Sustained Reverse Left Ventricular Structural Remodeling With Cardiac Resynchronization at One Year Is a Function of Etiology
Quantitative Doppler Echocardiographic Evidence From the Multicenter InSync Randomized Clinical Evaluation (MIRACLE)

Martin G. St John Sutton, MB, FRCP; Ted Plappert, CVT; Kathryn E. Hilpisch, BS; William T. Abraham, MD; David L. Hayes, MD; Edward Chinchoy, PhD

Background—Cardiac resynchronization therapy (CRT) is an effective therapy for patients with moderate to severe heart failure and prolonged QRS duration. The purpose of this study was to determine whether reverse left ventricular (LV) remodeling and symptomatic benefit from CRT were sustained at 12 months, and if so, in what proportion of patients this occurred.

Methods and Results—Serial Doppler echocardiograms were obtained at baseline and 6 and 12 months after CRT in 228 patients enrolled in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial. Measurements were made of LV end-diastolic (EDV) and end-systolic (ESV) volumes, ejection fraction, LV mass, severity of mitral regurgitation (MR), peak transmitral velocities during early (E wave) and late (A wave) diastolic filling, and myocardial performance index. At both 6 and 12 months, respectively, CRT was associated with reduced LV EDV (P < 0.0001 and P < 0.0001) and LV ESV (P < 0.0001 and P < 0.0001), improved ejection fraction (P < 0.0001 and P < 0.0001), regression of LV mass (P = 0.012 and P < 0.0001), and reduced MR (P < 0.0001 and P < 0.0001). LV filling time, transmitral E/A ratio, and myocardial performance index all improved at 12 months compared with baseline (P < 0.001, P = 0.031, and P < 0.0001). Reverse LV remodeling with CRT occurred in more patients at 6 than at 12 months (74% versus 60%, respectively; P < 0.05) and was greater in patients with a nonischemic than an ischemic etiology.

Conclusions—Reverse LV remodeling and symptom benefit with CRT are sustained at 12 months in patients with New York Heart Association class III/IV heart failure but occur to a lesser degree in patients with an ischemic versus a nonischemic etiology, most likely owing to the inexorable progression of ischemic disease.

Key Words: heart failure • echocardiography • remodeling • pacing

Patients with moderate to severe heart failure (New York Heart Association [NYHA] symptom class III/IV) have a poor prognosis in spite of optimal pharmacological therapy, which includes angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-adrenergic receptor blockers, diuretics, and aldosterone antagonists. Studies show that these agents attenuate rather than reverse the progressive structural and functional ventricular remodeling that typifies heart failure.

Cardiac resynchronization therapy (CRT) has recently become an established therapy for patients with NYHA class III/IV systolic heart failure and prolonged QRS duration. In addition to improvements in exercise capacity, NYHA symptom class, and quality of life, evidence of the arrest or reversal of ventricular remodeling has been demonstrated with CRT.1–4 Furthermore, these beneficial effects of CRT have been achieved in patients already receiving optimal medical therapy that includes ACE/ARBs and β-blockers. Most CRT trials involve short-term follow-up of small cohorts of patients, and many have been open-label studies. In contrast, data from the MUltisite STimulation In Cardiomyopathies (MUSTIC) trial, which was double-blind, demonstrated improvements in left ventricular (LV) structure with CRT at 1 year in a small patient cohort,5,6 with continued clinical benefit.7 However, a remaining unanswered but important question is how long the struc-
tural and functional improvements with continuous CRT will be sustained. The aim of the present study was 3-fold: To determine, via quantitative echocardiography in a large patient cohort, whether reverse LV remodeling persisted after 1 year of continuous CRT; to assess the proportion of patients in whom reverse remodeling was sustained; and to ascertain whether differences existed between ischemic and nonischemic patients after 12 months.

Methods
The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study was a prospective, double-blind, controlled evaluation of patients receiving optimal medical heart failure therapy who were randomized to CRT ON or CRT OFF and followed up for a minimum of 6 months. The primary end points were improvement in NYHA symptom class, 6-minute hall walk distance, and QoL score with the Minnesota Living with Heart Failure (MLWHF) Questionnaire. Patients in the MIRACLE study who were initially randomized to CRT ON were followed up for up to 12 months, at which time they underwent clinical assessment and a repeat quantitative Doppler echocardiogram to determine whether the reverse remodeling reported at 6 months was sustained at 12 months.

The study population consisted of 228 patients with QRS duration ≥130 ms, LV end-diastolic diameter (EDD) ≥55 mm, and an LV ejec tion fraction (LVEF) ≤35%. All patients were in NYHA symptom class III/IV and on an optimal heart failure medical regimen that was unchanged for a minimum of 1 month for diuretics, ACE inhibitors/ARBs, and digitals and a minimum of 3 months for β-blockers before randomization. The dose of β-blockers and ACE inhibitors during the first 6 months of the study (during the double-blind period) was kept constant, but from 6 to 12 months, the study was open-label, during which changes in pharmacological therapy were at the discretion of the treating physician. Patients were subsequently divided by origin of heart failure into 2 groups, ischemic and nonischemic, to assess differences in LV reverse remodeling between 6 and 12 months. The treatment and randomization assignment to ischemic etiology on the basis of clinical history of prior myocardial infarction with ECG evidence of infarct location, prior percutaneous coronary intervention, or prior coronary bypass surgery, similar to the assignment used in other CRT trials2,4,9,10 (MIRACLE ICD, MUSTIC, COMPANION [Comparison of Medical Therapy, Pacing, and Defibrillation on Heart Failure], and CARE-HF [Cardiac Resynchronization-Heart Failure]). Coronary angiography was not a prerequisite for the assignment of an ischemic cause of heart failure in the MIRACLE trial or the trials described above and may have led to misclassification in patients, and as such, this is a potential limitation of the present study.

The timing of the delay between atrial sensed activity and delivery of simultaneous biventricular pacing was individually adjusted in all patients to maximize LV filling without truncation of left atrial contraction, using a Doppler echocardiographic method previously described.11 Doppler echocardiograms at baseline before device implantation and at 6 and 12 months after initiation of CRT were analyzed in a core laboratory by a single sonographer blinded to treatment group and study sequence. Although ventricular pacing pulses were visible on the simultaneously recorded ECG, each echocardiogram was analyzed without reference to previous echocardiographic studies. Videotaped echocardiograms were analyzed on a TomTec computer workstation to obtain LV end-diastolic and end-systolic volume (LVEDV and LVESV), the deceleration time (DT) of the E wave, LV filling time, and the isovolumic relaxation time (IVRT) were also measured. The myocardial performance index (MPI) was calculated as the sum of the isovolumic contraction time (ICT) and IVRT divided by the ejection time (ET): MPI=(ICT+IVRT)/ET.11,13 The interventricular mechanical delay, which was used as an indicator of interventricular dysynchrony, was defined as the time interval between the onset of antegrade blood flow in the right ventricular outflow tract and the onset of antegrade blood flow in the LV outflow tract. Interventricular mechanical delay was estimated from pulsed-wave Doppler velocity signals recorded from the right ventricular and LV outflow tracts immediately proximal to the respective semilunar valves.14 LV volumes, LVEF, LV mass, LV shape, diastolic function, and severity of MR were assessed at baseline and at 6 and 12 months to characterize the time-dependent changes in LV remodeling with CRT and to determine whether reverse remodeling persisted to 12 months. Echocardiographic and clinical indices, including NYHA symptom class, 6-minute hall walk distance, and QoL, were evaluated in all patients with data sets at 1 or more of the following time points: Baseline, 6 months, and 12 months. The blinded phase of the MIRACLE study ended when all patients completed their 6-month visit, at which time they were informed of their randomized assignment. Only patients randomized to CRT ON for the first 6 months were eligible for this analysis of continuous CRT from baseline through 12 months. The institutional review board at each investigator site approved the study protocol, and all patients gave written informed consent.

Statistical Methods
Descriptive statistics for baseline demographics are presented as both means and SDs for continuous variables or percentages for discrete variables. Differences between means for ischemic and nonischemic patient groups were assessed with unpaired t tests. For discrete variables, distributions between groups were compared with χ² tests. Random-effects regression models were used to identify significant changes in echocardiographic and clinical parameters over time with measurements at baseline and 6 and 12 months for all CRT patients. Patients were included in each analysis if measurements were available at 1 or more time points. If the overall test of time effect was significant in a model, then pairwise differences were examined. Similar statistical methodology was used to assess changes in echocardiographic and clinical parameters between CRT ischemic and CRT nonischemic patients. Because there were differences between ischemic and nonischemic patients with respect to several baseline risk factors (age, gender, QRS duration, LVEF, LVESV, and LVEDV), the models for these analyses included covariates for each risk factor. The relationship between etiology and LVEDV over time was evaluated with a mixed linear regression model. Potential confounding factors were identified by comparing baseline variables between ischemic and nonischemic patients. Age, gender, heart rate, and QRS width were significantly different between ischemic and nonischemic patients, and these variables were adjusted for in the mixed linear model.

All statistical analyses were conducted with software from SAS, Inc. Statistical tests with probability values less than 0.05 were considered statistically significant.

Results
Baseline clinical demographics are shown for all 228 patients with continuous CRT therapy and with the popu-
In addition, LV mass decreased significantly from baseline at 6 and 12 months (P=0.012 and P<0.0001, respectively). The improvement in LVEF and concomitant reduction in LV mass at 12 months was associated with decreases in systolic and diastolic sphericity indices (P=0.003 and P=0.001, respectively), consistent with change in LV cavity shape toward a more ellipsoidal configuration. The change to a more mechanically advantageous LV systolic cavity shape at 6 and 12 months (P=0.004 and P=0.003, respectively) was likely due to acute changes in the pattern of contraction after the initiation of CRT. This reverse LV remodeling with CRT was accompanied by a decrease in the severity of MR at 6 and 12 months, although whether the change in LV shape preceded the reduction in MR or vice versa was not discernible from the present study.

Diastolic measures of LV function demonstrated systematic improvement after 6 months of CRT, with further sustained improvements at 12 months. LV filling time increased progressively from baseline to 12 months. The transmirtal E/A velocity ratio and myocardial performance index both decreased from baseline through 12 months, which indicates improvement in diastolic LV function. Furthermore, there was shortening of interventricular mechanical delay and isovolumic contraction time at 6 and 12 months, consistent with increased interventricular and intraventricular synchrony (Table 2).

We sought to explain our finding that both LVEDV and LVESV increased from 6 to 12 months, which indicated late recurrent LV dilatation. Consistent with previous reports,3,15 CRT does not appear to have the same effect on reverse remodeling in patients with ischemic heart failure as in those with nonischemic heart failure. For this reason, we evaluated the time-dependent changes in LV volumes by cause of heart failure at 6 and 12 months using a random effects model (Table 3). The models were adjusted for age, gender, and baseline values of heart rate, QRS duration, ejection fraction, and end-diastolic and end-systolic volumes because of differences between ischemic and nonischemic patients with respect to these variables (Table 1). When these variables were adjusted for, the changes in LVEDV remained significantly different between patients with ischemic versus nonischemic heart failure. In the ischemic heart failure patients, the favorable reduction in LV volumes at 6 months had regressed by 12 months (Table 3). By contrast, in the nonischemic patients, the reduction in LV volumes at 6 months was more than 3-fold greater than in the ischemic patients, and this difference

---

### Table 1. Baseline Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CRT Group (n=228)</th>
<th>Nonischemic† (n=113)</th>
<th>Ischemic† (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.9±10.7</td>
<td>61.1±11.0</td>
<td>66.6±9.7*</td>
</tr>
<tr>
<td>Male gender</td>
<td>68.4</td>
<td>53.1</td>
<td>83.5*</td>
</tr>
<tr>
<td>Ethnicity, % white</td>
<td>89.9</td>
<td>87.6</td>
<td>92.1</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>90.4</td>
<td>91.2</td>
<td>89.6</td>
</tr>
<tr>
<td>Beta-Blockade use</td>
<td>62.3</td>
<td>63.7</td>
<td>60.9</td>
</tr>
<tr>
<td>Diuretic use</td>
<td>93.9</td>
<td>96.5</td>
<td>91.3</td>
</tr>
<tr>
<td>ACE-I or ARB use</td>
<td>93.0</td>
<td>95.6</td>
<td>90.4</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>167.1±20.4</td>
<td>171.3±19.5</td>
<td>163.0±20.4*</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24.0±6.8</td>
<td>23.2±7.2</td>
<td>24.8±6.3*</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>74.5±10.7</td>
<td>75.9±12.0</td>
<td>73.0±9.0</td>
</tr>
<tr>
<td>LVEDV, cm³</td>
<td>305.7±111.4</td>
<td>325.2±128.2</td>
<td>284.1±84.5*</td>
</tr>
<tr>
<td>LVESV, cm³</td>
<td>237.5±102.2</td>
<td>256.1±117.9</td>
<td>216.7±76.5*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>68.9±14.5</td>
<td>70.7±15.3</td>
<td>66.9±13.3</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>112.1±21.1</td>
<td>111.3±19.9</td>
<td>113.0±22.3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>69.1±12.2</td>
<td>70.4±11.6</td>
<td>67.8±12.7</td>
</tr>
</tbody>
</table>

Continuous variables are stated as mean ± SD; other values are percentages. ACE-I indicates angiotensin-converting enzyme inhibitor. Other abbreviations as in text.

*P<0.05, ischemic vs nonischemic.
was sustained at 12 months (Table 3). The different schedules of remodeling by heart failure origin may explain the changes in LV volumes between 6 and 12 months when the patient cohort is considered as a whole.

The salutary effects of CRT on NYHA symptom class, 6-minute hall walk distance, and QoL score achieved at 6 months were sustained at 12 months (Table 2). Furthermore, there were no differences with regard to clinical end points in the ischemic versus nonischemic patients at 6 or 12 months (Table 3). Prior analysis of the same 3 primary end points in the MIRACLE Study Program, which includes patients from the MIRACLE, MIRACLE ICD, and InSync III clinical trials who received continuous CRT, showed that the significant improvements in NYHA symptom class, 6-minute hall walk distance, and QoL measured by the MLWHF questionnaire were sustained up to 18 months. There was no difference in clinical end points between the ischemic and nonischemic groups at any time point out to 18 months.

### Discussion

Moderate to severe (NYHA III/IV) heart failure is characterized by progressive ventricular remodeling consisting of LV dilatation, cavity distortion, and deterioration in pump function that portends a poor prognosis. Most large multicenter heart failure trials have shown that pharmaceutical agents, including angiotensin-converting enzyme (ACE) inhibitors, ARBs, and β-adrenergic receptor blockers, attenuate rather than reverse LV remodeling, with a few notable exceptions. In the majority of patients, CRT is associated with symptomatic improvement, increased exercise capacity, improved QoL, and reduced death and hospitalization. CRT confers incremental benefit over optimal medical therapy by resynchronizing right and left ventricular contraction that mediates reversal of the remodeling process. Improvements in cardiac structure, geometry, and function with CRT likely contribute to the consistent symptomatic benefits.

The major findings of the present study were that CRT resulted in progressive reverse remodeling that persisted to
12 months in patients with moderate to severe heart failure. Although LV volumes were reduced compared with baseline after 12 months of CRT, the percentage of patients demonstrating progressive reduction in LV size decreased from 6 to 12 months, which reflects a variability of response when LV volumes are used as an end point. Most previous studies have been unblinded; only a few have described changes in echocardiographic measurements of LV size, and those that did usually involved small patient cohorts and short follow-up periods of between 1 and 6 months.\(^6,15,20-22\) The only randomized, double-blind CRT trial with 12-month follow-up used linear echocardiographic measurements of LV size and also showed reverse LV remodeling in heart failure patients in sinus rhythm.\(^3\) We showed that after 12 months of CRT, not only did LV volumes decrease, but LV function (LVEF) improved progressively, LV mass regressed, LV cavity shape was restored toward normal, and the severity of MR decreased, and we showed that the magnitude of these changes was greater in nonischemic than ischemic heart failure patients.

Supportive evidence for the sustained reverse remodeling at 12 months was provided by concomitant improvements in LV diastolic function parameters. There was progressive lengthening of LV diastolic filling time and shortening of interventricular mechanical delay, which indicates a sustained decrease in LV dyssynchrony. The changes in transmitral velocity (E/A) ratio at 6 months were sustained at 12 months, and myocardial performance index improved from 6 to 12 months owing to progressive shortening of isovolumic contraction time and IVRT. Importantly, this ongoing structural and functional reverse remodeling with CRT impacted favorably and significantly on NYHA symptom class, 6-minute walk distance, and QoL at 6 months, and these beneficial effects continued through 12 months.

In spite of the major changes in LV architecture, myocardial mass, and systolic and diastolic function and the accompanying clinical improvement to 12 months, there was evidence of late, recurrent LV cavity dilatation between 6 and 12 months. The significant reduction in LVEDV and LVESV present at 6 months was attenuated at 12 months. This late LV dilatation was unlikely due to changes in heart failure medications between 6 and 12 months, because review of the case record forms showed that only 10 patients increased their dose of \(\beta\)-blockers, and only 7 patients were started on \(\beta\)-blockers. \(\beta\)-Blockers would be expected to facilitate further LV volume reduction and continued reverse remodeling rather than the LV dilatation that we observed. We demonstrated that age \(\leq 65\) years, female gender, QRS duration >170 ms, and LVEF <25% all correlated with decreases in LVEDV and reverse remodeling from baseline to 6 months. In contrast, by 12 months, the only parameters that correlated with changes in LVEDV were QRS duration >170 ms and LVEF <25%.

Because LV cavity dilatation is associated with deterioration in contractile function and adverse clinical outcome, and because of previously reported differential remodeling by cause of heart failure,\(^8\) we divided our patient cohort into those with nonischemic and those with ischemic heart failure. At 6 months, changes in LV volumes in the nonischemic patients were more than 2-fold greater in ischemic patients, although both groups were significantly improved from baseline. However, by 12 months, LV volumes in the ischemic patients had returned almost to baseline values, whereas in nonischemic patients, both LVEDV and LVESV remained significantly reduced at 12 months compared with baseline values (Table 3). Comparison of baseline variables between the ischemic and nonischemic patients revealed a number of potential confounding factors. Age, gender, heart rate, QRS duration, and end-diastolic and end-systolic volumes were all significantly different between ischemic and nonischemic patients. However, when these variables were adjusted for, the changes in LV volumes remained significantly different between ischemic and nonischemic patients. The late, recurrent LV dilatation that occurred between 6 and 12 months in the ischemic patients may be related to the natural progression of LV dysfunction due to

### TABLE 3. Differences Between Ischemic and Nonischemic Patients (Treatment Group Only)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ischemic CRT Patients</th>
<th>Nonischemic CRT Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 Months</td>
</tr>
<tr>
<td>LVEDV, cm(^3)</td>
<td>284.84 (n=96)</td>
<td>270.86 (n=95)</td>
</tr>
<tr>
<td>LVESV, cm(^3)</td>
<td>217.77 (n=96)</td>
<td>199.76 (n=95)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24.8±6.3 (n=96)</td>
<td>27.5±6.5 (n=95)</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>347.78 (n=71)</td>
<td>343.78 (n=71)</td>
</tr>
<tr>
<td>LVEDD, cm</td>
<td>7.3±0.9 (n=73)</td>
<td>7.2±0.9 (n=56)</td>
</tr>
<tr>
<td>LVESD, cm</td>
<td>6.3±0.9 (n=72)</td>
<td>6.1±1.1 (n=56)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.1±0.3 (n=115)</td>
<td>2.3±0.7 (n=106)</td>
</tr>
<tr>
<td>QoL score</td>
<td>59±19 (n=115)</td>
<td>40±24 (n=106)</td>
</tr>
<tr>
<td>6MHW distance, m</td>
<td>307±85 (n=115)</td>
<td>325±130 (n=107)</td>
</tr>
</tbody>
</table>

6MHW indicates 6-minute hall walk. Values are reported as mean±SD.

\(^*P<0.05\), within-group change from baseline to follow-up, and \(†P<0.05\), change from 6 months to 12 months. \(‡P<0.05\), between-group (ischemic vs non-ischemic) changes from baseline to follow-up at months and 12 months. \(P\) values are based on the random effects model.
regional loss of viable myocardium that is known to occur in patients with advanced heart failure of ischemic origin.

Conclusions

This study demonstrates that reverse LV remodeling is sustained to 12 months with CRT in patients with moderate to severe heart failure. The sustained improvement in NYHA symptom class, 6-minute hall walk distance, and QoL reflects the ongoing favorable structural and functional LV remodeling demonstrated by quantitative echocardiography. However, when LV cavity volumes were used as an end point, the percentage of patients demonstrating improvement was strongly influenced by etiology, demonstrated by the greater reduction in LV volumes observed in nonischemic patients versus ischemic patients. This late recurrent LV dilatation in patients with ischemic heart failure may relate to the deterioration in LV function due to repetitive episodes of ischemia and progressive regional loss of viable myocardium that are known to occur in ischemic heart disease rather than the loss of efficacy of resynchronization. Longer-term follow-up will determine whether and at what point in time LV reverse remodeling with CRT in patients with ischemic heart failure is counterbalanced by the inexorable progression of ischemic disease. Given the current efforts and resources investing potential CRT responders, accurate identification of ischemic heart failure patients in particular and their definition of response to CRT is of pivotal importance.

Acknowledgments

This study was supported by Medtronic, Inc, Minneapolis, Minn. The authors wish to express their gratitude to Jane Moore and Doug Smith for their editorial comments and to James Johnson, Jodi Koehler, and Susan Petersen-Stjekal for their statistical and clinical support.

Disclosures

Dr St. John Sutton, Mr Plappert, and Dr Abraham are consultants for Medtronic, Inc; K.E. Hilpisch and Dr Chinchoy are employees of and have ownership interest in Medtronic, Inc; Dr Abraham receives research grants and honoraria from Medtronic, Inc; and Dr Hayes is a speaker for and receives honoraria from Medtronic, Inc, Guidant, St Jude Medical, and ELA Medical.

References


**CLINICAL PERSPECTIVE**

Cardiac resynchronization therapy (CRT) is a novel and effective treatment for patients with New York Heart Association (NYHA) class III/IV heart failure refractory to optimal medical therapy and with prolonged QRS duration. CRT improves exercise capacity, NYHA symptom class, and quality of life and reverses ventricular remodeling. How long the reverse remodeling and symptomatic benefit are sustained is unknown. Quantitative analysis of serial echocardiograms from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial demonstrated continuing reverse structural and functional remodeling at 1 year. Left ventricular (LV) volumes, mass, and severity of mitral regurgitation decreased, whereas ejection fraction and diastolic function improved. The only parameters that correlated with reverse remodeling at 1 year were baseline ejection fraction <25% and QRS duration >170 ms. The favorable reduction in LV volumes in the ischemic heart failure patients at 6 months had regressed by 1 year, whereas in the nonischemic patients, the reduction in LV volumes at 6 months was more than 3-fold greater than that in ischemic patients, and this difference was sustained at 1 year. When adjustments were made for differences in age, gender, and baseline heart rate, QRS duration, LV volumes, and ejection fraction, the changes in LV volumes remained significantly different between patients with ischemic versus nonischemic heart failure. These important clinical data show that reverse LV remodeling and symptom benefit with CRT are sustained at 1 year in advanced (NYHA class III/IV) heart failure, although reverse remodeling is less extensive in ischemic than in nonischemic patients.
Sustained Reverse Left Ventricular Structural Remodeling With Cardiac Resynchronization at One Year Is a Function of Etiology: Quantitative Doppler Echocardiographic Evidence From the Multicenter InSync Randomized Clinical Evaluation (MIRACLE)

Martin G. St John Sutton, Ted Plappert, Kathryn E. Hilpisch, William T. Abraham, David L. Hayes and Edward Chinchoy

_Circulation_. 2006;113:266-272; originally published online January 9, 2006; doi: 10.1161/CIRCULATIONAHA.104.520817

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/113/2/266

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/