Cardiac Resynchronization Therapy Improves Heart Rate Variability in Patients with Symptomatic Heart Failure

Philip B. Adamson, MD; Karen J. Kleckner, MS; Warren L. VanHout, BSEE; Sriram Srinivasan, MS; William T. Abraham, MD

Background—Cardiac resynchronization therapy (CRT) using biventricular pacing improves symptoms and functional capacity in patients with moderate to severe heart failure. The present study examined whether an improvement in ventricular performance from resynchronization therapy changes the autonomic control of heart rate.

Methods and Results—Heart rate variability (HRV) was examined in 50 patients implanted with the InSync biventricular pacing system who were randomized to therapy-on (n=25) or therapy-off (n=25). HRV was computed as the standard deviation of the atrial cycle length sensed from the system over 2 months of continuous monitoring. HRV was compared between CRT-on and CRT-off groups. HRV was higher in patients randomized to CRT-on compared with CRT-off (148±47 ms for CRT-on versus 118±45 ms for CRT-off; P=0.02), despite the lack of difference in mean atrial cycle length (844±129 ms for CRT-on versus 851±110 ms for CRT-off; P=0.82). Changes in plasma catecholamines were not different between the CRT-on and CRT-off groups from baseline to the 3-month follow-up.

Conclusions—Improvement in ventricular performance from CRT shifts cardiac autonomic balance toward a more favorable profile that is less dependent on sympathetic activation. (Circulation. 2003;108:266-269.)

Key Words: heart failure ■ pacing ■ heart rate ■ nervous system, autonomic

Sympathetic nervous activation and vagal withdrawal in response to decreased cardiac output are critical mechanisms responsible for increased mortality and morbidity in patients with heart failure.1-4 The extent of sympathetic nervous activation, as measured by circulating norepinephrine levels, directly correlates with cardiac mortality and symptom severity.2,5 Cardiac autonomic control can also be quantified by measuring heart rate variability (HRV),5 which stratifies risk for cardiac mortality in patients after myocardial infarction6 or in those with chronic heart failure.6,7 HRV patterns that reflect elevated sympathetic activity or reduced cardiac vagal control predict increased mortality risk.5 To underscore further the autonomic mechanisms in heart failure progression, β-blocker therapy profoundly decreases myocardial toxicity8 and improves mortality and morbidity.9 It is not clear, however, if interventions that favorably alter clinical end points are reflected by changes in indirect markers, such as HRV.10

An intervention that favorably impacts morbidity and functional capacity in some heart failure patients is cardiac resynchronization therapy (CRT).11 The present study tested the hypothesis that an improvement in cardiac performance with CRT is reflected in cardiac autonomic control, as measured by HRV.

Methods

Patient Population and Primary End Points

A total of 76 patients with New York Heart Association class III or IV heart failure due to left ventricular systolic dysfunction (ejection fraction <35%) who had significant interventricular conduction delays (QRS duration ≥130 ms) were enrolled in the “pilot phase” of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial. A detailed description of the trial’s design has been published.11 The InSync Model 8040 biventricular pacing system (Medtronic Inc) was used in the study, and patients were randomized to either therapy on (CRT-on, VDD mode) or therapy off (CRT-off, VVI mode) after successful implantation. The lower rate limit was set at 30 bpm to allow the device to track intrinsic heart rate (HR). Patients and care providers were blinded to device therapy status. All patients with atrial rate histogram data available entered this study.

Atrial Cycle Length Evaluation

The InSync HR histogram diagnostic tool evaluated all paced and sensed atrial and ventricular events. In the study, only atrial sensed cycle lengths were measured; they were then converted to HR, and a HR frequency histogram was constructed with a 10-bpm resolution. Histogram data were acquired between the 1-month follow-up visit and the 3-month visit in 48 patients. In 2 patients, the analysis included data from implantation to 3 months because data were not cleared at 1 month. Mean atrial cycle length (ACL) was calculated from the HR histogram information using the cycle length corresponding to the HR at the midpoint of each bin as the cycle length.
for that particular bin. HRV was calculated as the SD of all atrial intervals sensed over the follow-up period. ACLs and their SDs were compared between CRT-on and CRT-off groups. Additional HRV comparisons were made between patients with and without β-blocker therapy. Because the lower rate limit was 30 bpm, the HR histogram information reflected sinus activity undisturbed by atrial pacing.

Transthoracic Echocardiography and Plasma Catecholamine Assessment

Two-dimensional echocardiograms were obtained at baseline and 3 months after randomization. All images were analyzed in a core laboratory that measured left ventricular volumes (modified biplane Simpson’s method of disks), left ventricular ejection fraction, and mitral regurgitation jet area (average of apical 4-chamber and apical long-axis views).

Plasma catecholamines were measured in 36 patients at baseline and at the 3-month follow-up visit. Blood was obtained while the patients were resting quietly supine, and catecholamine analyses were performed in a core laboratory.

Statistical Analysis

Demographic data and changes in echo parameters and catecholamines were compared between groups using the t test for continuous variables and the χ² test for discrete variables. Mean ACL and SD of the ACL were compared using a t test with a univariate analysis for all comparisons. Data are presented as mean±SD unless otherwise noted. P<0.05 represented statistically significant differences.

### TABLE 1. Patient Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CRT-Off (n=25)</th>
<th>CRT-On (n=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.7±11.6</td>
<td>60.3±10.1</td>
<td>0.634</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>72.0</td>
<td>68.0</td>
<td>1.000</td>
</tr>
<tr>
<td>QRS width, ms</td>
<td>159.2±15.9</td>
<td>163.3±21.5</td>
<td>0.454</td>
</tr>
<tr>
<td>NYHA, % class III</td>
<td>92.0</td>
<td>92.0</td>
<td>1.000</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>22.2±6.4</td>
<td>22.2±7.0</td>
<td>1.000</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>67.4±10.2</td>
<td>72.3±10.5</td>
<td>0.099</td>
</tr>
<tr>
<td>ACE inhibitor use, %</td>
<td>92.0</td>
<td>96.0</td>
<td>0.602</td>
</tr>
<tr>
<td>β-Blocker use, %</td>
<td>48.0</td>
<td>48.0</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are mean±SD or percentage. NYHA indicates New York Heart Association; LV, left ventricular; and EDD, end-diastolic diameter.

### Results

#### Patient Population

Of the 76 patients who entered the pilot phase of the MIRACLE trial, 50 patients finished 3 months of follow-up and had atrial rate histogram data available for analysis. Clinical characteristics were not different between the CRT-on and CRT-off groups (Table 1). Only 3 patients were not on angiotensin-converting enzyme (ACE) inhibition at baseline, which precluded an analysis of ACE inhibitor effects on HRV. One patient in the CRT-off group was started on β-blocker therapy and 1 patient in the CRT-off group was started on an ACE inhibitor 1 month after implantation.

#### Atrial Rate Histograms and HRV

Atrial rate histograms were obtained from 68±19 days of continuous monitoring, and no atrial-paced intervals occurred during the follow-up period. One patient had atrial fibrillation for <10% of the time, and the HR information from the episode of atrial fibrillation was excluded from analysis. The mean ACL was not different between the groups (844±129 ms for CRT-on versus 851±110 ms for CRT-off; P=0.82). Aggregate atrial rate histograms from all patients are shown in the Figure and are grouped by β-blocker use. The SD of ACL was 25% higher in the CRT-on group after 3 months of therapy (148±47 ms for CRT-on versus 118±45 ms for CRT-off; P=0.02).

Twenty-four patients (48%) were taking β-blockers; they were evenly distributed between the CRT-on (n=12) and the CRT-off groups (n=12). β-Blocker therapy did not influence the ACL in either the CRT-on or CRT-off groups. HRV was 27% higher in patients receiving β-blocker therapy randomized to CRT-on compared with CRT-off (143±32 ms for CRT-on and β-blocker versus 113±37 ms for CRT-off and β-blocker; P=0.04). HRV in patients without β-blocker therapy was 25% higher between CRT-on and CRT-off groups, but the difference between the absolute numbers was not significant (154±58 ms for CRT-on and no β-blocker versus 123±53 ms for CRT-off with no β-blocker; P=0.18).

#### Echocardiographic Indexes and Catecholamines

Comparing CRT-on with CRT-off groups, left ventricular end-diastolic volume decreased, systolic and diastolic diam-
etters decreased, and mitral regurgitation jet area decreased (Table 2). Of the 36 patients from whom baseline and 3-month follow-up plasma catecholamines were available, 19 were randomized to CRT-on and 17 to CRT-off. No differences in baseline catecholamines or changes over time were detected between groups (Table 3). The apparent change in plasma epinephrine in the CRT-on group was caused by 3 patients with very high baseline values.

### Discussion

This study demonstrates that an improvement in cardiac performance from CRT favorably alters the autonomic control of HR and that β-blocker therapy seemed to potentiate the autonomic improvement with CRT. In general, imbalances in cardiac autonomic control arise in patients with congestive heart failure resulting from decreased parasympathetic input and increased sympathetic nervous control. Such imbalances, which favor sympathetic nervous control, are associated with increased risk for cardiac mortality and progressive disease.

In the present study, CRT increased overall time-domain HRV, which likely represents changes in both sympathetic and parasympathetic activity. Although reductions in sympathetic nerve activity occur during abrupt, short-term biventricular pacing in an electrophysiology laboratory setting,12 the long-term effects of CRT in the present study had no effect on circulating catecholamines. These findings suggest that the beneficial autonomic effects of CRT were mostly associated with increased parasympathetic HR control, although resting ACL was unchanged. If neural control changes were responsible for differences in HRV, mechanisms may include baroreflex gain resetting due to improved stroke volume or changes in afferent nervous signaling from resynchronized ventricular activation. Because HRV was measured over such a long period of time, influences not related to catecholamine activation, such as activity or sleeping patterns, may also have influenced the measurements. Regardless of the exact mechanism, however, CRT shifted cardiac autonomic balance toward less sympathetic dominance. Therefore, by improving cardiac performance and efficiency, CRT favorably alters the autonomic control of the heart, which may have contributed to the reversal of adverse remodeling demonstrated by echocardiography.

### HRV and Implanted Devices

The novel methods used in the present study to quantify HRV illustrate the type of useful information that can be obtained from an implanted device. Traditional methods to measure HRV rely on continuous surface ECG recordings from 24- to 48-hour Holter monitoring,5 without the possibility of longer-term recordings. An implanted device overcomes the technical limitations of surface ECG recordings, thus providing a more accurate means to exclude premature ventricular contractions and decrease noisy signals, which may decrease the integrity of variability calculations.13 Furthermore, long-term analyses based on months of continuous monitoring decrease the impact of including non-sinus atrial impulses in the measurements.

### Limitations

This study was observational, and the long-term recordings used to calculate HRV may quantify nonautonomic influences on HR, such as renin-angiotensin effects or differences in activity. Future development of techniques to quantify spectral analysis of HRV based on long-term atrial sensed cycle lengths might elucidate meaningful very low frequency HR events, similar to spectral analysis of shorter recordings.14 The opportunity to quantify lower frequency (very long period) components, without significant noise or complicated beat exclusion algorithms, may provide profound insight into physiological control systems theories. Although HRV in this study did not include atrial paced cycle lengths, intermittent atrial pacing may induce sinoatrial node remodeling and, thus, change long-term HRV.

### Conclusions

CRT favorably impacts cardiac autonomic control, thus resulting in less sympathetic dominance in patients with severely symptomatic heart failure. This was associated with a reversal of ventricular remodeling and may contribute to improvement in long-term functional capacity and quality of life. Devices primarily implanted to deliver therapy are also capable of providing meaningful diagnostic information derived from long-term HRV and, possibly, other HR-based measurements.

### References


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**TABLE 2. Changes in Echocardiographic Parameters From Baseline to 3 Months of Follow-Up**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CRT-Off</th>
<th>CRT-On</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV, cm³</td>
<td>15.2±46.1</td>
<td>-20.2±50.2</td>
<td>0.022</td>
</tr>
<tr>
<td>LVEDD, cm</td>
<td>0.01±0.48</td>
<td>-0.41±0.51</td>
<td>0.023</td>
</tr>
<tr>
<td>LVESD, cm</td>
<td>0.11±0.61</td>
<td>-0.42±0.79</td>
<td>0.038</td>
</tr>
<tr>
<td>MR jet area, cm²</td>
<td>-0.7±3.3</td>
<td>-4.2±5.5</td>
<td>0.026</td>
</tr>
</tbody>
</table>

LVEDV indicates left ventricular end-diastolic volume; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; and MR, mitral regurgitation.

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**TABLE 3. Changes in Plasma Catecholamines Comparing Baseline to 3 Months**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CRT-Off</th>
<th>CRT-On</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine, pg/mL</td>
<td>66±190</td>
<td>34±72</td>
<td>22±17</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>582±361</td>
<td>516±277</td>
<td>390±263</td>
</tr>
<tr>
<td>Dopamine, pg/mL</td>
<td>15±10</td>
<td>17±17</td>
<td>20±22</td>
</tr>
</tbody>
</table>

No significant difference was found in any parameter. Three patients who had very high baseline values that decreased at 3 months accounted for the apparent trend seen in epinephrine in the CRT-on group.


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