Left Ventricular Reverse Remodeling With Biventricular Versus Right Ventricular Pacing in Patients With Atrioventricular Block and Heart Failure in the BLOCK HF Trial

Martin St. John Sutton, MBBS; Ted Plappert, CVT; Philip B. Adamson, MD; Pei Li, PhD; Shelly A. Christman, PhD; Eugene S. Chung, MD; Anne B. Curtis, MD

Background—Biventricular pacing in heart failure (HF) improves survival, relieves symptoms, and attenuates left ventricular (LV) remodeling. However, little is known about biventricular pacing in HF patients with atrioventricular block because they are typically excluded from biventricular trials.

Methods and Results—The Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial randomized patients with atrioventricular block, New York Heart Association symptom classes I to III HF, and LV ejection fraction ≤50% to biventricular or right ventricular pacing. Doppler echocardiograms were obtained at randomization (after 30 to 60 days of right ventricular pacing postimplant) and every 6 months through 24 months. Data analysis comparing changes in 10 prespecified echo parameters over time was conducted using a Bayesian design. LV end systolic volume index was also evaluated as a predictor of mortality/morbidity. Of 691 randomized subjects, 624 had paired Doppler echocardiogram data for ≥1 analyses at 6, 12, 18, or 24 months. Biventricular pacing significantly reduced LV volume indices and intraventricular mechanical delay, and improved LV ejection fraction, consistent with LV reverse remodeling. These parameters showed little change with right ventricular pacing alone, indicating no systematic reverse remodeling with right ventricular pacing. LV end systolic volume index was predictive of mortality/morbidity; the estimated risk increased up to 1% for every 1 mL/m² increase in LV end systolic volume index.

Conclusions—LV end systolic volume index is a significant predictor of mortality/morbidity in this population. Cardiac structure and function are improved with biventricular pacing for patients with atrioventricular block and LV systolic dysfunction.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00267098.

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whether biventricular pacing has a consistently greater and more favorable effect than RV pacing on LV reverse remodeling and attenuation of progressive LV dysfunction; and (2) to detect differences in LV architecture, function, and intraventricular mechanical delay (IVMD) associated with biventricular versus RV pacing using transthoracic echocardiography.

Methods

Enrollment criteria for the BLOCK HF trial have been published previously. The Institutional Review Board of each participating institution approved the study protocol and all patients provided written informed consent. All patients had a standard class I or IIa indication for permanent pacing because of AVB, NYHA classes I to III systolic HF, and LV ejection fraction (LVEF) ≤ 50%. Patients with permanent atrial arrhythmias who had intrinsic AVB or AVB because of AV nodal ablation, as well as patients meeting class I indications for implantable cardiac defibrillators were enrolled. All subjects received a cardiac resynchronization therapy (CRT) pacemaker (CRT-P), or CRT defibrillator (CRT-D) if there was an indication for defibrillation therapy, and were RV paced for 30 to 60 days, while HF medical therapy was optimized. Subjects were subsequently randomly assigned 1:1 to biventricular or RV pacing, and underwent an echocardiographic examination at randomization and 6-, 12-, 18-, and 24-month postrandomization.

Echocardiograms and Doppler velocity signals were digitized to calculate changes in LVEF, LVESVI, LV end diastolic volume index (LVEDVI), LV dimension at end diastole (LVEDD), LV dimension at end systole (LVESD), LV mass, mitral regurgitation (MR), cardiac index, IVMD, defined as the time difference between peak septal and peak posterior wall excursion, and transmitral peak E-wave and A-wave velocity ratio. LV volumes were estimated according to Simpson method and indexed to body surface area, and LVEF was calculated using a standardized protocol. The severity of MR was assessed as the regurgitant jet area/left atrial area. All two-dimensional echocardiographic measurements were made by a senior sonographer (T.P.) with >30 years of experience in quantitative analysis of echocardiograms at the Echo Core laboratory.

Statistics

At the time the trial was designed, the lack of data for patients in this population receiving biventricular therapy added uncertainty to the sample size and follow-up requirements for the primary objective. Thus, an adaptive Bayesian study design allowing up to 1200 patients to undergo randomization was used, featuring sample size re-estimation to account for worsening or improvement over time. Additional subgroup analyses were conducted to determine whether relationships existed that were not apparent when the whole data set was explored. These compared changes in the 10 predefined echo parameters: history of atrial fibrillation (AF) versus no AF, left bundle branch block (LBBB) versus no LBBB, and RV lead apical versus nonapical placement.

Reproducibility

We assessed intraobserver reproducibility of the echo parameters in 100 non-BLOCK patients with HF. Concordance Correlation Coefficients were 0.88 for LVEDVI, 0.90 for LVESVI, 0.71 for LVEF, 0.91 for transmitral peak A-wave, and 0.78 for transmitral peak E-wave.

Results

A total of 918 patients were enrolled from December 2003 through November 2011 at 58 sites in the United States and 2 sites in Canada. Of enrolled subjects, 691 were randomized, with 624 (442 CRT-P and 182 CRT-D) having paired data for ≥1 analyses of echo parameters (Figure 1). Reasons for missing echo data included no body surface area recorded, echocardiogram not performed or not analyzable, or follow-up visit missed. Within device groups, average demographics and cardiac function values were comparable between arms at randomization (Table 1). For most echo parameters, results were consistent across time points regarding statistical significance (Table 2), and poolability analyses did not show significant differences between CRT-D (average enrollment LVEF, 33%) and CRT-P (average enrollment LVEF, 43%) subjects.

Linear LV Dimensions and Volumes

The randomization arms differed significantly with regard to change in LVESVI (Table 2), but the small differences were unlikely clinically or biologically meaningful. Biventricular subjects had an average of 0.1 cm reduction in LVEDD at all time points (Figure 2). In contrast, RV subjects showed no change.

Biventricular subjects showed a significantly greater reduction in LVESVI and LVEDVI than RV subjects at each time point (Figure 2; Table 2). The average reduction in LVESVI among biventricular subjects varied from 6 to 8.8 mL/m², whereas RV subjects, on average, had little change. The average reduction in LVEDVI among biventricular subjects ranged from 6.2 to 9.8 mL/m², whereas the average reduction among RV subjects varied from 0.1 to 1.1 mL/m² (Figure 2).
A reduction in LVESVI ≥15% was more often encountered in biventricular compared with RV subjects (Figure 3). At 6 months, 44% of biventricular subjects experienced ≥15% reduction in LVESVI compared with 25% of RV subjects. A total of 68% of biventricular subjects had any reduction in LVESVI at 6 months, compared with only 50% of RV subjects. This was a consistent finding at each time point and typifies the magnitude of response to biventricular pacing in patients with HF.2–7

LV Ejection Fraction
Biventricular subjects experienced significant improvements in LVEF compared with RV subjects. (Table 2; Figure 2). On average, biventricular subjects experienced a 3% increase in LVEF at 6 months, whereas RV subjects experienced a 0.3% decrease. Similar changes were seen in biventricular subjects at 12, 18, and 24 months; RV subjects’ LVEF did not improve at any time point.

LV Mass
There was a consistent trend for greater reduction in LV mass in biventricular compared with RV subjects (Figure 2). The average reduction in LV mass in biventricular subjects ranged from 8.4 to 19.4 g, whereas in RV subjects the average reduction ranged from 4.2 to 7.2 g. A significant difference between arms was observed at 12 and 24 months.

Intraventricular Mechanical Delay
Average IVMD was similar at randomization but shortened significantly in biventricular subjects at 6 months (49.9 ms; Figure 2) compared with virtually no change in RV subjects (~4.2 ms; Figure 2). These significant differences persisted throughout 24 months.

Mitral E/A Wave Velocity Ratio, Cardiac Index, and MR
The mean values for transmitral peak E- and A-waves, E/A velocity ratio, cardiac index, and MR for biventricular versus RV and CRT-P versus CRT-D subjects were similar during 24 months of follow-up.

Modeling Analyses
The results of modeling accounting for all time points were similar to those of the individual time point analyses, as there was a significant difference between arms with regard to LVEF, LVESVI, LVEDVI, LVEDD, IVMD, and LV mass. The quadratic effect for time was not significant for any of the 10 parameters, whereas the linear time effects were significant for LVESVI, LVEDVI, and LV mass, suggesting greater reductions over time.
Effect Modification
We assessed the potential effect modification of baseline covariates, such as age, sex, LVESVI, LVEF, and NYHA on LV reverse remodeling. Interaction terms for biventricular therapy with these covariates were not significant with the exception of randomization LVESVI in predicting LVESVI and LVEDVI over time. This showed a treatment effect that was consistent across baseline LVEF and NYHA class. However, the treatment effect was greater for subjects with higher baseline LVESVI ($P=0.03$), although the incremental effect was small. With regard to age and sex, we could not confirm the disproportionate beneficial reverse remodeling in women compared with men as reported previously.\(^6,14\) There was no detectable independent confounding effect of age during follow-up.

Predictive Value of LVESVI
All 653 subjects with measurable LVESVI at randomization were included in the analyses assessing how LVESVI affects the risk of clinical outcomes. For all the 4 study end points (mortality, mortality or HF urgent care, mortality or HF hospitalization, and HF hospitalization), elevated LVESVI measures at either randomization or follow-up were found to significantly increase relative risk (Table 3). The estimated hazard ratios ranged from 1.007 for mortality to 1.01 for first HF hospitalization, meaning that a 10 mL/m\(^2\) increase in LVESVI would be associated with a 7% increase in the risk of death, and 10% increase in the risk of HF hospitalization.
Subgroup Analyses

We performed additional subgroup analyses to determine whether any discoverable relationships existed using the following: history versus no history of AF, LBBB versus no LBBB, and RV lead apical versus non-apical location. The only analysis that showed a consistently significant difference was

Table 2. Posterior Probabilities for Overall Echo Parameter Analyses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>6 Mo</th>
<th>12 Mo</th>
<th>18 Mo</th>
<th>24 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>(1.89, 4.82)*</td>
<td>(1.62, 4.84)*</td>
<td>(0.42, 4.07)*</td>
<td>(1.62, 5.60)*</td>
</tr>
<tr>
<td>LVESVI</td>
<td>(−10.12, −4.21)*</td>
<td>(−10.59, −3.83)*</td>
<td>(−11.86, −4.57)*</td>
<td>(−11.69, −2.85)*</td>
</tr>
<tr>
<td>LVEDVI</td>
<td>(−9.09, −2.56)*</td>
<td>(−9.47, −2.04)*</td>
<td>(−12.91, −4.68)*</td>
<td>(−11.37, −1.74)*</td>
</tr>
<tr>
<td>LVESD</td>
<td>(−0.24, −0.01)*</td>
<td>(−0.29, −0.04)*</td>
<td>(−0.29, −0.03)*</td>
<td>(−0.39, −0.10)*</td>
</tr>
<tr>
<td>LV mass</td>
<td>(−12.13, 3.95)</td>
<td>(−19.33, −0.86)*</td>
<td>(−18.19, 1.62)</td>
<td>(−21.11, −0.96)*</td>
</tr>
<tr>
<td>MR</td>
<td>(−2.83, 1.51)</td>
<td>(−2.84, 1.78)</td>
<td>(−2.38, 2.43)</td>
<td>(−3.34, 2.05)</td>
</tr>
<tr>
<td>CI</td>
<td>(−0.03, 0.20)</td>
<td>(−0.02, 0.20)</td>
<td>(−0.22, 0.06)</td>
<td>(−0.10, 0.19)</td>
</tr>
<tr>
<td>IVMD</td>
<td>(10.04, 48.64)*</td>
<td>(2.84, 40.87)*</td>
<td>(6.25, 47.19)*</td>
<td>(2.00, 44.53)*</td>
</tr>
<tr>
<td>E/A-wave ratio</td>
<td>(−0.18, 0.09)</td>
<td>(−0.29, 0.06)</td>
<td>(−0.14, 0.22)</td>
<td>(−0.09, 0.31)</td>
</tr>
</tbody>
</table>

BIV–RV, biventricular-right ventricular; CI, cardiac index; IVMD, intraventricular mechanical delay; LV, left ventricular; LVEDD, LV dimension at end diastole; LVEDVI, LV end diastolic volume index; LVEF, LV ejection fraction; LVESD, LV dimension at end systole; LVESVI, LV end systolic volume index; and MR, mitral regurgitation.

*P<0.05

Figure 2. Average absolute improvement in echo parameters over time. The number of subjects providing data at each time point is presented on the x axis. BIV indicates biventricular; IVMD, intraventricular mechanical delay; LV, left ventricular; LVEDD, LV end diastolic dimension; LVEDVI, LV end diastolic volume index; LVEF, LV ejection fraction; LVESVI, LV end systolic volume index; and RV, right ventricular.
between randomized arms was history of AF. Among subjects with a history of AF, MR reductions between 2.21% and 4.53% over time were observed in biventricular-paced subjects, compared with changes between 0.14% and 1.33% in RV-paced subjects. Conversely, among subjects with no history of AF, the biventricular arm saw less average change (ranging from a 0.35% reduction to a 1.14% increase), whereas the RV arm saw both the average reductions and the average improvements of >1% to 2% over time.

Discussion

In this echo analysis of the BLOCK HF trial, cardiac structure and function were improved with biventricular pacing for patients with AVB and LV systolic dysfunction. Relative to randomization, which followed 30 to 60 days of RV pacing, biventricular pacing significantly reduced LV volume indices and IVMD, and improved LVEF, consistent with LV reverse remodeling. These parameters showed little change with RV pacing alone, indicating no systematic reverse remodeling with RV pacing. In addition, LVESVI was found to be a significant predictor of mortality and HF hospitalization in this population.

As heart disease progresses into HF, heart size increases, cardiac function deteriorates, and symptoms of HF ensue.15 This dynamic process is known as LV remodeling. Understanding the extent of LV remodeling can help to assess the prognosis of HF—the greater the extent of remodeling, the poorer the prognosis. Relatively small increases in ventricular volume have been associated with an increased risk of death in patients with coronary artery disease, recent MI or HF.16–19 Therefore, treatments that prevent or reverse LV remodeling are clinically beneficial. Almost all successful contemporary therapies for HF, including drug therapy and CRT attempt to reduce LV size and, thereby reverse remodel the LV. Early HF trials demonstrated that drug therapy that limited or reversed LV remodeling resulted in improved long-term survival.20 However, most large multicenter HF trials have shown that pharmaceutical agents attenuate rather than reverse remodel the LV, with a few notable exceptions.21,22 In addition to improvements in exercise capacity, NYHA class, and quality of life, evidence of the arrest or reversal of ventricular remodeling has been demonstrated with CRT.2–8,23–26

Although most previous CRT trials have excluded patients with AVB, these new data from BLOCK HF provide evidence that biventricular pacing in patients with high-grade AVB and LV dysfunction (LVEF ≤50%) is associated with progressive reverse remodeling, improvement in LVEF, and attenuation of disease progression. These changes were sustained through 24 months of follow-up. In contrast, traditional RV pacing was not associated with progressive LV reverse remodeling or change in LVEF at follow-up. Importantly, in the BLOCK HF trial, randomization occurred after implant and 30 to 60 days of RV pacing, while HF medical therapy was optimized, so changes or lack of changes observed are relative to this time point. The difference in LV remodeling between biventricular and RV pacing could not be explained by any skewed distribution at randomization of patients with CRT-D who had larger LV volumes, lower EF, and greater prevalence of NYHA class III than patients with CRT-P because patients with CRT-D were equally distributed across the 2 randomized arms.

The importance of LV size, particularly LVESVI and its relationship to clinical outcomes, has been previously documented.27–31 The REVERSE trial reported that significant reverse LV remodeling at a threshold of >15% reduction in LVESVI at 12 months was associated with a clinical response to CRT.30 In a quantitative echocardiographic substudy of the Survival and Ventricular Enlargement (SAVE) trial, LVESVI

Table 3. LVESVI as a Predictor of Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI) for 1 mL/m² Increase in LVESVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.0119</td>
<td>1.007 (1.001, 1.012)</td>
</tr>
<tr>
<td>Mortality/HF urgent care</td>
<td>0.0042</td>
<td>1.007 (1.002, 1.011)</td>
</tr>
<tr>
<td>Mortality/HF hospitalization</td>
<td>0.0002</td>
<td>1.008 (1.004, 1.012)</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>0.0001</td>
<td>1.010 (1.005, 1.015)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; HF, heart failure; and LVESVI, left ventricular end systolic volume index.
was shown to be the most powerful predictor of outcome that included death, development of HF, or recurrent myocardial infarction. Similarly, in the BLOCK HF trial, more than two thirds of the biventricular subjects had an improvement in LVEF that was durable over time. Biventricular pacing resulted in greater LVEF reductions than RV pacing and for every 10 mL/m² increase in LVEF, there was a 7% increased risk of death, 7% increased risk of death or HF urgent care, 8% increased risk of death or HF hospitalization, and 10% increased risk of HF hospitalization (Table 3). In BLOCK HF, LVEF was smaller than in NYHA class II subjects in REVERSE and NYHA class III/IV subjects in MIRACLE and MIRACLE ICD, indicating less advanced HF and a better prognosis.

In the BLOCK HF trial, subjects in both the pacing arms had similarly prolonged IVMD at randomization because of a comparable degree of intraventricular dysynchrony. However, coincident with biventricular pacing, there was a reduction in IVMD consistent with decreased dyssynchrony and restoration of more normal coordinated LV and RV contraction patterns that was sustained through 24 months. By contrast, there was no change in IVMD in RV-paced subjects. The trigger for reverse remodeling in HF patients with AVB may have been the onset of biventricular pacing. A robust direct relationship previously has been demonstrated between improvement in LV volume indices and IVMD with CRT in the REVERSE trial.

We found no evidence for RV pacing–induced cardiomyopathy, which has been reported to involve up to 20% of patients. Our failure to detect either LV dilation or progressive decrease in LVEF may reflect that the randomization visit served as the baseline measure, which came after 30 to 60 days of RV pacing per the study design. An alternative explanation for our findings is that RV pacing–induced cardiomyopathy must be mild, rare, or occur only after considerably longer RV stimulation.

We examined the potential modifying effects of several possible confounders that included age, sex, NYHA class, and LVEF. Previous studies have reported a greater response to CRT in women and NYHA class II, or with RV lead apical placement compared with nonapical placement, with biventricular or RV pacing. However, among subjects with a history of AF, reductions in MR over time were observed in biventricular subjects as compared with RV subjects.

Limitations
A potential short-coming of this study was the degree of missing echo data, because in part, of subjects failing to return for follow-up echocardiograms and clinic visits, technically limited echo data that precluded quantification, and the absence of body surface area. In addition, the trial was designed to allow follow-up of all subjects through 12 months, and was stopped once a prespecified end point was met. This prevented some subjects from completing an 18- or 24-month visit. However, all available comparative data were used in the statistical analyses of each echo parameter at each time point, and the modeling analysis, which used all available data at all scheduled visits, produced similar results to those of the individual time point analyses.

Finally, a further limitation to be noted is the relative paucity of data on mitral and tricuspid valve regurgitation, although both seemed mild. We also report the interaction of AF and MR.

Conclusions
In patients with AVB and NYHA classes I to III systolic HF, biventricular pacing results in reverse structural and functional LV remodeling, whereas traditional RV pacing does not. Worsening LVEF was associated with increased risk of adverse clinical outcomes. Biventricular pacing resulted in superior improvement in LVEF compared with RV pacing through 24 months. This detailed echocardiographic analysis has important clinical implications in supporting the use of biventricular pacing de novo rather than RV pacing for this patient population.

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Disclosures
Dr Curtis received fees for serving on the advisory boards of Biosense Webster, St. Jude Medical, Sanofi-Aventis, Pfizer, and Bristol-Myers Squibb; received consulting fees from Medtronic; receiving lectures fees from Sanofi-Aventis, St. Jude Medical, and Medtronic; and receiving payment for the development of educational presentation from Horizon CME, WebMD Health Services, and the North American Center for Continuing Medical Education. Dr Chung reports receiving consulting fees from Boston Scientific, Medtronic, and CardioMEMS; payment for the development of educational presentations from Boston Scientific; and grant support through his institution from Gambro, Medtronic, and Boston Scientific. Dr Adarson reports receiving consulting fees from Medtronic, St. Jude Medical, and CardioMEMS; and lecture fees from St. Jude Medical. Drs Pei and Christman report being employees of and holding stock and stock options in Medtronic. Dr St. John Sutton reports receiving consulting fees from Medtronic and BioControl Medical. The other authors report no conflicts.

References
Reverse Remodeling With Biventricular Pacing

St. John Sutton et al


CLINICAL PERSPECTIVE

Biventricular pacing has proved to be efficacious in heart failure (HF) with ventricular dyssynchrony manifested by wide QRS duration. However, little is known about biventricular pacing in HF patients with atrioventricular block. Thus to date, these patients have been excluded from HF trials. The Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) trial randomized patients with atrioventricular block, New York Heart Association classes I to III HF, and LV ejection fraction ≤50% to biventricular or right ventricular (RV) pacing. Doppler echocardiograms were obtained at randomization and every 6 months through 24 months. Compared with RV pacing, biventricular pacing significantly reduced LV volumes and intraventricular mechanical delay, and improved LV ejection fraction, which is consistent with LV reverse remodeling. These parameters showed little or no change with RV pacing alone, indicating no reverse remodeling postrandomization with RV pacing. LV end systolic volume index was a significant predictor of mortality/morbidity and HF hospitalization in this unique population with an estimated increased risk ≤1% for every 1 mL/m² increase in LV end systolic volume index. This detailed echocardiographic analysis of the BLOCK HF trial has important clinical implications in supporting the use of biventricular pacing de novo rather than RV pacing for HF patients with atrioventricular block.


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