Left Ventricular Reverse Remodeling but Not Clinical Improvement Predicts Long-Term Survival After Cardiac Resynchronization Therapy

Cheuk-Man Yu, MD, FRCP; Gabe B. Bleeker, MD; Jeffrey Wing-Hong Fung, MRCP, FHKAM; Martin J. Schalij, MD, PhD; Qing Zhang, BM, MM; Ernst E. van der Wall, MD, PhD; Yat-Sun Chan, MRCP, FHKAM; Shun-Ling Kong, BN, MN; Jeroen J. Bax, MD, PhD

Background—In patients with severe heart failure and dilated cardiomyopathy, cardiac resynchronization therapy (CRT) improves left ventricular (LV) systolic function associated with LV reverse remodeling and favorable 1-year survival. However, it is unknown whether LV reverse remodeling translates into a better long-term prognosis and what extent of reverse remodeling is clinically relevant, which were investigated in this study.

Methods and Results—Patients (n=141) with advanced heart failure (mean ± SD age, 64 ± 11 years; 73% men) who received CRT were followed up for a mean ± SD of 695 ± 491 days. The extent of reduction in LV end-systolic volume (LVESV) at 3 to 6 months relative to baseline was examined for its predictive value on long-term clinical outcome. The cutoff value for LV reverse remodeling in predicting mortality was derived from the receiver operating characteristic curve. Then the relation between potential predictors of mortality and heart failure hospitalizations were compared by Kaplan-Meier survival analysis, followed by Cox regression analysis. There were 22 (15.6%) deaths, mostly due to heart failure or sudden cardiac death. The receiver operating characteristic curve found that a reduction in LVESV of ≥9.5% had a sensitivity of 70% and specificity of 70% in predicting all-cause mortality and of 87% and 69%, respectively, for cardiovascular mortality. With this cutoff value, there were 87 (61.7%) responders to reverse remodeling. In Kaplan-Meier survival analysis, responders had significantly lower all-cause mortality (6.9% versus 30.6%, log-rank χ²=13.26, P=0.0003), cardiovascular mortality (2.3% versus 24.1%, log-rank χ²=17.1, P<0.0001), and heart failure events (11.5% versus 33.3%, log-rank χ²=8.71, P=0.0032) than nonresponders. In the Cox regression analysis model, the change in LVESV was the single most important predictor of all-cause mortality (β=1.048, 95% confidence interval=1.019 to 1.078, P=0.001) and cardiovascular mortality (β=1.072, 95% confidence interval=1.033 to 1.112, P<0.001) mortality. Clinical parameters were unable to predict any outcome event.

Conclusions—A reduction in LVESV of 10% signifies clinically relevant reverse remodeling, which is a strong predictor of lower long-term mortality and heart failure events. This study suggests that assessing volumetric changes after an intervention in patients with heart failure provides information predictive of natural history outcomes. (Circulation. 2005;112:1580-1586.)

Key Words: pacing ■ prognosis ■ heart failure ■ echocardiography ■ mortality

Cardiac resynchronization therapy (CRT) is an established treatment for patients with advanced chronic heart failure with electromechanical delay.1-4 Apart from the beneficial effects of CRT on symptoms and exercise capacity, left ventricular (LV) reverse remodeling5-6 and improvement in clinical outcome were also observed in large, multicenter clinical trials.2-4 Whether the observed LV reverse remodeling is clinically relevant is unclear.

However, large heart failure trials demonstrated that drug therapy that limited or reversed LV remodeling resulted in improved long-term survival.7 In those studies, LV end-systolic volume (LVESV) was the strongest predictor of survival among clinical and echocardiographic parameters.8 For example, in the multicenter trials of angiotensin-converting enzyme (ACE) inhibitors (eg, the SAVE study), LV volumes were strong predictors of long-term mortality and cardiovascular events, independent of the effect of the ACE inhibitor captopril.9 The extent of LV reverse remodeling after CRT was reported to be a >20% reduction in LVESV, which is much larger than that observed in medical therapy for heart failure or sudden cardiac death. The receiver operating characteristic curve found that a reduction in LVESV of ≥9.5% had a sensitivity of 70% and specificity of 70% in predicting all-cause mortality and of 87% and 69%, respectively, for cardiovascular mortality. With this cutoff value, there were 87 (61.7%) responders to reverse remodeling. In Kaplan-Meier survival analysis, responders had significantly lower all-cause mortality (6.9% versus 30.6%, log-rank χ²=13.26, P=0.0003), cardiovascular mortality (2.3% versus 24.1%, log-rank χ²=17.1, P<0.0001), and heart failure events (11.5% versus 33.3%, log-rank χ²=8.71, P=0.0032) than nonresponders. In the Cox regression analysis model, the change in LVESV was the single most important predictor of all-cause mortality (β=1.048, 95% confidence interval=1.019 to 1.078, P=0.001) and cardiovascular mortality (β=1.072, 95% confidence interval=1.033 to 1.112, P<0.001) mortality. Clinical parameters were unable to predict any outcome event.

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failure. This phenomenon was observed in the first 3 to 6 months after CRT. Because the mechanism of benefit of device therapy is somewhat different from that of medical therapy, it is currently unclear whether the LV reverse remodeling observed in patients undergoing CRT is predictive of improved long-term clinical outcome. Moreover, what extent of LV reverse remodeling is needed to result in improved survival is also unclear. Therefore, the aims of the current study were (1) to examine whether the LV reverse remodeling observed at 3 to 6 months is associated with better long-term clinical outcome in heart failure patients who received CRT and (2) to determine what extent of LV reverse remodeling predicts improved outcome in this population.

Methods

Patients

This is a prospective, follow-up study that involved 2 university hospitals. The study population included 141 heart failure patients (mean±SD age, 64±11 years; 73% men) who underwent CRT and had a baseline and a 3- to 6-month follow-up echocardiographic study to assess potential LV reverse remodeling. The inclusion criteria included severe symptomatic heart failure despite optimized medical therapy, LV systolic dysfunction with an LV ejection fraction (EF) <40%, and QRS duration >120 ms. Serial echocardiographic studies with tissue Doppler imaging (TDI) were performed before and 3 to 6 months after CRT to assess LV reverse remodeling. These patients had been prescribed optimal medical therapy before consideration for CRT. Medication use was unchanged within the first 6 months of CRT, and any changes afterward were avoided unless clinically mandatory. Clinical assessments were performed at the same times, including New York Heart Association (NYHA) class, Minnesota Living With Heart Failure quality-of-life questionnaire, and a 6-minute hall-walk distance. Two patients died (1 refractory heart failure, 1 sudden cardiac death) before the 3- to 6-month echocardiographic follow-up; therefore, data for these patients were excluded from the current analysis. The study was approved and conducted in compliance with the regulations of the local ethics committees of both institutions, and informed consent was obtained from all patients.

Pacemaker Implantation

CRT devices were implanted as previously described. The LV pacing lead was inserted by a transvenous approach through the coronary sinus into either the lateral or posterolateral cardiac vein whenever possible. All patients who received CRT devices had biventricular stimulation of the heart with implantation of right ventricular leads.

Echocardiography

Standard echocardiography, including TDI studies, was performed with commercially available equipment (Vivid 7, GE Vingmed Ultrasound). The LV end-diastolic volume (LVEDV), LVESV, and LV EF were assessed by the biplane Simpson’s equation in apical 4-chamber and 2-chamber views. The interobserver and interobserver variabilities for volumetric assessment were 4% and 5%, respectively. The severity of mitral regurgitation was assessed by the percentage jet area relative to left atrial size in the apical 4-chamber view. At least 3 consecutive beats of sinus rhythm were measured, and the mean was calculated.

TDI was performed in the apical 4-chamber view for long-axis motion of the ventricle, as previously described. Two-dimensional echocardiography with TDI color-imaging views was optimized for pulse repetition frequency, color saturation, sector size, and depth, allowing the highest possible frame rate. At least 3 consecutive beats were stored, and the images were analyzed off-line with a customized software package (EchoPac 6.1 for PC, GE Vingmed Ultrasound). The myocardial velocity curves were constructed off-line, and the septal-to-lateral delay at the basal segments was measured as an index of systolic dysynchrony, with the beginning of the QRS complex as the reference point.

Long-Term Follow-Up and Assessment of Cardiovascular Events

All patients were followed up regularly (typically every 2 to 3 months) in the heart failure clinic, with regular clinical assessment, ECG, and device interrogation to ensure that biventricular pacing was being maintained. Only outcomes occurring after the 3- to 6-month follow-up echocardiograms were related to echocardiographic changes in LV volume. The occurrence of cardiovascular events was adjudicated by cardiologists blinded to the echocardiographic findings. The cause of death was ascertained by reviewing the clinical record and test results, report of close relatives, and postmortem findings. For cardiovascular hospitalization, the diagnosis of heart failure was based on clinical symptoms (limitation of activity, fatigue, and dyspnea or orthopnea), physical signs (edema, elevated jugular venous pressure, rales, or third heart sound with gallop), or radiological evidence of pulmonary congestion. Acute coronary syndrome was defined according to current guidelines based on the presence of typical chest pain or discomfort and elevation of cardiac enzymes, such as creatine kinase-MB, troponin I, or troponin T. ECG changes were not used as a criterion, because these patients had baseline left bundle branch block and subsequent ventricular pacing, which hampers assessment of myocardial ischemia or infarction.

Statistical Analysis

Results are presented as mean±SD. Data were compared with paired or unpaired Student t test when appropriate. Comparison of proportions was performed by χ² analysis with Yates’ correction. Receiver-operating-characteristic (ROC) curves were analyzed to assess the best cutoff value of LVESV to predict mortality. Life table–estimated actuarial survival was calculated by Kaplan-Meier curves, wherein the log-rank χ² values were presented. Cox regression multivariable survival analysis was used to evaluate the predictive value of multiple factors on mortality. The data from patients in this dataset have not been published previously. P<0.05 was considered statistically significant.

Results

Among 141 patients, 12 were in NYHA class II, 106 in class III, and 23 in class IV. The cause of heart failure was ischemic in 68 (48%) and nonischemic in 73 (52%) patients. Medications included diuretics in nearly all patients, ACE inhibitors or angiotensin receptor blockers in 91%, β-blockers in 75%, spironolactone in 49%, and digoxin in 16%. Echocardiographic studies demonstrated LV reverse remodeling 3 to 6 months after CRT. The LVESV decreased significantly by 17.6±18.4% (P<0.001), whereas LVEDV decreased by 11.0±14.3% (P<0.001). LV EF increased by 6.3±6.9% (P<0.001).

Clinical Outcome of Patients During Long-Term Follow-Up

The mean duration of follow-up was 695±491 days (range, 90 to 1922). There were 22 (15.6%) deaths. The causes of death included heart failure in 9 patients, sudden cardiac death in 6, myocardial infarction in 1, cerebrovascular accident in 1, and noncardiac-related deaths in 5; thus, 17 patients died of cardiovascular causes. Table 1 compares the clinical and echocardiographic parameters between survivors and those who died during follow-up. All baseline characteristics were comparable except for a slightly higher mean NYHA...
class in the patients who died during follow-up. Also, the extent of LV dysynchrony at baseline was larger in the survivors. The reduction in clinical parameters (NYHA class, quality-of-life score, and 6-minute walking distance) tended to improve more in survivors, although the differences were not statistically significant. The extent of LV reverse remodeling and improvement in LV EF were significantly larger in survivors. The mean reduction in LVESV in survivors was 19.8 ± 17.7% compared with 5.9 ± 18.0% (P = 0.001) in those who died during follow-up; the mean reduction of LVEDV in survivors was 12.4 ± 14.2% versus 3.0 ± 12.6% (P = 0.004) in the patients who died during follow-up. Nineteen patients were hospitalized for decompensated heart failure. Twenty-one were hospitalized for other cardiovascular causes, including acute coronary syndrome in 7, arrhythmias in 11, stroke in 2, and percutaneous coronary intervention in 1.

What Extent of LV Reverse Remodeling Predicts Survival?

This study attempted to determine a clinically useful cutoff value for the change in LVESV to assess whether LV reverse remodeling after CRT can predict a favorable long-term clinical outcome. Based on ROC curve analysis, a reduction in LVESV of 9.5% was identified as the optimal cutoff value to predict long-term survival (area under the curve [AUC], 0.711; P = 0.002; see Figure 1A). With this cutoff value, a sensitivity and specificity of 70% were obtained to predict all-cause mortality. Similarly, a reduction in LVESV of 9.5% had a sensitivity and specificity of 87% and 69%, respectively, to predict cardiovascular mortality (AUC, 0.774; P = 0.001; see Figure 1B). Furthermore, the change in LVESV was consistently better than the change in LVEDV in predicting all-cause and cardiovascular mortality (Figure 1A and 1B). The AUCs for LVEDV to predict all-cause and cardiovascular mortality were 0.688 (P = 0.005) and 0.720 (P = 0.005), respectively.

LV Reverse Remodeling After CRT and Prediction of Long-Term Prognosis

Based on the aforementioned findings, a reduction in LVESV of ≥10% was used as the cutoff value to define patients with clinically relevant LV reverse remodeling. There were 87 (61.7%) patients with a reduction in LVESV of ≥10% (called “responders”) and 54 (38.3%) patients with <10% reduction in LVESV (called “nonresponders”). During long-term follow-up, 81 of 87 (93.1%) responders to LV reverse remodeling survived, compared with only 38 of 54 (70.4%) nonresponders (χ² = 13.1, P < 0.001). Kaplan-Meier life-table survival analysis demonstrated that responders to LV reverse remodeling had significantly lower all-cause mortality (n = 22 who had the censored event, 6.9% versus 30.6%; log-rank χ² = 13.26, P = 0.0003; Figure 2A) and cardiovascular mortality (n = 17, 2.3% versus 24.1%; log-rank χ² = 17.1, P < 0.0001) compared with nonresponders. Furthermore, patients with reverse remodeling had a lower rate of heart failure events (both fatal and nonfatal; n = 28, 11.5% versus 33.3%; log-rank χ² = 8.71, P = 0.0032; Figure 2B), all-cause mortality or heart failure hospitalization (n = 33 who had the censored event, 13.8% versus 38.9%, log-rank χ² = 9.92, P = 0.0016) (Figure 2C), and the composite end point of all-cause mortality or cardiovascular hospitalization (n = 54 who had the censored event, 29.1% versus 55.8%; log-rank χ² = 9.18, P = 0.0025).

Baseline assessment of LV dyssynchrony was also compared with long-term survival. It was observed that survival was associated with significantly more severe dyssynchrony (P < 0.001) (Table 1). Patients who had a baseline dyssynchrony > 60 ms had a lower all-cause mortality (6.6% versus 21.8%; log-rank χ² = 4.46, P = 0.03).

### TABLE 1. Comparison of Baseline Clinical and Echocardiographic Parameters Between Survivors and Nonsurvivors After CRT

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n = 119)</th>
<th>Nonsurvivors (n = 22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64 ± 11</td>
<td>65 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female, %</td>
<td>74/26</td>
<td>68/32</td>
<td>χ² = 0.39, P = NS</td>
</tr>
<tr>
<td>Ischemic vs nonischemic</td>
<td>57 vs 62</td>
<td>11 vs 11</td>
<td>NS</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>157 ± 38</td>
<td>151 ± 34</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.0 ± 0.5</td>
<td>3.3 ± 0.5</td>
<td>0.038</td>
</tr>
<tr>
<td>6-Minute hall walk, m</td>
<td>302 ± 124</td>
<td>278 ± 142</td>
<td>NS</td>
</tr>
<tr>
<td>Quality-of-life score</td>
<td>37 ± 21</td>
<td>39 ± 20</td>
<td>NS</td>
</tr>
<tr>
<td>LVESV, cm³</td>
<td>165 ± 67</td>
<td>181 ± 77</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDV, cm³</td>
<td>217 ± 76</td>
<td>232 ± 60</td>
<td>NS</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>24.9 ± 7.3</td>
<td>24.0 ± 11.2</td>
<td>NS</td>
</tr>
<tr>
<td>LV dyssynchrony, ms</td>
<td>62.9 ± 47.3</td>
<td>28.3 ± 23.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Medications, %

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>98</td>
<td>100</td>
<td>χ² = 0.02, P = NS</td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin receptor blocker</td>
<td>90</td>
<td>95</td>
<td>χ² = 0.34, P = NS</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>75</td>
<td>77</td>
<td>χ² = 0.03, P = NS</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>48</td>
<td>55</td>
<td>χ² = 0.58, P = NS</td>
</tr>
<tr>
<td>Digoxin</td>
<td>16</td>
<td>18</td>
<td>χ² = 0.08, P = NS</td>
</tr>
</tbody>
</table>
Clinical parameters were evaluated for their predictive value for mortality. However, only NYHA class at baseline was significantly higher (P<0.038) in those who died. There was no difference in 6-minute hall-walk distance or quality-of-life score between the 2 groups or the changes in these parameters 3 to 6 months after CRT (Table 1). Therefore, clinical parameters of heart failure assessment were unable to predict long-term outcome in these patients.

The predictive value of clinical/echocardiographic parameters for all-cause mortality was compared by the Cox regression multivariable analysis model. It was found that the reduction in LVESV was the only independent predictor of all-cause mortality (β=1.048, 95% confidence interval=1.019 to 1.078, P<0.001) (Table 2) and cardiovascular mortality (β=1.072, 95% confidence interval=1.033 to 1.112, P<0.001), whereas LV dyssynchrony at baseline, cause (ischemic versus nonischemic), and other clinical or echocardiographic parameters listed in Table 1 were insignificant.

Discussion
This study examined the relation between LV reverse remodeling and long-term clinical outcome. Patients who died during follow-up exhibited less LV reverse remodeling compared with survivors. Based on the ROC curve, a cutoff value of <10% reduction in LVESV yielded the best prediction of all-cause and cardiovascular mortality. In addition to LV reverse remodeling, baseline LV dyssynchrony was predictive of survival. On multivariable analysis, however, LV reverse remodeling was the best predictor of long-term survival. Of note, improvement in clinical status 3 to 6 months after CRT was not predictive of long-term clinical outcome.

Definition of LV Reverse Remodeling After CRT and Its Prognostic Significance
Previous studies reported that CRT not only improves clinical status (NYHA class, quality of life, and exercise capacity) but also reverses LV remodeling and improves systolic function. However, the lack of a favorable response to CRT was observed in approximately one third of patients in clinical studies. The definition of nonresponders is difficult but has been proposed to be the lack of a clinical response or the absence of LV reverse remodeling. Initial studies arbitrarily defined responders to LV reverse remodeling by a reduction in LVESV of >15% 3 to 6 months after CRT. However, no study examined the potential link between LV reverse remodeling and long-term clinical outcome, and it was not known whether such an arbitrarily defined cutoff value of 15% was clinically relevant. Because improvement in LVESV represents favorable structural and functional changes in the LV after CRT, this may predict a favorable long-term clinical outcome. In pharmacological trials, LV reverse remodeling (in particular, a reduction of LVESV) was associated with a better prognosis, in particular in clinical trials with ACE inhibitors and β-blockers. Because CRT benefits cardiac function by a different mechanism from that which primarily involves coordination of regional contraction, rather than direct intervention in neurohormonal pathways, the possibility that a reduction in LV volume in patients who receive CRT would predict better long-term clinical outcome has not been explored.

The present study is the largest to directly examine the relation between LV reverse remodeling and outcomes in patients with heart failure in the contemporary treatment era. A new cutoff value derived from the ROC curves of mortality prediction concluded that a reduction in LVESV of ≥10% was clinically relevant, because this value has a high sensitivity and specificity for prediction of long-term all-cause and cardiovascular mortality. Furthermore, this cutoff value of LV reverse remodeling also predicts heart failure events and composite end points of cardiovascular hospitalization or mortality. Therefore, volumetric assessment by echocardiography is not only a surrogate marker of a favorable cardiac response to CRT but also an objective measure that predicts long-term clinical outcome.

Lack of Predictive Value of Clinical Parameters on Long-Term Outcome
Another important observation in the current study is the lack of predictive value of baseline clinical status or
change in clinical status after CRT on long-term clinical outcome. The clinical parameters in the present study included NYHA class, 6-minute hall-walk distance, and quality-of-life score. These parameters are frequently used as standard "soft" clinical end points for assessment of treatment efficacy in heart failure trials, including CRT,1–4 and have been used as criteria to assess "clinical" response to CRT.20 However, in the present study, improvements in quality of life and walking distance were not significantly different between those who survived and those who died.

Figure 2. Kaplan-Meier curves for all-cause mortality (A), fatal and nonfatal heart failure (CHF) hospitalizations (B), and mortality or heart failure hospitalizations (C) dichotomized by the status of LV reverse remodeling. Responders are defined as those with a reduction of LVESV (LVVs) of ≥10%, whereas nonresponders are those with a <10% reduction in LVESV.
during long-term follow-up, whereas the difference in NYHA class was only marginal. Therefore, evaluation of the volumetric response provides information complementary to clinical assessment, especially in predicting long-term clinical outcome after CRT. Because measurement of LV volume was performed off-line in a blinded fashion, the influence of a placebo effect was minimized.

**Clinical Implications and Conclusion**

The present study established the missing link between the LV reverse remodeling response and long-term clinical outcome after CRT. A reduction in LV volume consistently translated into better clinical outcome, regardless of the modality of therapy (medical or device). The results indicate that LV reverse remodeling 3 to 6 months after CRT not only explains the structural and functional benefits of the resynchronized ventricle but also implies the translation of cardiac structural benefit into a lower clinical “hard” event rate. Of note, improvement in clinical parameters was not predictive of long-term survival. Baseline LV dyssynchrony was predictive of long-term survival, but multivariable analysis identified reverse LV remodeling as the best predictor of long-term survival. Accordingly, the LV reverse-remodeling response is a useful criterion that determines long-term clinical outcome and provides complementary information to clinical parameters such as NYHA class, 6-minute walking distance, or quality-of-life score. Moreover, ROC curve analysis demonstrated that a 10% improvement in LVEVS had the best predictive accuracy for long-term survival and may be considered an objective measure to assess clinically useful responses to CRT in future clinical trials.

**Limitations of the Study**

In this study, the number of events was relatively small. This probably reflects the benefit of CRT in the improvement of clinical outcome, which was recently proven by the CARE-HF study. However, with the relatively large number of patients undergoing CRT, we were able to achieve the objective of examining and confirming that LV reverse remodeling is an independent predictor of long-term clinical outcome. Large, multicenter trials are needed to confirm our findings and validate whether a 10% reduction in LVEVS is the best volumetric parameter to predict favorable clinical outcome.

**TABLE 2. Comparison of Changes in Clinical and Echocardiographic Parameters Between Survivors and Nonsurvivors After CRT**

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<th>Nonsurvivors (n = 22)</th>
<th>P</th>
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<tbody>
<tr>
<td>ΔNYHA class</td>
<td>−0.87 ± 0.66</td>
<td>−0.75 ± 0.79</td>
<td>NS</td>
</tr>
<tr>
<td>Δ6-Minute hall walk, m</td>
<td>85 ± 104</td>
<td>56 ± 103</td>
<td></td>
</tr>
<tr>
<td>ΔQuality-of-life score</td>
<td>−13.7 ± 17.5</td>
<td>−12.0 ± 20.0</td>
<td>NS</td>
</tr>
<tr>
<td>ΔLVEVS, %</td>
<td>−19.8 ± 17.7</td>
<td>−5.9 ± 18.0</td>
<td>0.001</td>
</tr>
<tr>
<td>ΔLVEDV, %</td>
<td>−12.4 ± 14.2</td>
<td>−3.0 ± 12.6</td>
<td>0.004</td>
</tr>
<tr>
<td>ΔLV EF, %</td>
<td>7.0 ± 6.7</td>
<td>2.8 ± 7.4</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Δ indicates change.


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