Effect of Cardiac Resynchronization Therapy on Left Ventricular Size and Function in Chronic Heart Failure

Martin G. St John Sutton, MD; Ted Plappert; William T. Abraham, MD; Andrew L. Smith, MD; David B. DeLurgio, MD; Angel R. Leon, MD; Evan Loh, MD; Dusan Z. Kocovic, MD; Westby G. Fisher, MD; Myrvin Ellestad, MD; John Messenger, MD; Kristin Kruger; Kathryn E. Hilpisch; Michael R.S. Hill, PhD; for the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group

Background—Cardiac resynchronization therapy (CRT) has recently emerged as an effective treatment for patients with moderate to severe systolic heart failure and ventricular dyssynchrony. The purpose of the present study was to determine whether improvements in left ventricular (LV) size and function were associated with CRT.

Methods and Results—Doppler echocardiograms were obtained at baseline and at 3 and 6 months after therapy in 323 patients enrolled in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial. Of these, 172 patients were randomized to CRT on and 151 patients to CRT off. Measurements were made of LV end-diastolic and end-systolic volumes, ejection fraction, LV mass, severity of mitral regurgitation (MR), peak transmitral velocities during early (E-wave) and late (A-wave) diastolic filling, and the myocardial performance index. At 6 months, CRT was associated with reduced end-diastolic and end-systolic volumes (both \( P < 0.001 \)), reduced LV mass (\( P < 0.01 \)), increased ejection fraction (\( P < 0.001 \)), reduced MR (\( P < 0.001 \)), and improved myocardial performance index (\( P < 0.001 \)) compared with control. \( \beta \)-Blocker treatment status did not influence the effect of CRT. Improvements with CRT were greater in patients with a nonischemic versus ischemic cause of heart failure.

Conclusions—CRT in patients with moderate-to-severe heart failure who were treated with optimal medical therapy is associated with reverse LV remodeling, improved systolic and diastolic function, and decreased MR. LV remodeling likely contributes to the symptomatic benefits of CRT and may herald improved longer-term survival. (Circulation. 2003;107:1985-1990.)

Key Words: heart failure ■ echocardiography ■ remodeling ■ pacing

Heart failure (HF) is associated with substantial mortality and morbidity and remains the most common hospital discharge diagnosis in patients >65 years of age.1 Development of HF is characterized by progressive left ventricular (LV) remodeling and deteriorating function. Cardiac resynchronization therapy (CRT), delivered via atrial-synchronous biventricular pacing, has emerged as an effective treatment for moderate-to-severe HF patients with ventricular dyssynchrony. In particular, CRT has been shown to improve symptom class, exercise capacity, and quality of life, even in patients who are already receiving optimal pharmacological therapies.2 Although these favorable clinical effects of CRT in chronic HF are now proven, the mechanisms of benefit remain poorly understood. Some investigators have suggested a favorable effect of CRT on LV size and function. However, previous studies analyzing the effects of CRT on echocardiographic parameters have been small, uncontrolled, or both.3–5

The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study was a prospective, double-blind, randomized, controlled trial of patients on optimal medical HF treatment regimen who were randomized to CRT or no CRT and who were followed for a minimum of 6 months. The purpose of the present study was to determine whether objective changes in LV size and function were associated with CRT in the MIRACLE trial and accompanied the observed patient benefits.
Methods

Study Population

The MIRACLE trial compared the effects of CRT versus a control group on 3 primary end points: New York Heart Association (NYHA) symptom class, quality of life (Minnesota Living with Heart Failure Questionnaire), and exercise capacity (6-minute hall walk distance) in patients with NYHA symptom class III/IV chronic HF. All patients were on an optimal HF medical regimen that was unchanged for a minimum period of 1 month in the case of diuretics, ACE inhibitors, and digitalis and for 3 months for β-blockers and who had a QRS duration ≥ 130 ms, an LV end-diastolic diameter ≥ 55 mm by echocardiography, and ejection fraction (EF) ≥ 35%. The institutional review board at each center approved the study protocol, and all patients gave written informed consent.

Study Design

All patients (n = 453) who had a device successfully implanted were randomized either to the control group (biventricular pacing turned off, n = 225) or to the CRT group (biventricular pacing turned on, n = 228). The pacing mode (pacing on or off) was unknown to the patients and to the HF investigators. Timing of the delay between sensed atrial activity and delivery of the biventricular pacing was adjusted to maximize LV filling time using Doppler echocardiography and the method developed by Ritter.6

Doppler echocardiograms were obtained in all patients at baseline before device implantation and were repeated at the 3 and 6-month follow-up visits when the primary end points were reevaluated. Doppler echocardiograms were analyzed in a core laboratory by a single sonographer who was blinded to treatment group. Although ventricular pacing pulses were often observed on the simultaneously recorded ECG, each study was analyzed individually and without reference to echocardiographic images or measurements from other visits. Videotaped echocardiograms were analyzed on a TomTec computer workstation to obtain end-diastolic (EDV) and end-systolic (ESV) LV volumes using the method of discs.7,8 EF was calculated as the time difference between the onset of forward flow in the right ventricular and LV outflow tracts and was used as an indicator of synchrony of right ventricular and LV contraction. Cardiac index was estimated as the product of LV outflow tract velocity time integral and cross-sectional area of the LV outflow tract.

LV volumes, EF, severity of MR, and measurements of diastolic function were reassessed at 3 and 6 months to characterize the time-dependent changes in LV remodeling in the CRT group versus the control group. Correlations between changes in echocardiographic measurements of LV size and function and the changes in primary end points were assessed.

Statistical Methods

The baseline characteristics of the 2 groups (CRT versus control) were compared using an unpaired t test for continuous variables and a χ² test for discrete variables. Doppler echocardiographic measurements are summarized as medians along with the 95% confidence interval for the median. Nonparametric tests were used to assess the within-group and between-group differences of the changes in measurements from baseline to the 3- and 6-month follow-up. The Spearman rank correlation statistic was used for comparing the changes in echocardiographic parameters and the change in clinical end points. Multivariate ANOVA methods were used to identify whether group differences were still significant after adjusting for baseline echocardiographic measurements. P<0.05 was considered significant for all tests. All statistical analyses were conducted using software from SAS.

Results

Of the 453 patients who were enrolled and randomized, 323 patients had echocardiograms analyzable for volumes and EF at all 3 time points. Of this study cohort, 151 patients were randomized to the control group and 172 were randomized to the CRT group. Baseline demographics were not significantly different between the 2 groups (Table 1). ACE inhibitors or angiotensin-receptor blockers were used in >90% of patients, and β-adrenergic receptor blockers were administered in >55% patients (Table 1). Echocardiographic measurements at baseline and differences between baseline and 3 and 6-month follow-ups for the control and CRT groups are shown in Table 2.

Significant reductions in LVEDV (P<0.001) and LVESV (P<0.001) occurred at 3 months in the CRT group compared with the control group, and reductions in LVEDV and LVESV continued between 3 and 6 months in the CRT group (Figure 1). No changes from baseline were observed in patients in the control group at 3 or 6 months of follow-up.
The reverse remodeling and reduction in LV volumes observed in the CRT group was accompanied by a significant improvement in EF compared with the control group at 3 months (2.3% versus 0.6%; \( P < 0.01 \)), with further improvement at six months (3.6% versus 0.4%; \( P < 0.001 \); Figure 2).

In the CRT group, severity of MR decreased significantly at 3 months (2.1 cm² versus 0.1 cm² jet area; \( P < 0.01 \)) and at 6 months (2.5 cm² versus 0.5 cm² jet area; \( P < 0.001 \)). No change in MR was observed in the control group (Figure 2).

In the CRT group, cardiac index increased from baseline to 6 months (0.11 L · min⁻¹ · m⁻²; \( P < 0.05 \)), but cardiac index declined in the control group (−0.03 L · min⁻¹ · m⁻²; Table 2). LV mass decreased significantly from baseline to 6 months in the CRT group compared with the control group (−12.0 g versus 10.6 g; \( P < 0.01 \); Table 2). LV shape did not change significantly at 6 months in either group (Table 2).

Optimization of atrioventricular delay and synchronous biventricular pacing resulted in significant prolongation of normalized LV filling time (\( P < 0.001 \); Figure 3), shortening of the IVMD (\( P < 0.001 \); Figure 3), and shortening of the ICT (\( P < 0.05 \), Table 2) between baseline and the 3 and 6-month follow-ups in the CRT group versus control. Although diastolic filling time was prolonged, neither peak A-wave velocity, E/A wave velocity ratio, nor isovolumic relaxation time changed significantly in the CRT group or in the control group from baseline to 6 months. Deceleration slope and deceleration time of the E-wave (during rapid filling) increased significantly at 3 and 6 months in the CRT group (\( P < 0.05 \)) but did not change in the control group (Table 2). The myocardial performance index improved significantly at 3 and 6 months (\( P < 0.001 \)) in the CRT group but did not change in the control group (Table 2). After adjusting for baseline echocardiographic parameters in a multivariate analysis, the results were unchanged, demonstrating a significant treatment effect.

Significant but weak correlations were observed between changes in clinical outcomes and changes in echocardiographic parameters. Change in NYHA class was correlated with changes in cardiac index and changes in normalized LV filling time. Change in NYHA class was not correlated with changes in LV mass, MR jet area, or LV shape.
with a change in MR ($r=0.15; P=0.03$), IVMD ($r=0.12; P=0.05$), ICT ($r=0.17; P=0.006$), and LVEDV ($r=0.13; P=0.02$). Change in quality-of-life score was correlated with change in MR ($r=0.14; P=0.03$) and IVMD ($r=0.19; P=0.003$), and change in 6-minute hall walk distance was correlated with MR ($r=0.16; P=0.02$), ICT ($r=0.20; P=0.001$), and EF ($r=0.15; P=0.009$).

Significant reverse remodeling and improvement in EF occurred in patients with HF due to ischemic and nonischemic LV dysfunction. However, the changes in LVEDV and EF from baseline to 6 months in the CRT group were significantly (2-fold) greater in patients with nonischemic LV dysfunction than in patients with equivalent LV dysfunction due to ischemic heart disease (Figure 4). Importantly, changes in LVEDV and EF in the CRT group were independent of β-adrenergic receptor blocking drug therapy (Figure 4). Baseline differences observed between subgroups are indicated in Figure 4.

**Discussion**

The major finding of this echocardiographic analysis from the MIRACLE study was that CRT caused significant reverse LV remodeling. That is, CRT produced significant improvement in LV size and function in these failing hearts. These beneficial effects occurred in NYHA class III and IV HF patients already receiving a stable and optimal medical regimen for HF. Reversed LV remodeling induced by CRT was associated with improved NYHA functional class, exercise capacity, and quality of life and may explain the symptomatic improvements reported in other small, nonrandomized biventricular pacing trials in HF.9–11

The MIRACLE study demonstrated that CRT with optimization of atrioventricular delay was associated with improved exercise capacity and NYHA symptom class in patients with moderate-to-severe HF on optimal medical regimens. The echocardiographic observations indicate that these clinical improvements were driven by improving ventricular function and synchrony. The rationales were that (1) prolonging LV filling time would improve LVEF; (2) that shortening IVMD would coordinate right ventricular and LV contraction, improve interventricular dyssynchrony, and optimize ventricular interaction; and (3) that shortening ICT would coordinate LV contraction and improve intraventricular dyssynchrony.5 LV filling time was significantly prolonged and IVMD and ICT were significantly shortened in the CRT group. None of these parameters changed in the control group. The mechanisms for the structural and functional changes associated with CRT are complex, but they are likely mediated by the combination of optimal atrioventricular coupling and improved intra- and interventricular synchrony, as evidenced by the observed changes in objective echocardiographic measurements.

Evidence for reverse remodeling in the CRT patients was not subtle. There was significant reduction in LVEDV and
CRT with optimized atrioventricular delay prolonged LV filling and reduced LV dyssynchrony by shortening IVMD, although transmirtal peak velocities during rapid filling and atrial contraction did not change. However, the E-wave deceleration slope significantly decreased and the deceleration time was significantly prolonged in the CRT group, which is consistent with improved diastolic function, compared with no change in the control group. Furthermore, myocardial performance index improved significantly in the CRT patients at 6 months but did not change in the control group.

Measurements of LV performance (EF and velocity of circumferential fiber shortening) have previously not correlated with exercise capacity, exercise duration, or peak myocardial oxygen consumption (peak $\dot{V}O_2$) in HF patients. Similarly, in the present study, correlations between clinical outcomes and echocardiographic parameters were weak. The change in NYHA class was related to changes in MR, IVMD, ICT, and LVEDV; change in quality-of-life score was associated with changes in MR and IVMD; and change in 6-minute hall walk distance was correlated with MR, ICT, and EF. These results suggest that improvements in clinical outcomes predominate in patients with improvements in echocardiographic parameters.

Quality of life, functional status, and exercise capacity improved with CRT, regardless of the cause of HF (ischemic versus nonischemic). However, improvement in the echocardiographic parameters of size and function in the nonischemic HF patients was greater than that occurring in the ischemic HF patients. This finding is similar to the effects of $\beta$-blocker treatment in patients observed in ischemic versus nonischemic HF.

CRT produced LV reverse remodeling, regardless of $\beta$-blocker treatment status. Control patients receiving $\beta$-blocker treatment showed no further improvement in LV size or function at 6 months, even though both groups received $\beta$-blockers for at least 3 months before enrollment into the MIRACLE study. In contrast, CRT patients taking $\beta$-blockers exhibited a highly significant improvement in LV remodeling. The effects of CRT on LV remodeling seem to be complementary to those seen with $\beta$-blockade.

In conclusion, CRT in patients with moderate-to-severe HF is associated with reverse LV remodeling, as evidenced by reduction in LV volumes, improved systolic and diastolic function, and decreased severity of MR. These structural and functional changes in the LV occur by 3 months after initiation of CRT and are sustained at 6 months, with associated improvements in NYHA symptom class, quality of life, and functional capacity. Importantly, major LV remodeling occurred in patients already on optimal HF medical therapy, including ACE inhibitors or angiotensin-receptor blockers, $\beta$-adrenergic receptor blockers, and diuretics. Reverse remodeling occurred regardless of the cause of HF but was more extensive in patients with nonischemic compared with ischemic LV dysfunction. This progressive and sustained reverse remodeling is very likely the cause for the symptomatic benefits and may herald improved event-free long-term survival with CRT in HF patients with ventricular dyssynchrony.
Heart Failure Etiology

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Use of β-blockers

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**Figure 4.** Graphs at top compare median changes from baseline with 2-sided 95% confidence intervals by cause of HF. Graphs at bottom compare median changes from baseline with 2-sided 95% confidence intervals by whether patient was on a therapeutic dose of β-blocker treatment at least 3 months before randomization. Baseline median and 95% confidence intervals are provided for each group. Control group is indicated by open circles, CRT group by diamonds. *P<0.05, CRT vs control within subgroup. †P<0.05, treatment versus treatment between subgroup.

**Acknowledgment**

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**References**

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for the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group

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