Echocardiography-Guided Left Ventricular Lead Placement for Cardiac Resynchronization Therapy

Results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region Trial

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Background—Cardiac resynchronization therapy improves mortality and morbidity in patients with heart failure (HF) with wide QRS complex and diminished left ventricular (LV) function, but response is variable.

Methods and Results—The Speckle Tracking Assisted Resynchronization Therapy for Electrode Region (STARTER) was a prospective, double-blind, randomized controlled trial testing the hypothesis that an incremental benefit to cardiac resynchronization therapy would be gained by echo-guided (EG) transvenous LV lead placement versus a routine fluoroscopic approach. EG LV lead placement was attempted at the site of latest time to peak radial strain by speckle tracking echocardiography. The prespecified primary end point was first HF hospitalization or death. Of 187 New York Heart Association class II to IV patients with HF (62% ischemic; ejection fraction 26±6%; QRS 159±27 ms), 110 were randomized to EG and 77 to routine strategies. Primary events included 30 deaths and 37 HF hospitalizations over 1.8 years. Using intention-to-treat, patients randomized to an EG strategy had a significantly more favorable event-free survival (hazard ratio, 0.48; 95% confidence interval, 0.28–0.82; P=0.006). Exact or adjacent concordance of LV lead with latest site could be achieved in 85% of the EG group and occurred fortuitously in 66% of controls (P=0.010) and was associated with an improvement in event-free survival (hazard ratio, 0.40; 95% confidence interval, 0.22–0.71; P=0.002).

Conclusions—A strategy of EG LV lead placement for cardiac resynchronization therapy improved patient outcomes by reducing the combined risk of death or HF hospitalizations and has implications for delivery of cardiac resynchronization therapy.


Key Words: cardiac resynchronization therapy ■ death ■ heart failure hospitalization ■ LV lead position ■ speckle tracking echocardiography.

Cardiac resynchronization therapy (CRT) has become an integral treatment modality for patients with heart failure (HF), diminished left ventricular (LV) ejection fraction, and a wide QRS complex, conferring symptomatic relief, functional improvement, and survival benefit to the majority of recipients.1–4 Despite these benefits, approximately one third of patients do not respond to CRT,1 and much resultant attention has focused on attempts to improve response. Although several reasons have been implicated in nonresponse, such as degree of LV scar burden5–9 and lack of mechanical dysynchrony,6,8,10 the position of the LV pacing electrode with respect to the site of latest LV mechanical activation seems to be of increasing importance as a factor related to CRT response.13–16 We therefore prospectively tested the hypothesis that an incremental clinical benefit of CRT would be gained by echocardiography-guided (EG) transvenous LV lead placement targeting the site of latest LV mechanical activation compared with the routine approach by performing a prospective, randomized, double-blinded study.

Clinical Perspective on p 434

Methods

The Speckle Tracking Assisted Resynchronization Therapy for Electrode Region (STARTER) was a prospective, single-center, double-blinded, randomized trial comparing the EG LV lead positioning through the transvenous approach during CRT implantation to a routine approach without imaging guidance. Patients were enrolled and implanted at the University of Pittsburgh Medical Center between June 2005 and March 2011. Patients and healthcare providers were blinded to their treatment assignment, except for the implanting physician.
Enrolled Patients
STARTER enrolled patients who were at least 18 years of age, New York Heart Association class II, III, or IV symptoms on optimal medical therapy LV ejection fraction ≤35%, and QRS width ≥120 ms. The study received institutional review board approval, and all patients gave written informed consent. Patients who had persistent atrial arrhythmias (n=44) were included as long as they underwent atrioventricular nodal ablation at the same time because the CRT device implantation or their ventricular response rate was slow enough to allow a high percentage (>90%) of biventricular pacing. Also, patients with chronic right ventricular pacing undergoing upgrade to a CRT device were eligible for this study (n=40). All patients received CRT defibrillators except for 4 patients (2 in each study arm) who received CRT pacemakers. Eligible patients were randomized to EG treatment arm versus routine control arm in a 3:2 ratio.

Echocardiography
All echocardiographic studies (GE Vivid 7 system, Horten, Norway) were analyzed by the core laboratory at University of Pittsburgh Medical Center Presbyterian. LV volumes were assessed by biplane Simpson rule using manual tracing of digital images. For speckle tracking radial strain, digital grayscale 2 dimensional (2D) cine loop images were acquired at end-expiratory apnea from basal and mid-LV short-axis views with frame rates of 60 to 90 Hz for offline analysis (GE EchoPac BT08-BT11). In brief, circular regions of interest were placed on the endocardial and epicardial borders and manually adjusted for optima time-strain curves. The times to peak strain from 8 free-wall segments (4 from each view) were determined from a minimum of 3 consecutive beats and averaged. The site of latest activation was determined as the segment with latest peak strain (Figure 1A). Patients whose latest peak strain occurred equivalently in >1 segment were reported as such. No cases were encountered where septal or anteroseptal regions coincided with the latest site of mechanical activation. Dyssynchrony was determined as the time difference between peak strain in the anteroseptal segment to peak strain in the posterior wall, as previously described.4,19–21 Using this approach, our intraobserver variability in time to peak strain analysis from the identical digital cineloops was 6±5%, and the interobserver variability was 8±7%. Although a formal quantitative exclusion of scar with a predetermined cutoff was not performed, segments with likely scar (thin wall ≤0.5 mm and an abnormal increase in acoustic reflectance)21 that had low amplitude strain curves with significant noise were handled as missing data, and therefore were not selected as a site of latest mechanical activation.

The labeling of the 4 free-wall segments from basal and mid-LV levels were anterolateral, lateral, posterolateral, or posterior to correspond to the regions of the coronary venous anatomy (Figure 1B). The corresponding naming of segments by the speckle tracking software was as shown in Figure 1B and as follows (with speckle tracking software labels listed first): anterior=anterolateral, lateral=lateral, posterior=posterolateral, and inferior=posterior. A pictorial report of site of latest mechanical activation was given to the implanting physician only for patients randomized to the EG group.

Device Implantation Procedure
CRT was performed using a transvenous approach with the right ventricular lead placed in or near the right ventricular apex. A right atrial lead was placed in all but 19 patients who had persistent atrial arrhythmias. Coronary venography was performed in left anterior oblique projection in all patients. The fluoroscopic images were divided into corresponding anatomic regions described above in the left anterior oblique view (Figure 1B) and into equal thirds in the right anterior oblique view: basal, mid-LV, and apical regions for documentation of LV lead position. Patients randomized to the EG study group had their LV lead placement attempted in the latest LV mechanical activation site as reported by speckle tracking echocardiography, described above. Patients who were randomized to control had their LV leads placed in the routine manner, targeting posterior or lateral LV regions.

Determination of LV Lead Concordance
Polar maps using a 16-segment model of the time to peak strain in relation to LV lead position were constructed after device implantation. Exact concordance was defined as when the LV lead was positioned in the same segment of latest mechanical activation. Adjacent segments were defined as segments that were immediately adjacent to the latest activation site, including touching diagonally using the 10 free-wall segments of the 16-segment model. Timing of apical segments was not determined prospectively, so patients with apical lead positioning could only be classified as adjacent or remote.

Follow-Up Echocardiography
LV volumes and LV ejection fraction (LVEF) were determined from follow-up echocardiography obtained 6 to 12 months after CRT, as prespecified in our protocol. Dyssynchrony after CRT was determined by speckle tracking as before CRT. To demonstrate the effects of CRT on resynchronization of the LV, dyssynchrony was assessed post hoc in patients with existing follow-up echocardiographic dysynchrony data.
Follow-Up for Clinical End points
The predefined primary end point was a composite of death or first HF hospitalization after CRT. Clinical events were adjudicated independently by 2 investigators not involved in patient care. Predefined secondary end points included a composite of death, heart transplantation, or LV assist device implantation, change in LVEF, and change in LV end-systolic volumes (LVESV). In addition, response to CRT was predefined as ≥15% relative reduction in LVESV on follow-up echocardiography and no primary end point, or as ≥25% absolute increase in LVEF (EF units) and no primary end point. All analyses were performed by intention-to-treat according to the randomization status, as well as by lead concordance status. The study was terminated on April 25, 2012 after an interim analysis indicated that the specified primary end point was reached in >30% of enrolled patients, and that there was a significant difference in event rates between the 2 study groups.

Sample Size and Statistical Analysis
The sample size calculation was based on the 2-sided primary hypothesis. It assumed a 67% 1-year survival free from HF hospitalization in the control group. To demonstrate 80% event-free survival rate in the echo-guided group, a total of 195 patients are needed in both groups, assuming a type I error of 10% and a power of 5%.

All analyses were performed according to the intention-to-treat principle. All continuous variables were expressed as means±SD and were compared using the Student t test or ANOVA, as appropriate. Continuous predefined subgroups were dichotomized around their mean value. Discrete variables were expressed as percentages and compared using the χ2 test. Time to events were calculated according to the Kaplan–Meier method and compared using the log-rank test. The effect of treatment assignment on the primary end point in predefined subgroups was analyzed using the Cox proportional hazards model. All analyses were conducted using the IBM PASW software version 19 (Armonk, NY). P values ≤0.05 were considered statistically significant.

Results
Patient Population and Procedural Data
A total of 187 (110 EG and 77 routine) patients were randomized in STARTER. Baseline characteristics were similar between the 2 study groups (Table 1). The majority of patients in both study groups belonged to New York Heart Association class III, and a high percentage of subjects were receiving β-blockers (88%) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (82%). There were 165 patients with complete baseline data. Ninety-six (87%) were in the EG group (6 excluded because of poor echocardiographic images, 7 had LV lead placement failure, and 1 had procedure cancellation), and 69 patients (90%) were in the routine group (2 were excluded because of poor echocardiographic images, 3 had LV lead placement failure, and 3 had procedure cancellation). The total procedural time (130±60 minutes versus 134±52 minutes; P=0.662) and fluoroscopic time (35±27 minutes versus 32±21 minutes; P=0.482) were similar between the 2 study groups.

There were a total of 15 complications related to CRT implantation. These included device infection requiring explantation (n=3), pneumothorax (n=1), LV lead dislodgement (n=4), atrial lead dislodgement (n=1), coronary sinus staining during venography (n=2), and diaphragmatic stimulation from LV pacing requiring device reprogramming (n=4). These complications were not influenced by the treatment assignment.

Table 1. Baseline Characteristics of Patient Population by Treatment Assignment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Echocardiographic-Guided CRT (n=110)</th>
<th>Routine Control CRT (n=77)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66±11</td>
<td>67±13</td>
<td>0.61</td>
</tr>
<tr>
<td>Male, %</td>
<td>70%</td>
<td>78%</td>
<td>0.29</td>
</tr>
<tr>
<td>NYHA HF classes II/III/IV, %</td>
<td>16/64/20</td>
<td>8/71/21</td>
<td>0.21</td>
</tr>
<tr>
<td>Ischemic heart disease, %</td>
<td>58%</td>
<td>67%</td>
<td>0.27</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>37%</td>
<td>36%</td>
<td>0.98</td>
</tr>
<tr>
<td>LVEF</td>
<td>26±6</td>
<td>26±7</td>
<td>0.80</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>140±59</td>
<td>144±63</td>
<td>0.57</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>186±68</td>
<td>192±73</td>
<td>0.73</td>
</tr>
<tr>
<td>ORS duration, ms</td>
<td>157±27</td>
<td>162±27</td>
<td>0.27</td>
</tr>
<tr>
<td>RV pacing, %</td>
<td>20</td>
<td>23</td>
<td>0.77</td>
</tr>
<tr>
<td>Atrial arrhythmias, %</td>
<td>25</td>
<td>27</td>
<td>0.89</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.2±0.4</td>
<td>1.3±0.6</td>
<td>0.20</td>
</tr>
</tbody>
</table>

CRT indicates cardiac resynchronization therapy; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA HF, New York Heart Association class of heart failure; and RV, right ventricle.

As expected after CRT, patients overall had significant improvement in New York Heart Association class (2.9±0.5 at baseline versus 2.0±0.8), LVEF (27±6% at baseline versus 37±12%), LV end-diastolic volume (187±73 mL at baseline versus 155±67 mL), and LVESV (140±61 mL at baseline versus 102±59 mL; P<0.001 for all).

Treatment Effects on Primary End points
During a mean follow-up of 1.8±1.3 years, 67 (36%) patients reached the primary end point. There were 30 deaths (15 in EG and 15 in routine arms; P=0.19) and 37 HF hospitalizations (16 in EG and 21 in routine arms; P=0.049). Six patients (3 in each arm) who were hospitalized for HF underwent the implantation of LV assist device, and 2 (1 in each arm) underwent heart transplantation. The event-free survival was significantly improved in the EG compared with the routine control group (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.28–0.82; P=0.006; Figure 2). The 2-year event-free survival was 77% in the EG versus 57% in the routine control group, indicating a 26% reduction in event rates.

The favorable treatment effect of EG group was retained when all the following predefined subgroups were tested for potential differences in CRT response: age, sex, type of cardiomyopathy, baseline LVEF, LVESV, and LV end-diastolic volume. When dichotomizing the cohort around the mean of QRS width (159 ms), an effect of treatment assignment on the primary end point was demonstrated with a more pronounced advantage of the EG over routine strategy in patients with narrower QRS complexes (HR, 0.35; 95% CI, 0.17–0.72; P=0.004 for QRS≤159 ms compared with HR, 0.59; 95% CI, 0.26–1.33; P=0.200 for QRS>159 ms).

LV Lead Position and Concordance With the Site of Latest Mechanical Activation
The site of latest mechanical activation among the 8 free-wall segments was as follows: basal anterolateral (4%), basal lateral...
in 12% of controls ($P=0.011$). When expanding to include segments immediately adjacent to site of latest activation, LV lead position was either exactly concordant or adjacent in 85% of patients in the EG study group, whereas this occurred fortuitously in 66% of controls ($P=0.010$). Pacing at LV regions concordant or adjacent to the site of latest mechanical activation conferred a significantly higher event-free survival compared with pacing at remote sites (HR, 0.40; 95% CI, 0.22–0.71; $P=0.002$; Figure 3, top). The 2-year event-free survival was 73% in concordant or adjacent versus 46% in remote LV lead positions, indicating a 37% reduction in event rates. Patients with either exact concordant or adjacent leads were grouped together because when analyzed separately outcomes in these subgroups were similar. Concordance of LV lead position with latest activation was also significantly associated with the composite secondary end point of death, LV assist device implantation, or heart transplantation (HR, 0.31; 95% CI, 0.15–0.67; $P=0.002$; Figure 3, bottom). The 2-year survival was 87% in concordant or adjacent versus 63% in remote LV lead positions, indicating a 27% reduction in event rates.

Figure 2. Kaplan–Meier plots of the results of the primary end point of freedom from heart failure hospitalization or death after cardiac resynchronization therapy (CRT), including all randomized patients with intention-to-treat analysis. Patients randomized to echocardiographic-guided left ventricular (LV) lead positioning strategy had a significantly more favorable clinical outcome in comparison to routinely treated patients.

Figure 3. Kaplan–Meier plots of clinical outcome results after cardiac resynchronization therapy (CRT) in patients with left ventricular (LV) leads concordant or adjacent to the segment of latest mechanical activation by speckle tracking echocardiography and LV lead position was achieved in 30% of patients in the EG study group and occurred fortuitously.

Table 2. Left Ventricular Lead Location by Fluoroscopy and Relationship to Site of Latest Mechanical Activation

<table>
<thead>
<tr>
<th>Echocardiographic-Guided CRT (n=96)</th>
<th>Routine Control CRT (n=69)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution of LV lead location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAO projection</td>
<td></td>
<td>0.867</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Lateral</td>
<td>40%</td>
<td>46%</td>
</tr>
<tr>
<td>Posterolateral</td>
<td>36%</td>
<td>30%</td>
</tr>
<tr>
<td>Posterior</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>RAO projection</td>
<td></td>
<td>0.114</td>
</tr>
<tr>
<td>Basal</td>
<td>39%</td>
<td>17%</td>
</tr>
<tr>
<td>Mid-ventricular</td>
<td>39%</td>
<td>43%</td>
</tr>
<tr>
<td>Apical</td>
<td>23%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Relationship of LV lead location to site of latest mechanical activation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exact concordance</td>
<td>30%</td>
<td>12%</td>
</tr>
<tr>
<td>Concordant or adjacent</td>
<td>85%</td>
<td>66%</td>
</tr>
<tr>
<td>Remote</td>
<td>15%</td>
<td>33%</td>
</tr>
</tbody>
</table>

CRT indicates cardiac resynchronization therapy; LAO, left anterior oblique; LV, left ventricle; and RAO, right anterior oblique.
There were 121 patients with follow-up echocardiograms available, attributable to either death occurring before the follow-up echocardiogram or failure to return for imaging. Significantly greater reverse remodeling demonstrated by LVESV decrease was seen in the EG versus routine arm and in concordant or adjacent versus remote lead locations (Table 3). Although the increase in LVEF was not significantly different between the EG versus routine patients, it was significantly greater in concordant or adjacent versus remote lead locations (Table 3). Using echocardiographic and clinical data (n=149), EG patients had significantly higher response rates defined by either ≥15% relative decrease in LVESV or ≥5% absolute increase in LVEF from baseline and no primary event (Table 3). Similarly, patients with LV leads concordant or adjacent to site of latest activation had significantly higher CRT response rates (Table 3).

**Effect of Resynchronization After CRT**

We examined effects of baseline dyssynchrony and resynchronization post hoc for mechanistic support of the effect of LV lead position in the 127 patients with repeat speckle tracking echocardiogram after CRT. Resynchronization was defined as a 50% decrease in radial dyssynchrony (difference in time to peak anteroseptal to posterior wall strain) from before to after CRT, providing that they had at least 95 ms dysynchrony measure at baseline. This cutoff of 95 ms was based on a subgroup analysis of the MADIT-CRT trial.23 Reduction in dyssynchrony was significantly greater in the EG versus the routine groups (∆−152±179 ms in EG group versus −91±173 ms in routine group; P=0.038; Figure 4A and 4B). Resynchronization was achieved in 61% of patients (70% in EG group versus 48% in routine group; P=0.021). It was significantly associated with freedom from HF hospitalization or death (HR, 0.28; 95% CI, 0.14–0.56; P<0.001; Figure 4C), as well as freedom from death, LV assist device implantation, or heart transplantation (HR, 0.30; 95% CI, 0.11–0.80; P=0.011).

**Discussion**

This randomized clinical trial of 2 different CRT delivery strategies demonstrated that LV lead placement directed toward the site of latest mechanical activation by speckle tracking echocardiography reduced the composite end point of HF hospitalization or death compared with routine fluoroscopic lead placement. The benefits of the EG approach were achieved without any increase in the duration of the implantation, radiation exposure, or procedural complications. Furthermore, patients in whom exact or adjacent concordance was achieved had an even more pronounced reduction in the primary end point, as well as in the important secondary end point of death, heart transplant, or LVAD. We also observed a greater benefit in LV reverse remodeling with the EG strategy and higher CRT response rates compared with the routine approach. Finally, achieving resynchronization of radial strain was associated with more favorable clinical outcomes providing mechanistic support for our findings.

The importance of the site of LV lead pacing during CRT has been previously demonstrated by our group and others26–30 with consistent results supporting the benefit of pacing the LV at the site of latest mechanical activation. Delgado et al showed an incremental benefit of LV lead positioning at the site of latest mechanical activation over the presence of dyssynchrony and absence of scar in a large series of CRT recipients with ischemic heart disease. Recently, the TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy) trial,31 which prospectively randomized patients to a targeted LV lead placement at or close to the site of latest mechanical activation versus nontargeted approach demonstrated superiority of the targeted approach for the primary end point of LVESV reduction. Conceivably independently, STARTER examined a similar hypothesis and demonstrated the superiority of a strategy of echocardiographic guidance during LV lead placement for CRT for the primary end point of death or HF hospitalization. Furthermore, STARTER extended these previous findings by adding resynchronization data to provide mechanistic support for our outcomes. The similar findings between TARGET and STARTER, as well as their consistency, with the results of several previous retrospective studies combine to support the importance of the LV pacing site for CRT.

The incremental benefit seen in the EG group is supported by a higher percentage of concordance between the LV pacing site and the site of latest mechanical activation, which in turn was associated with a higher rate of mechanical resynchronization. Pacing the latest site of mechanical activation is likely to reduce the total LV electromechanical activation time to a greater extent compared with pacing at other sites. Response to CRT has been shown to be multifactorial with likely determinants, including the presence of myocardial scar versus viable tissue.5,7 Nevertheless, our results demonstrate that, given a nonselected population of CRT recipients, a strategy of echocardiographic guidance is associated with improved clinical and echocardiographic outcomes compared with routine strategy. Although exact concordance could be achieved in only 30% of patients in EG group and fortuitously occurred in 12% of the routine group, adjacent concordance was achieved in the majority of patients in the EG group (85%) and conferred clinical and echocardiographic benefits.
These results suggest that there is relatively a large sweet spot for optimal LV pacing as previously suggested by animal studies, but emphasize that an EG approach has a measurable clinical benefit.

The favorable results after CRT in our patient population are in keeping with the results of published large randomized clinical trials. The 1-year event-free survival in our routine control group was comparable to the event rate of death or cardiovascular hospitalization in the treatment arms of both the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure and Cardiac Resynchronization-Heart Failure trials. Our present data therefore demonstrate an incremental benefit of the EG strategy beyond the expected benefits previously reported with routine CRT therapy. Achieving higher success rates of delivering the LV lead to its intended optimal pacing site beyond the constraints of the coronary venous anatomy could possibly be achieved in the future using minimally invasive epicardial or even transeptal endocardial approaches. Whether the higher LV lead concordance rates using these techniques would translate into additional improvement in outcomes after CRT remains to be demonstrated.

The present study has limitations. It was a single-center trial limited to 3 affiliated hospitals and 5 different implanting physicians. However, the clinical demographics of patients enrolled in STARTER were very similar to those enrolled in other large, randomized CRT trials. Still, the results of this study may need to be replicated in a multicenter setting. Although the number of patients enrolled in STARTER was relatively small, this study was powered to detect differences by treatment strategy in the primary end point of death or first HF hospitalization, as well as in several prespecified secondary end points. Furthermore, the consistency between our results and those of the TARGET trial support the validity of these findings. The number of patients included in the follow-up echocardiographic analyses represents about two third of the randomized patients. This is primarily driven by the fact that patients who had events before their follow-up echocardiogram could not be included in these analyses, although clinical outcomes were available. There are technical limitations to speckle tracking echocardiography, which requires adequate image quality for offline analysis. Our laboratory, which is experienced in this method, had intraobserver and interobserver variability averaging <10% for time to peak
strain measurements, although no test–retest variability was performed in this study. The TARGET study further supports that this method may be used successfully by others. Another limitation is that we did not prospectively evaluate and exclude regional scar for LV lead placement.3,11 The incremental value of avoiding scar in addition to targeting the site of latest LV mechanical activation is worthy of future study.

In conclusion, we found that a strategy of echocardiographic guidance to LV lead placement was superior to a routine approach in CRT device implantation in patients with LV dysfunction and mild, moderate, or severe HF symptoms for the primary end point of death or HF hospitalization. The strategy of echocardiographic guidance was also associated with improved echocardiographic response to CRT. This approach has practical implications for improving patient care for CRT recipients.

Sources of Funding
This study was supported in part by an American Heart Association grant-in-aid (grant no. 0855526D to Dr Saba).

Disclosures
Dr Saba receives research grant support from Medtronic, Boston Scientific, and St. Jude Medical; Dr Schwartzman receives research grant support from Medtronic and Boston Scientific; Dr Jain receives research grant support from Medtronic; Dr Adelstein receives research grant support from St. Jude Medical; Dr Gorcsan receives research grant support from Biotronik, GE, Toshiba, Medtronic, and St. Jude Medical. The other authors have no conflicts to report.

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_Circ Heart Fail._ 2013;6:427-434; originally published online March 8, 2013;
doi: 10.1161/CIRCHEARTFAILURE.112.000078
_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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