and electrocardiographic parameters (rhythm and QRS width) at the time of device implantation. The cause of HF was considered ischemic on the basis of their clinical history of myocardial infarction (with electrocardiographic evidence of infarct location) or a history of revascularization.

Although derived in an earlier stage of HF, the MADIT-CRT score is unique as a clinical risk score in CRT candidates. We, therefore, calculated this using 7 variables (previous hospitalization of HF, female sex, nonischemic cause, left bundle branch block, QRS duration, LV end-diastolic volume, and LA volume), as described previously. Previous HF admission was assigned a numeric value of 1; female sex, nonischemic cause, left bundle branch block, QRS ≥150 ms, and LV end-diastolic volume ≥125 mL/m² were assigned a value of 2; and LA volume <40 mL/m² was assigned a value of 3.

Echocardiography
Standard echocardiographic examinations with Doppler studies were performed using commercially available echocardiographic systems and stored digitally. Baseline and subsequent echocardiograms were systematically reviewed and measured by 2 experienced readers. The parasternal images were used to measure LV end-diastolic and end-systolic dimensions. The 2- and 4-chamber images were used to calculate LV end-diastolic and end-systolic volumes, and LVEF was calculated using the modified Simpson biplane method. LV dimensions and volumes were indexed according to body surface area. LA area was calculated in the apical 4-chamber view. Right ventricular (RV) fractional area change (RVFAC) was calculated from the apical 4-chamber view using the percentage change in areas of the RV fractional area change; and TAPSE, tricuspid annular plane systolic excursion.

Table 1. Baseline Characteristics (n=334)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Male sex (%)</th>
<th>Age, y</th>
<th>Body surface area, m²</th>
<th>Ischemic cause (%)</th>
<th>NYHA functional class (%)</th>
<th>Mediation (%)</th>
<th>ACE inhibitor/ARB</th>
<th>LBBB or continuous RV pacing (%)</th>
<th>GRS width, ms</th>
<th>Conventional echo</th>
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</thead>
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<tr>
<td></td>
<td>224 (67.1)</td>
<td>65±12</td>
<td>2.0±0.3</td>
<td>176 (52.7)</td>
<td>37 (11.1)</td>
<td>283 (84.7)</td>
<td>275 (82.3)</td>
<td>215 (64.4)</td>
<td>158±31</td>
<td>LVEDD, cm/m²</td>
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<td>Time delay septal-to-lateral wall, ms</td>
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<td>5.1±2.9</td>
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ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DT, deceleration time; E/A, ratio of passive/active transmural flow; LA, left atrium; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; LVGLS, left ventricular global longitudinal strain; MADIT-CRT score, Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy score (originally derived in a lower risk group); MR, mitral regurgitation; NYHA, New York Heart Association; PA, pulmonary artery; RA, right atrium; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; and TAPSE, tricuspid annular plane systolic excursion.
views. The septal-to-lateral time delay was calculated from the systolic strain profiles of basal septal LV walls.

**Outcomes**

All study patients had echocardiographic follow-up: 69% of patients were followed up within 6 to 12 months after CRT, 16% within 3 to 6 months after CRT, and 15% within 1 to 3 months after CRT. An echocardiographic response was defined as percent reduction in LV end-systolic volumes within 1 year of enrollment. LV reverse remodeling was defined by a ≥15% reduction in LV end-systolic volume. Patients were followed for 57±22 months for a composite of death from any cause (determined with medical record or the Social Security Death Index), heart transplantation, support with an LV assist device, or HF hospitalization.

**Validation**

A separate validation group of patients undergoing CRT (n=72) was obtained from a second center (Princess Alexandra Hospital, Brisbane, Australia). The same echocardiographic measurements were obtained and scored independently. Patients were followed up for 64±27 months.

**Statistical Analysis**

Categorical variables are presented as frequency and percentage. Continuous variables are presented as mean±SD. Categorical variables were compared with χ² test, and continuous variables were compared with Student t test. Binary logistic regression was used in the prediction of LV reverse remodeling, and multivariable analysis was performed on parameters that were significant on the univariate analysis. Numeric variables were made binary by the use of cut points with the goal of defining a simple, easily implemented scoring method. Thresholds for categorization of these numeric variables were specified using generally accepted criteria or best cutoff values from receiver operating characteristic curves.

The echocardiographic parameter with the lowest regression coefficient among the 6 variables in the model was assigned a numeric value of 1, and the other 5 variables were assigned scores based on the values of their regression coefficients relative to that of the lowest value. Thus, each of the binary echocardiographic parameters was assigned

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**Table 2. Univariate Analysis in the Prediction of Left Ventricular Reverse Remodeling**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Remodeling (+)</th>
<th>Remodeling (-)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66±12</td>
<td>64±11</td>
<td>1.01 (0.99–1.03)</td>
<td>0.279</td>
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<tr>
<td>Female sex</td>
<td>74 (46%)</td>
<td>36 (21%)</td>
<td>3.24 (2.00–5.23)</td>
<td>&lt;0.001</td>
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<tr>
<td>Nonischemic cause</td>
<td>88 (55%)</td>
<td>69 (40%)</td>
<td>1.82 (1.18–2.81)</td>
<td>0.007</td>
</tr>
<tr>
<td>NYHA functional classes III and IV</td>
<td>141 (88%)</td>
<td>156 (90%)</td>
<td>0.77 (0.39–1.53)</td>
<td>0.451</td>
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<tr>
<td>ECG findings</td>
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<tr>
<td>LBBB</td>
<td>80 (50%)</td>
<td>53 (31%)</td>
<td>2.25 (1.44–3.52)</td>
<td>&lt;0.001</td>
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<tr>
<td>QRS duration, ms</td>
<td>159±30</td>
<td>158±32</td>
<td>1.00 (0.99–1.01)</td>
<td>0.716</td>
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<tr>
<td>Echocardiography</td>
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<tr>
<td>LVEDD, cm²/m²</td>
<td>3.0±0.5</td>
<td>3.2±0.6</td>
<td>0.47 (0.31–0.72)</td>
<td>0.001</td>
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<tr>
<td>LVESD, cm²/m²</td>
<td>2.6±0.5</td>
<td>2.8±0.6</td>
<td>0.45 (0.30–0.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDV, mL/m²</td>
<td>91±31</td>
<td>103±42</td>
<td>0.99 (0.99–1.00)</td>
<td>0.003</td>
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<tr>
<td>LVESV, mL/m²</td>
<td>68±26</td>
<td>80±37</td>
<td>0.99 (0.98–1.00)</td>
<td>0.002</td>
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<tr>
<td>LVEF (%)</td>
<td>25.1±6.6</td>
<td>23.6±7.4</td>
<td>1.03 (1.00–1.06)</td>
<td>0.051</td>
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<tr>
<td>LA area, cm²</td>
<td>24.9±6.6</td>
<td>29.4±8.0</td>
<td>0.91 (0.88–0.95)</td>
<td>&lt;0.001</td>
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<tr>
<td>Mitral E/A ratio</td>
<td>1.6±1.3</td>
<td>2.3±1.3</td>
<td>0.71 (0.59–0.85)</td>
<td>&lt;0.001</td>
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<tr>
<td>Mitral E-wave DT, ms</td>
<td>237±95</td>
<td>198±74</td>
<td>1.01 (1.00–1.01)</td>
<td>&lt;0.001</td>
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<td>Restrictive filling</td>
<td>23 (15%)</td>
<td>40 (23%)</td>
<td>0.56 (0.32–0.98)</td>
<td>0.043</td>
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<tr>
<td>Moderate or severe MR</td>
<td>62 (39%)</td>
<td>80 (46%)</td>
<td>0.73 (0.47–1.13)</td>
<td>0.154</td>
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<tr>
<td>RVEDA, cm²/m²</td>
<td>9.7±2.4</td>
<td>11.4±2.9</td>
<td>0.78 (0.71–0.85)</td>
<td>&lt;0.001</td>
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<td>RVESA, cm²/m²</td>
<td>5.4±2.1</td>
<td>8.3±2.8</td>
<td>0.62 (0.55–0.69)</td>
<td>&lt;0.001</td>
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<td>RVFAC, %</td>
<td>45.6±12.6</td>
<td>28.8±11.5</td>
<td>1.11 (1.09–1.14)</td>
<td>&lt;0.001</td>
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<tr>
<td>RA area, cm²</td>
<td>18.9±5.9</td>
<td>22.9±7.6</td>
<td>0.90 (0.86–0.94)</td>
<td>&lt;0.001</td>
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<td>TAPSE, cm</td>
<td>1.6±0.5</td>
<td>1.3±0.5</td>
<td>3.18 (1.97–5.13)</td>
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<td>Strain</td>
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<td>LVGLS, %</td>
<td>−8.1±2.7</td>
<td>−6.4±2.3</td>
<td>0.75 (0.68–0.83)</td>
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<td>Time delay S-L, ms</td>
<td>133±115</td>
<td>158±132</td>
<td>1.00 (0.99–1.00)</td>
<td>0.078</td>
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<td>MADIT-CRT score</td>
<td>6.0±3.1</td>
<td>4.2±2.5</td>
<td>1.25 (1.15–1.36)</td>
<td>&lt;0.001</td>
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</table>

CI indicates confidence interval; DT, deceleration time; HR, hazard ratio; LA, left atrium; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; LVGLS, left ventricular global longitudinal strain; MADIT-CRT score, Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy score (originally derived in a lower risk group); MR, mitral regurgitation; NYHA, New York Heart Association; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; and Time delay S-L, time delay septal-to-lateral wall.
a score based on the regression coefficient in the multivariable model. An echocardiographic score was derived by summation of the assigned numeric score. The optimal cutoff value of the echocardiographic score for predicting LV reverse remodeling was determined by the receiver operating characteristic curve analysis with bootstrapping. Comparison of areas under the curve of the echocardiographic score and MADIT-CRT score was performed with the method suggested by Hanley and McNeil. Reclassification was evaluated with net reclassification improvement methods described by Pencina et al. Net reclassification improvement measures the improvement in response classification using event-specific reclassification tables. Time-to-first-event analysis was performed using a Cox proportional hazards model with the combined end point of death, LV assist device implantation, heart transplantation, or hospital admission for HF. A 2-tailed P<0.05 was considered significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Chicago, IL) and MedCalc version 12.3.0.0 (MedCalc Software, Mariakerke, Belgium).

Reproducibility
The score parameters (LVGLS, LV end-diastolic dimension, LA area, RV end-diastolic area, RVFAC, and right atrial [RA] area) were evaluated in 20 random subjects by 2 investigators (J.P. and A.O.). Intra- and interobserver variabilities are measured by calculating the intraclass correlation coefficients.

Results
Patient Characteristics
Of the 578 consecutive patients undergoing CRT device implantation between February 2005 and August 2007 at the Cleveland Clinic, 334 (58%) met the specified inclusion criteria. Of the 224 patients who were excluded in this study, 154 (63.1%) had no follow-up echocardiographic study, 38 (15.6%) had no baseline echocardiographic images in this institution, 27 (11.1%) were associated with previous procedures, and only 25 (10.2%) had poor echocardiographic quality. Their baseline characteristics are described in Table 1.

LV Reverse Remodeling
Within 1 year after CRT implantation, 161 patients (48%) showed LV reverse remodeling. A reduction of ≥15% in LV end-diastolic volume occurred in 110 patients (33%), and an absolute improvement in LVEF of ≥5% was detected in 199 patients (60%). All baseline and echocardiographic data according to the presence of LV reverse remodeling are listed in Table 2. Female sex, nonischemic cause, and left bundle branch block on baseline ECG were significantly more prevalent in the LV reverse remodeling group. This group also had lower baseline LV dimensions, LV volumes, LA area, and lower LVGLS. There was higher incidence of restrictive filling in the nonresponder group. RV systolic function, assessed by RVFAC and tricuspid annular plane systolic excursion, was higher in the LV reverse remodeling group. RA area was significantly lower in the responder group.

Categorization of Echocardiographic Score Groups
We selected 6 echocardiographic variables based on univariate analysis. After the multivariate analysis in the prediction of LV reverse remodeling with 6 echocardiographic parameters, each was assigned a numeric value based on its relative effect. The regression model showed that the contribution was lowest for LA area (<26 cm²), intermediate for RV end-diastolic area index (<10.0 cm²/m²) and RA area (<20 cm²), high for LV end-diastolic dimension index (<3.1 cm/m²) and LVGLS (<−7.0%), and highest for RVFAC (≥35%). Accordingly, LA area was assigned a numeric value of 1; the intermediate factors, a value of 2 each; the high factors, a value of 6 each; and RVFAC, a value of 20 (Table 3). An echocardiographic score was constructed by adding the numeric values of the factors identified in each patient, and the echocardiographic score ranged from 0 to 37. Using receiver operating characteristic curve analysis for the prediction of LV reverse remodeling, a total score of >17 (95% confidence interval [95% CI], 13–17) showed optimal sensitivity (84%) and specificity (79%; Figure 1). This echocardiographic score was higher in sensitivity and specificity in the prediction of favorable remodeling than those of MADIT-CRT score, derived from a group with milder HF. Compared with quartiles of MADIT-CRT score, the echocardiographic score offered an improvement in reclassification of LV reverse remodeling by MADIT-CRT score (net reclassification improvement, 24.0%; P=0.005; Table 4).

The study group was categorized into approximate quartiles based on the sum of echocardiographic scores. Group 1 comprised 82 patients in the lowest score quartile (score 0–7), group 2 comprised 85 patients in the second quartile (score 8–19), group 3 comprised 89 patients in the third echocardiographic score quartile (score 20–31), and group 4 comprised 78 patients in the upper response score quartile (score 32–37). Echocardiographic score quartiles showed a direct correlation with percent reduction of cardiac volumes and improvement of LVEF (Figure 2A and 2B).

Follow-up
During the follow-up period of 57±22 months, there were 134 deaths, 11 heart transplantsations, 7 LV assist device implantations, and 93 hospital admissions among 167 patients. Cox proportional hazard regression analysis showed the higher echocardiographic score group to be independently associated with decreased risk of first admission for HF, heart transplantation, implantation of LV assist device, and death (hazard ratio [HR], 0.66; 95% CI, 0.57–0.77; P<0.001) and total mortality (HR, 0.67; 95% CI, 0.57–0.80; P<0.001; Table 5). Patients with higher echocardiographic score (group 4) showed higher event-free survival rate (P<0.001; Figure 3A) and lower total mortality (P<0.001; Figure 3B), independent of age, sex, ischemic cause, and initial functional class.

| Table 3. Multivariate Analysis With 6 Echocardiographic Variables in the Prediction of Left Ventricular Reverse Remodeling |
|--------------------------------------------------|----------------|----------------|-----------------|----------------|-----------|
| Variables                                      | β              | HR (95% CI)    | P Value         | Score          |
| LVEDD (<3.1 cm/m²)                             | 0.73           | 2.08 (1.14–3.78) | 0.017           | 6              |
| LVGLS (<−7.0%)                                 | 0.71           | 2.04 (1.14–3.65) | 0.016           | 6              |
| LA area (<26 cm²)                              | 0.14           | 1.14 (0.61–2.15) | 0.709           | 1              |
| RVEDA (<10.0 cm²/m²)                           | 0.22           | 1.24 (0.67–2.29) | 0.490           | 2              |
| RVFAC (≥35%)                                   | 2.67           | 14.41 (7.84–26.50) | <0.001           | 20             |
| RA area (<20 cm²)                              | 0.28           | 1.32 (0.69–2.50) | 0.400           | 2              |

CI indicates confidence interval; HR, hazard ratio; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVGLS, left ventricular global longitudinal strain; RA, right atrium; RVEDA, right ventricular end-diastolic area; and RVFAC, right ventricular fractional area change.
In a separate model of data obtained at the time of echocardiographic follow-up, the presence of LV reverse remodeling was associated with decreased risk of adverse clinical events (HR, 0.29; 95% CI, 0.21–0.41; P<0.001) and mortality (HR, 0.31; 95% CI, 0.21–0.45; P<0.001), independent of age, sex, ischemic cause, and initial functional class.

Validation
Among the 72 validation patients, the mean echo score was 24.8±11.0, with 10 (14%) in the highest risk, 5 (7%) in the second highest risk, 42 (58%) in the third highest risk, and 15 (21%) in the lowest risk groups. Twenty patients (28%) died during 64±27 months of follow-up. In a Cox proportional hazards model, echo score (HR, 0.53; 95% CI, 0.36–0.96; P=0.03) was associated with survival.

Variability
For intraobserver variability, the intraclass correlation coefficients of LV end-diastolic dimension were 0.99 (95% CI, 0.96–0.99; P<0.001), LVGLS 0.97 (95% CI, 0.88–0.99; P<0.001), LA area 0.95 (95% CI, 0.86–0.98; P<0.001), RV end-diastolic area 0.97 (95% CI, 0.92–0.99; P<0.001), RVFAC 0.92 (95% CI, 0.79–0.97; P<0.001), and RA area 0.96 (95% CI, 0.89–0.98; P<0.001). For interobserver variability, the intraclass correlation coefficients of LV end-diastolic dimension were 0.98 (95% CI, 0.95–0.99; P<0.001), LVGLS 0.97 (95% CI, 0.90–0.99; P<0.001), LA area 0.94 (95% CI, 0.84–0.98; P<0.001), RV end-diastolic area 0.88 (95% CI, 0.69–0.95; P<0.001), RVFAC 0.85 (95% CI, 0.63–0.94; P<0.001), and RA area 0.92 (95% CI, 0.95–0.99; P<0.001).

Discussion
In this study, we have identified 6 echocardiographic parameters that were associated with a favorable reverse remodeling effect after CRT. Combination of these factors (through an

Table 4. Incidence, Discrimination, and Calibration Estimates of Left Ventricular Reverse Remodeling After Cardiac Resynchronization Therapy

<table>
<thead>
<tr>
<th></th>
<th>Echocardiographic Score</th>
<th>Reclassified</th>
<th>Net Correctly Reclassified, %†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (0–7)</td>
<td>Group 2 (8–19)</td>
<td>Group 3 (20–31)</td>
</tr>
<tr>
<td>Individuals with LV reverse remodeling after CRT (n=161)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADIT-CRT score</td>
<td>Quartile 1 (0–4)</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Quartile 2 (5–6)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Quartile 3 (7–8)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Quartile 4 (9–14)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Individuals without LV reverse remodeling after CRT (n=173)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MADIT-CRT score</td>
<td>Quartile 1 (0–4)</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Quartile 2 (5–6)</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Quartile 3 (7–8)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Quartile 4 (9–14)</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Net reclassification improvement‡</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

CRT indicates cardiac resynchronization therapy; LV, left ventricle; and MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (originally derived in a lower risk group).

*The number of individuals who were reclassified upward and downward, respectively.
†The proportion correctly reclassified is in those who show left ventricular reverse remodeling after cardiac resynchronization therapy, the proportion of individuals reclassified to a higher risk minus the proportion reclassified to a lower risk; in those who do not have left ventricular reverse remodeling, the proportion of individuals reclassified to a lower risk minus the proportion reclassified to a higher risk.
‡The net reclassification improvement is the sum of correctly reclassified individuals with and without LV reverse remodeling.
echocardiographic score) could predict LV reverse remodeling and show a direct inverse correlation with adverse clinical outcomes and all-cause mortality.

**Definition of CRT Response**

Current American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines recommend the selection of CRT based on advanced HF symptoms, wide QRS duration (≥120 ms), and systolic LV dysfunction (LVEF <35%)\(^2\)\(^0\) to realize its benefits on LV reverse remodeling, decrease in HF symptoms and hospital admission, and reduced mortality.\(^1\)\(^–\)\(^3\),\(^2\)\(^1\) Although the concept of nonresponder is controversial, not all patients show symptomatic or functional improvement.\(^2\)\(^2\) Because of the potential for placebo effect, response has typically been defined by echocardiographic measurements,\(^2\)\(^3\) the most commonly used parameter being LV reverse remodeling (≥15% reduction in LV end-systolic volume index).\(^8\)\(^–\)\(^1\)\(^0\) This finding (which occurred in 48% of patients in our study) has been associated with lower rates of clinical events and mortality.\(^8\)\(^–\)\(^1\)\(^0\) However, the response rate in our study is slightly lower than that of other studies.\(^2\)\(^5\),\(^2\)\(^6\) Relatively low follow-up rate and the patient population may be somewhat different from the previously published studies, which partly account for the discrepancy.

**Echocardiographic Response Score**

More appropriate selection of patients for CRT may reduce the complications associated with inappropriate procedures and costs.\(^2\)\(^7\),\(^2\)\(^8\) An existing score has been obtained from clinical and simple echocardiographic variables in the MADIT-CRT trial, but more sophisticated echocardiographic variables can now be derived and could be readily applied because baseline 2-dimensional echocardiography is routine before CRT. We, therefore, sought to produce a multiparametric scoring system to identify favorable response validated against outcome. After binary logistic regression, we included 6 suitable parameters, including LV dimension (LV end-diastolic dimension index), LV systolic (LVGLS) and diastolic function (LA area), RV size (RV end-diastolic area index), and RV systolic (RVFAC) and diastolic function (RA area). Interestingly, the LV dysynchrony index (based on septal-to-lateral time delay) was not significant in the prediction of LV reverse remodeling.\(^2\)\(^9\) The constituents of the score reflect the physiological predictors of CRT response. As the marker of global LV function, we used LVGLS calculated by 2-dimensional speckle-tracking method instead of LVEF. LVGLS has the advantage of distinguishing contractility of the free wall from tethering or translational motion and can provide prognostic information that is incremental to LVEF.\(^2\)\(^9\),\(^3\)\(^0\) Furthermore, LVGLS revealed good correlation with global extent of scar tissue on contrast-enhanced MRI and can be used as a maker in the discrimination of viable myocardium.\(^1\)\(^4\)

LA area was one of the significant factors in the prediction of LV reverse remodeling in our study. LA function contributes to approximately one fourth of ventricular filling and can be an indicator of diastolic dysfunction. Patients with systolic HF usually have a dilated LA, which can predict clinical outcome irrespective of clinical data, LVEF, and exercise tolerance.\(^3\)\(^1\) Our finding is consistent with a previous study that

### Table 5. Multivariate Analysis in the Prediction of Adverse Clinical Events and All-Cause Mortality

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1: Prediction of adverse clinical events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>0.15</td>
<td>1.02 (1.00–1.03)</td>
<td>0.042</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.34</td>
<td>1.41 (0.96–2.08)</td>
<td>0.083</td>
</tr>
<tr>
<td>Ischemic cause</td>
<td>0.25</td>
<td>1.28 (0.91–1.79)</td>
<td>0.152</td>
</tr>
<tr>
<td>NYHA class &gt;III</td>
<td>0.70</td>
<td>2.01 (1.11–3.63)</td>
<td>0.021</td>
</tr>
<tr>
<td>LBBB</td>
<td>−0.25</td>
<td>0.78 (0.56–1.09)</td>
<td>0.781</td>
</tr>
<tr>
<td>QRS duration, mm</td>
<td>−0.01</td>
<td>0.99 (0.99–1.00)</td>
<td>0.001</td>
</tr>
<tr>
<td>Echocardiographic score (group)</td>
<td>−0.41</td>
<td>0.66 (0.57–0.77)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

| **Model 2: Prediction of total mortality** |       |             |         |
| Age, y               | 0.02  | 1.02 (1.00–1.04) | 0.039   |
| Male sex             | 0.41  | 1.50 (0.96–2.35) | 0.073   |
| Ischemic cause       | 0.39  | 1.48 (1.00–2.18) | 0.051   |
| NYHA class >III      | 1.01  | 2.92 (1.28–6.66) | 0.011   |
| LBBB                 | −0.00 | 1.00 (0.69–1.45) | 0.991   |
| QRS duration, mm     | −0.01 | 0.99 (0.98–1.00) | 0.001   |
| Echocardiographic score (group) | −0.40 | 0.67 (0.57–0.80) | <0.001 |

CI indicates confidence interval; HR, hazard ratio; LBBB, left bundle branch block; and NYHA, New York Heart Association.
showed that LA volume (<40 mL/m²) was a strong factor associated with favorable effect after CRT. RA area was also a significant factor in our study. This finding was supported by the previous reported study by D’Andrea et al, who showed that enlarged RA area and reduced RA systolic function were associated with impaired functional capacity and RA enlargement was a powerful independent parameter of unfavorable echocardiographic response to CRT.

RV parameters were also used in this echocardiographic scoring system. Because of the difficulty in the assessment of RV systolic function, the role of RV function in the appropriate selection of patients for CRT has been neglected. However, RV systolic dysfunction is a strong and independent predictor of adverse outcomes with HF and poor response to CRT. In this study, the presence of normal RV systolic function (assessed by RVFAC ≥ 35%) was strongly associated with LV reverse remodeling after CRT (HR, 14.41; 95% CI, 7.84–26.49; P < 0.001), adverse clinical outcome (HR, 2.24; 95% CI, 1.62–3.09; P < 0.001), and increased mortality (HR, 1.86; 95% CI, 1.30–2.70; P = 0.001), independent of age, sex, ischemic cause, and initial functional class.

Study Limitation

There are several important limitations. First, a substantial proportion of patients who underwent CRT implantation were not included in the analysis, most commonly because of lack of follow-up, which reflects the nature of the institution as a tertiary referral center. This may also have caused a survival bias among study patients because those who died early after implantation were not included in the present study. Thus, the score may not be applicable to all patients who underwent CRT, and the findings are most applicable to patients who survive for 1 year after implantation and who have regular follow-up hospital visits. Second, it would have been helpful to also report functional capacity. Nonetheless, LV reverse remodeling is a commonly used surrogate marker of a favorable response to CRT, and the relevance of this was verified by examining long-term clinical outcome. Third, the only existing score in CRT was derived from the MADIT-CRT trial, and we compared this with our echocardiographic score. However, because the baseline characteristics of MADIT-CRT participants are different from ours (less symptomatic, less severe LV dysfunction), that score may not be an ideal comparator. It could be argued that the nontrial population studied here is more representative of patients seen in standard practice. Fourth, this was a retrospective observational study with a relatively small sample size and no control group. The association of score with adverse outcomes during follow-up only implies that this is a higher risk subset and cannot be used to identify CRT as not being clinically beneficial in these patients compared with patients who are not treated with the device. Finally, the external validation of these data was limited to a small survival study. A prospective validation study with a relatively large sample size and regular follow-up will be needed to confirm the value of the application and the clinical effect of this echocardiographic score.

Conclusions

A multiparametric echocardiographic score accounting for RV and LV size and function and RA and LA area is helpful in selecting patients likely to have LV reverse remodeling with CRT and predicts clinical outcomes.

Acknowledgments

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

Cardiac resynchronization therapy (CRT) is recognized as an appropriate technique for improving morbidity, quality of life, and survival in patients with heart failure of varying severity who have a broad QRS (usually left bundle branch block). Although the prognostic benefit of CRT is well defined in populations, individual symptomatic benefit is more difficult to predict. Because CRT also has a burden relating to cost, complications (including infection), and the need for follow-up and device changes, several investigators have sought means of predicting response. Left ventricular (LV) reverse remodeling is most widely used. Although it is an imperfect surrogate for response, it is associated with survival benefit after CRT. However, many previous studies have been constrained by variability in these measurements (especially LV synchrony markers). We hypothesized that the use of multiple parameters may overcome the limitations caused by error in individual measurements and set out to develop a multiparametric echocardiographic scoring system with conventional and strain echocardiographic parameters in 334 consecutive patients who underwent baseline echocardiography before CRT and underwent follow-up echocardiograms at 1 year. LV reverse remodeling (n=161; 48%) was associated with pre-CRT LV end-diastolic dimension index <3.1 cm/m², left ventricular global longitudinal strain <-7%, left atrial area <26 cm², right ventricular end-diastolic area index <10.0 cm²/m², right atrial area <20 cm², and right ventricular fractional area change ≥35%. Combination of these into an echocardiographic score allowed prediction of LV reverse remodeling with a sensitivity of 84% and a specificity of 79%. The score was also independently associated with heart failure admission, heart transplantation/LV assist device, or death (hazard ratio, 0.97; 95% confidence interval, 0.95–0.98; P<0.001).
Echocardiographic Predictors of Reverse Remodeling After Cardiac Resynchronization Therapy and Subsequent Events

Jae-Hyeong Park, Kazuaki Negishi, Richard A. Grimm, Zoran Popovic, Tony Stanton, Bruce L. Wilkoff and Thomas H. Marwick

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