Left Ventricular Versus Simultaneous Biventricular Pacing in Patients With Heart Failure and a QRS Complex ≥120 Milliseconds

Bernard Thibault, MD; Anique Ducharme, MD, MSc; François Harel, MD, PhD; Michel White, MD; Eileen O’Meara, MD; Marie-Claude Guertin, PhD; Joel Lavoie, PhD; Nancy Frasure-Smith, PhD; Marc Dubuc, MD; Peter Guerra, MD; Laurent Macle, MD; Léna Rivard, MD; Denis Roy, MD; Mario Talajic, MD; Paul Khairy, MD, PhD; for the Evaluation of Resynchronization Therapy for Heart Failure (GREATER-EARTH) Investigators

Background—Left ventricular (LV) pacing alone may theoretically avoid deleterious effects of right ventricular pacing. Methods and Results—In a multicenter, double-blind, crossover trial, we compared the effects of LV and biventricular (BiV) pacing on exercise tolerance and LV remodeling in patients with an LV ejection fraction ≤35%, QRS ≥120 milliseconds, and symptoms of heart failure. A total of 211 patients were recruited from 11 centers. After a run-in period of 2 to 8 weeks, 121 qualifying patients were randomized to LV followed by BiV pacing or vice versa for consecutive 6-month periods. The greatest improvement in New York Heart Association class and 6-minute walk test occurred during the run-in phase before randomization. Exercise duration at 75% of peak VO2 (primary outcome) increased from 9.3±6.4 to 14.0±11.9 and 14.3±12.5 minutes with LV and BiV pacing, respectively, with no difference between groups (P=0.4327). LV ejection fraction improved from 24.4±6.3% to 31.9±10.8% and 30.9±9.8% with LV and BiV pacing, respectively, with no difference between groups (P=0.4530). Reductions in LV end-systolic volume were likewise similar (P=0.6788). The proportion of clinical responders (≥20% increase in exercise duration) to LV and BiV pacing was 48.0% and 55.1% (P=0.1615). Positive remodeling responses (≥15% reduction in LV end-systolic volume) were observed in 46.7% and 55.4% (P=0.0881). Overall, 30.6% of LV nonresponders improved with BiV and 17.1% of BiV nonresponders improved with LV pacing. Conclusion—LV pacing is not superior to BiV pacing. However, nonresponders to BiV pacing may respond favorably to LV pacing, suggesting a potential role as tiered therapy. Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00901212.

Key Words: cardiac resynchronization therapy ■ electric stimulation ■ heart failure ■ pacing

Cardiac resynchronization therapy (CRT) is an important adjunctive treatment modality for selected patients with heart failure.

Methods

Study Population

Patients were recruited from 11 sites across Canada. Each participating institution obtained approval from the local institutional review board. From the Montreal Heart Institute and Université de Montréal (B.T., A.D., F.H., M.W., E.O., J.L., M.D., P.G., L.M., L.R., D.R., M.T., P.K.), Montreal Heart Institute Coordinating Centre (M.-C.G.), and Centre Hospitalier de l’Université McGill (N.F.-S.), Montréal, Québec, Canada. The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl;doi:10.1161/CIRCULATIONAHA.111.032904/-/DC1.

Received March 17, 2011; accepted September 28, 2011.

Correspondence to Bernard Thibault, MD, Montreal Heart Institute, 5000 Belanger St, Montreal, QC, Canada H1T 1C8. E-mail ablation2000@bellnet.ca

© 2011 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.111.032904
review board. Eligibility criteria consisted of a clinical indication for an implantable cardioverter-defibrillator (ICD), a qualifying LV ejection fraction (LVEF) ≥35% measured within the previous 6 months, a QRS duration ≥120 milliseconds, and symptoms of heart failure with a 6-minute walk test distance ≤400 m.25 Patients in permanent atrial fibrillation, those limited by factors other than heart failure symptoms (eg, angina, intermittent claudication, significant heart valve stenosis, or osteoarthritis), and those with a recent myocardial infarction or cardiac surgery (<6 weeks) were excluded. Patients with prior pacemakers or ICDs considered for an upgrade to CRT were eligible provided that their percentage of ventricular pacing was ≤5%. Patients with previously implanted CRT systems were excluded.

Study Design

Details of the study design and protocol have been reported previously.23 In brief, a randomized, double-blind, crossover study was conducted. After written informed consent was obtained, all qualifying patients received a CRT-ICD system from St. Jude Medical (Minnetonka, MN). There was a 2- to 8-week run-in period during which CRT was programmed off and the AV delay was set to ≥325 milliseconds. This period allowed maturation of the CRT-ICD system and titration of pharmacological therapy as tolerated. At the end of this run-in phase, patients were required to conform to inclusion and exclusion criteria to remain eligible for randomization. Stable doses of β-blockers and angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers were mandated for a minimum of 4 weeks before a baseline assessment was conducted. Those no longer meeting eligibility criteria were excluded from the study and were offered the opportunity to be followed up in a nonrandomized registry.

In patients remaining eligible, a comprehensive baseline assessment was performed consisting of a medical questionnaire, physical examination, cardiology pulmonary exercise test using a RAMP protocol with gas exchange analyses, submaximal exercise with a constant-load protocol and 6-minute walk test, and quality-of-life questionnaires (ie, Short Form-36 and the Minnesota Living With Heart Failure questionnaire).26 LV function, geometry, and metrics of synchrony were assessed by echocardiography. In accordance with the crossover design, patients were then randomized to LV followed by BiV pacing or BiV followed by LV pacing. Each pacing modality was maintained for 6 months, with comprehensive testing at the end of each 6-month period.

Clinical and quality-of-life questionnaires were administered by independent staff blinded to device programming. Exercise testing, quality-of-life assessment, and imaging studies were performed locally, with source material transferred to independent core laboratories (Montreal Heart Institute) for blinded assessment. The study was initiated in 2003, registered at http://www.clinicaltrials.gov under the identifier NCT00901212, and funded by the Canadian Institutes for Health Research (grant 67914) in partnership with St. Jude Canada. Follow-up was completed in February 2010.

The authors were solely responsible for the design and conduct of the study, vouch for the data and analysis, and wrote the manuscript without assistance. The study was conducted in compliance with the Canadian Privacy Legislation and the World Medical Association Declaration of Helsinki (2002).

CRT-ICD Programming

At randomization, devices were programmed in the DDD mode at a base rate of 40 bpm. Faster rates were considered protocol deviations and required a waiver. Use of the activity sensor was strictly forbidden throughout the study for risk of interference with exercise testing. Optimal AV delays (AS-VP and AP-VP) were established at baseline with an ECG method; repeated 12-lead ECGs were performed with AV delays ranging from 80 to 250 milliseconds at each 10-millisecond increment. The longest AV delay that fully captured the LV (ie, no fusion with intrinsic conduction) during LV-only pacing was identified. This same AV delay was programmed during LV and BiV pacing for each patient, along with the rate-adaptive AV delay feature, and kept constant for the duration of the study. This approach eliminated the possibility of intrapatient variability in the programmed AV delay to confound comparisons between LV and BiV pacing.

Study Outcomes

Primary Outcome

The primary outcome consisted of submaximal exercise duration (expressed in minutes). Each patient’s maximal cardiopulmonary exercise capacity was assessed by use of a previously described continuous progressive exercise treadmill test with an individualized RAMP protocol. The submaximal treadmill test was performed using a constant-load protocol at an intensity corresponding to 75% of the peak VO2 determined by the maximal exercise test.25–27 After a 2-minute warm-up (1 mph, no slope), the slope and speed of the treadmill were programmed to predetermined settings corresponding to 75% of peak VO2. Heart rate was measured for 5 minutes into recovery. The test was terminated on exhaustion or after 25 minutes of exercise (itself an exclusion criterion from randomization) at baseline or after 45 minutes at 6 and 12 months.

Secondary Outcomes

Secondary outcomes included LVEF, LV end-systolic volume (LVESV), presence of interventricular and intraventricular delays, New York Heart Association (NYHA) functional class, quality-of-life metrics, distance covered during the 6-minute walk test, and N-terminal pro-B type natriuretic peptide (NT-proBNP) levels. A positive clinical response was defined as a ≥20% increase in exercise duration. A positive remodeling response was defined as a ≥15% reduction in LVESV.

Statistical Analyses

Data management and analyses were performed by the Montreal Heart Institute Coordinating Centre. A sample size of 102 patients was required to provide 99% power to detect a 5-minute difference in mean exercise duration between the 2 pacing modalities (deemed clinically relevant) while factoring in potential carryover effects and assuming a 2-tailed α of 0.5%. To allow for 15% loss to follow-up, 120 patients were targeted for randomization.

Data are presented as mean ±SD or count and frequency. For continuous efficacy end points, pacing strategies were compared by use of repeated measures ANOVA models that accounted for the correlated data structure and included a factor for time period (first or second) and pacing mode (BiV or LV).28 Potential carryover effects were assessed within ANOVA models by introducing a factor for sequence (BiV-LV versus LV-BiV) and confirmed to be absent for all outcomes. For NT-proBNP, data were log transformed before analysis to approximate normality. For NYHA, the analysis was based on a logistic regression model that considered the effect of sequence (BiV-LV versus LV-BiV) on the change in NYHA between the 2 periods. Prespecified subgroup analyses were performed for 5 baseline characteristics: sex, type of LV dysfunction (ischemic versus nonischemic), left bundle-branch block versus non–left bundle-branch block, QRS duration <150 versus ≥150 milliseconds, and estimated glomerular filtration rate <60 versus ≥60 mL min−1·1.73·2. Each subgroup analysis was performed with the ANOVA models described above, with the additional inclusion of the baseline characteristic in question and its interaction with pacing mode. Although stipulated by protocol, too few patients were without β-blockers or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers to perform valid subgroup analyses.

The proportions of responders with the 2 pacing modes were compared by use of McNemar tests. To assess the reproducibility of echocardiographic measurements, a random sample of 20 studies was evaluated twice by 2 core laboratory sonographers. Intraobserver and interobserver variability was assessed by calculating intraclass correlation coefficients. All analyses were performed under the intention-to-treat principle. All tests were 2 sided and conducted at the 0.05 significance level. Statistical analyses were performed with SAS version 9.1.
Results

Study Population
A total of 211 patients were enrolled to achieve the targeted objective of 121 randomized patients (Figure 1). Reasons for which enrolled patients were excluded from randomization (n = 90) were major problems with the CRT system (n = 26), including failure to implant the LV lead (n = 8); lead dislodgment or malfunction (n = 16) and RV anodal capture during LV pacing (n = 2); inability to perform exercise testing or exercise threshold surpassed (n = 21); prohibitive comorbid conditions, transplantation, or death (n = 18); withdrawal of consent (n = 14); LVEF ≤40% at baseline (n = 3); and other (n = 8). Of the 121 randomized patients, 112 completed the initial 6-month period and 103 completed the entire study. Dropouts occurred as a result of death (n = 7), major problems with the CRT system (n = 1), patient noncompliance (n = 7), and cardiac transplantation (n = 3, including 1 mechanical heart).

Patient Characteristics
Table 1 provides the baseline characteristics for randomized and nonrandomized patients. The mean qualifying LVEF was 23.6 ± 5.9%, and 66.9% had NYHA class III to IV symptoms. Overall, 51.2% had ischemic cardiomyopathy, 69.4% had left bundle-branch block, and 89.3% had primary prevention ICD indications. The mean optimized AV delay was 101 ± 16 milliseconds (range, 90–150 milliseconds). At inclusion, 114 patients (94.2%) and 120 patients (99.2%) were on β-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, respectively, with stable proportions that ranged between 95.0% and 100% during the course of the study. During the run-in period, the metoprolol-equivalent daily dose of β-blockers increased from 55.0 ± 46.3 to 62.9 ± 48.4 mg (P < 0.0001). During the same time frame, doses of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers did not increase significantly.

Exercise Duration
During exercise, all patients had confirmed LV and BiV capture in accordance with their randomized programmed settings. As shown in Figure 2, exercise duration with submaximal testing increased from 9.3 ± 6.4 minutes at baseline to 14.0 ± 11.9 and 14.3 ± 12.5 minutes with LV and BiV pacing, respectively, with no difference between the 2 pacing modes (P = 0.4327). This represents a >50% improvement in exercise capacity with both modes of pacing. No statistically significant interaction was noted between pacing mode and predefined subgroups (sex, type of heart failure, QRS duration, QRS morphology, and estimated glomerular filtration rate).

LV Size and Function
As depicted in Figure 3, the LVEF improved from 24.4 ± 6.3% at baseline to 31.9 ± 10.8% and 30.9 ± 9.8% with LV and BiV pacing, respectively, representing a 6% to 7% absolute increase in LVEF, with no difference between the 2 pacing modalities (P = 0.4530). Reduction in LVESV was similar in both groups (P = 0.6788), from 162.4 ± 57.2 mL at baseline to 130.3 ± 59.9 and 130.4 ± 63.4 mL with LV and BiV pacing, respectively, corresponding to a 19.7% relative reduction. The mean absolute septolateral delay was similar with LV (54.5 ± 43.5 milliseconds) and BiV (59.4 ± 42.2 milliseconds) pacing (P = 0.4376) and was no different from baseline (58.0 ± 41.8 milliseconds). However, LV pacing resulted in a shorter interventricular delay than BiV pacing (10.6 ± 27.5 versus 18.3 ± 22.9 milliseconds; P = 0.0050).

There was a statistically significant interaction between type of LV dysfunction and the impact of pacing mode on LVESV (P = 0.0307). In patients with ischemic cardiomyopathy, LVESV decreased to a lesser extent with LV compared with BiV pacing.
A similar trend was observed with NT-proBNP levels, with the baseline value decreasing from a median of 1621 pg/mL (range, 52–21 127 pg/mL) to 1032 pg/mL (range, 34–13 045 pg/mL) with LV pacing and 894 pg/mL (range, 24–15 397 pg/mL) with BiV pacing (P = 0.0933). Finally, good intraobserver (intraclass correlation coefficient, 0.95–1.00) and interobserver (intraclass correlation coefficient, 0.78–0.96) correlations were noted for echocardiographic parameters, the lowest values being for intra-LV dyssynchrony.

### Table 1. Baseline Characteristics of Randomized and Enrolled Nonrandomized Patients

<table>
<thead>
<tr>
<th></th>
<th>Randomized Patients (n = 121)</th>
<th>Nonrandomized Patients (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.9 ± 8.8</td>
<td>66.7 ± 8.8</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>91 (75.2)</td>
<td>71 (78.9)</td>
</tr>
<tr>
<td>Preimplantation New York Heart Association class III–IV, n (%)</td>
<td>81 (66.9)</td>
<td>57 (63.3)</td>
</tr>
<tr>
<td>Baseline New York Heart Association class III–IV, n (%)</td>
<td>37 (30.6)</td>
<td>24 (26.7)</td>
</tr>
<tr>
<td>Preimplantation left ventricular ejection fraction, %</td>
<td>23.6 ± 5.9</td>
<td>22.8 ± 5.5</td>
</tr>
<tr>
<td>Baseline left ventricular ejection fraction, %</td>
<td>24.4 ± 6.3</td>
<td>25.0 ± 8.0</td>
</tr>
<tr>
<td>Preimplantation 6-min walk test, m</td>
<td>302.7 ± 82.2</td>
<td>299.6 ± 76.6</td>
</tr>
<tr>
<td>Baseline 6-min walk test, m</td>
<td>363.2 ± 72.3</td>
<td>337.1 ± 92.1</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy, n (%)</td>
<td>62 (51.2)</td>
<td>62 (68.9)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>59 (48.8)</td>
<td>58 (64.4)</td>
</tr>
<tr>
<td>Prior bypass or PCI</td>
<td>44 (36.4)</td>
<td>42 (46.7)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>63 (52.1)</td>
<td>53 (58.9)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>41 (33.9)</td>
<td>26 (28.9)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease, n (%)</td>
<td>20 (16.5)</td>
<td>16 (17.8)</td>
</tr>
<tr>
<td>Prior valve surgery, n (%)</td>
<td>6 (5.0)</td>
<td>7 (7.8)</td>
</tr>
<tr>
<td>Prior ventricular tachycardia/fibrillation, n (%)</td>
<td>13 (10.7)</td>
<td>13 (14.4)</td>
</tr>
<tr>
<td>Prior atrial fibrillation/flutter, n (%)</td>
<td>27 (22.3)</td>
<td>20 (22.2)</td>
</tr>
<tr>
<td>ICD upgraded to CRT-ICD, n (%)</td>
<td>8 (6.6)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Pacemaker upgraded to CRT-ICD, n (%)</td>
<td>3 (2.5)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>154.9 ± 23.2</td>
<td>160.2 ± 23.8</td>
</tr>
<tr>
<td>Typical LBBB morphology, n (%)</td>
<td>84 (69.4)</td>
<td>53 (58.9)</td>
</tr>
<tr>
<td>Typical RBBB morphology, n (%)</td>
<td>5 (4.1)</td>
<td>12 (13.3)</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>132.8 ± 14.7</td>
<td>131.2 ± 13.0</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>109.0 ± 31.3</td>
<td>112.9 ± 37.8</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min</td>
<td>64.6 ± 18.0</td>
<td>62.2 ± 19.7</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>139.0 ± 3.0</td>
<td>138.9 ± 2.8</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.4 ± 0.4</td>
<td>4.3 ± 0.5</td>
</tr>
<tr>
<td>NT-proBNP, median (range), pg/L</td>
<td>1621 (52–21 127)</td>
<td>1260 (163–14 146)</td>
</tr>
<tr>
<td>β-Blocker therapy, n (%)</td>
<td>114 (94.2)</td>
<td>76 (84.4)</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs, n (%)</td>
<td>120 (99.2)</td>
<td>83 (92.2)</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
<td>56 (46.3)</td>
<td>40 (44.4)</td>
</tr>
<tr>
<td>Loop diuretic, n (%)</td>
<td>100 (82.6)</td>
<td>74 (82.2)</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>57 (47.1)</td>
<td>42 (46.7)</td>
</tr>
</tbody>
</table>

PCI indicates percutaneous coronary intervention; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; LBBB, left bundle-branch block; RBBB, right bundle-branch block; NT-proBNP, N-terminal pro-B type natriuretic peptide; ACE, angiotensin-converting enzyme; and ARB, angiotensin receptor blocker. Unless otherwise indicated, baseline (as opposed to preimplantation) data are provided.

### Functional Status and Quality of Life

Figure 4 portrays the NYHA functional class over the course of the study. At the time of inclusion, 66.9% of patients had class III to IV symptoms. The largest reduction in the proportion of patients with class III to IV symptoms occurred during the run-in phase before randomization (with CRT off), i.e., from 68.9% to 30.6% (P < 0.0001). A nonsignificant correlation was noted between a reduction in NYHA functional class symptoms and an increase in β-blocker dose (P = 0.0599). A modest reduction in the proportion of patients...
with NYHA class III to IV symptoms was noted thereafter (20.6% with LV and 25.0% with BiV pacing), with no difference between the 2 pacing modalities ($P=0.8911$). The same pattern was observed for the 6-minute walk test. The distance increased from 302.7±82.2 to 363.2±72.3 m from before implantation to baseline ($P<0.0001$) and improved modestly thereafter (387.3±81.0 m with LV pacing, $P=0.0166$; 377.1±93.3 m with BiV pacing, $P=0.0836$), with no difference between the 2 pacing modalities ($P=0.6855$). Likewise, a nonsignificant correlation was noted between distance covered during the 6-minute walk test and an increase in β-blocker dose ($P=0.0962$).

Results of quality-of-life assessments (Short Form-36 and Minnesota Living with Heart Failure questionnaire) are presented in Table 2, with lower scores indicating superior quality of life. No differences in physical and mental components of quality of life were noted between the 2 pacing modalities.

Response to Therapy
A clinical response defined by a ≥20% improvement in duration of submaximal exercise was noted in 47 of 98 patients (48.0%) with LV pacing and 54 of 98 patients (55.1%) with BiV pacing ($P=0.1615$). Similarly, a favorable reverse LV remodeling response defined by a ≥15% relative reduction in LVESV was observed in 43 of 92 patients (46.7%) and 51 of 92 patients (55.4%) with LV and BiV pacing, respectively ($P=0.0881$). Among the 51 clinical nonresponders with LV pacing, 16 (31.4%) responded to BiV pacing; conversely, among the 44 nonresponders with BiV pacing, 9 (20.5%) responded to LV pacing. As for reverse remodeling, 30.6% of patients (15 of 49) who did not respond to LV pacing responded to BiV pacing, whereas the proportion of BiV nonresponders who benefited from LV pacing was 17.1% (7 of 41). Finally, agreement between clinical and reverse remodeling responses was 51.1% (47 of 92 patients) and 56.7% (51 of 90 patients) with LV and BiV pacing, respectively.

Adverse Events
Overall, 7 patients died during the course of the study (LV pacing, 3; BiV pacing, 4). The causes of death were heart failure (n=3), sudden death (n=1), pneumonia (n=1), cancer (n=1), and stroke (n=1). Eighteen patients presented a total of 30 hospitalizations for heart failure: 16 during LV pacing and 14 with BiV pacing. Atrial fibrillation, as detected by devices, occurred in 9.7% of patients, with the pacing mode having no influence on the prevalence rate or atrial fibrillation burden. At least 1 episode of ventricular tachycardia or fibrillation was detected in 11.3% of patients, with no difference according to pacing mode.

Discussion
In this randomized clinical trial, we tested the hypothesis that LV pacing is superior to BiV pacing in improving exercise capacity and reverse LV remodeling. This hypothesis was
Table 2. Quality-of-Life Scores in Randomized Patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>LV Pacing</th>
<th>BiV Pacing</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 physical score</td>
<td>34.1±9.0</td>
<td>38.3±9.4</td>
<td>37.3±10.1</td>
<td>0.48</td>
</tr>
<tr>
<td>SF-36 mental score</td>
<td>46.9±11.4</td>
<td>48.8±10.0</td>
<td>48.8±11.4</td>
<td>0.99</td>
</tr>
<tr>
<td>MLWHF emotional score</td>
<td>9.8±7.0</td>
<td>7.0±6.2</td>
<td>7.0±5.8</td>
<td>0.91</td>
</tr>
<tr>
<td>MLWHF physical score</td>
<td>20.9±10.7</td>
<td>16.5±10.4</td>
<td>17.3±11.2</td>
<td>0.62</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; BiV, biventricular; SF-36, Short Form-36; and MLWHF, Minnesota Living With Heart Failure questionnaire.

supported by preliminary experimental data\textsuperscript{11–15} and grounded on the principle that avoiding RV pacing may be desirable.\textsuperscript{16–18} The results of our study suggest that LV pacing alone appears less favorable than previously suggested,\textsuperscript{13,15} with the 2 pacing strategies resulting in similar improvements in exercise capacity and reverse LV remodeling. Underlying reasons as to why LV mechanics may improve to a greater or similar extent with BiV and LV-only pacing remain speculative and merit further investigation. Nevertheless, our findings are consistent with a pilot study that demonstrated a similar proportion of responders (defined as an absolute increase in LV EF ≥5% and/or a ≥10% relative increase 6-minute walk test distance) with LV compared with BiV pacing.\textsuperscript{20} An echocardiographic study found that, compared with LV pacing, BiV pacing was associated with a trend toward greater improvement in LV volume.\textsuperscript{19} However, the Biventricular Versus Left Univentricular Pacing With ICD Back-Up in Heart Failure Patients (B-LEFT HF) trial found that LV pacing was noninferior to BiV pacing in terms of a composite outcome consisting of NYHA functional class and ≥5-mm reduction in LV end-systolic diameter at 6 months.\textsuperscript{21}

The Evaluation of Resynchronization Therapy for Heart Failure (GREATER-EARTH) trial is unique in several respects, including its crossover design, prerandomization phase that allowed up titration and stabilization of pharmacological therapy, and approach to exercise tolerance testing. The study also underscores the complexities of determining comparative benefits of the 2 types of pacing. Importantly, the greatest improvement in end points such as NYHA functional class and 6-minute walk test occurred during the run-in period without pacing. Functional parameters further improved with LV and BiV pacing, but to a lesser and similar extent. Underlying reasons for early improvements before randomization remain speculative and are likely multifactorial. They may include benefits of pharmacological therapy, a training effect, and/or a placebo effect.\textsuperscript{30,31} In terms of pharmacological therapy, the dose of β-blockers, but not angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, increased significantly during the run-in period. Beneficial effects of β-blockers in patients with heart failure are well known. Dose adjustments likely contributed to early improvement, as reflected by the trend toward a greater reduction in NYHA functional symptoms with increased doses.

The optimal method to assess clinical response to CRT remains a topic of debate.\textsuperscript{32,33} Our findings raise concern over composite end points that rely on subjective measures such as NYHA functional class, particularly if a baseline evaluation is not performed after implantation and before active therapy.\textsuperscript{34} Although the 6-minute walk test has obvious advantages, including ease of administration and patient compliance, it is highly dependent on patient motivation and may be subjected to external factors, including onlookers.\textsuperscript{30,31,35,36} At the other end of the spectrum, maximal cardiopulmonary exercise testing (peak VO\textsubscript{2}) provides robust data but may be poorly tolerated by patients with heart failure, requires careful calibration, and is insensitive for the detection of therapeutic responses.\textsuperscript{37} The submaximal exercise treadmill test, as performed in our study, has been proposed as an alternative method that combines ease of administration with excellent reproducibility and greater sensitivity in assessing therapeutic responses.\textsuperscript{38–41} It was well tolerated by our population of patients with heart failure. Arguably, it also provides more clinically meaningful results; eg, walking 5 minutes longer at 75% of maximal capacity provides more information than walking 30 m further in 6 minutes.

Defining the overall response to CRT also remains controversial, with poor correlations between clinical and echocardiographic parameters. In our GREATER-EARTH trial, the proportion of clinical (≥20% exercise duration) and echocardiographic (≥15% reduction in LVESV) responders was comparable to that in prior studies.\textsuperscript{28,42} Our crossover design provided the additional advantage of assessing whether nonresponders to 1 strategy may reap benefit from the alternate pacing modality. Interestingly, >20% of nonresponders to BiV pacing responded clinically when crossed over to LV pacing, and 17% developed positive LV remodeling responses. Although these provocative findings suggest that a trial of LV pacing may be warranted in the absence of a favorable response to BiV pacing, it remains to be determined whether a similar or superior response may have been obtained by ventriculo-ventricular optimization. Randomized clinical trials, however, have failed to demonstrate a clinical benefit from ventriculo-ventricular optimization.\textsuperscript{9,10} Adequately powered studies are required to refine pacing strategies to improve success rates in initially nonresponsive patients.\textsuperscript{43}

In addition to providing a clinically pertinent rationale for attempting a trial of crossover from 1 pacing mode to the other in initial nonresponders, these results may prove relevant to future innovations in CRT. Currently, there is little reason not to place an RV lead in a CRT system, with such a lead being an essential component of a defibrillation system. However, the rationale for eliminating an RV lead will likely become increasingly relevant, considering the development of new LV leads (eg, multipolar and/or with defibrillation capacity) and novel implantation techniques (eg, multisite LV pacing, endocardial LV pacing via a transseptal approach, and other epicardial approaches). Nevertheless, the notable complication risk associated with device revision, particularly when it involves the addition of a transvenous lead,\textsuperscript{44} is a deterrent to an LV-only approach. In the event that an RV lead becomes dysfunctional for pacing while remaining adequate for defibrillation, our findings may support a trial of LV-only pacing without RV lead reintervention.

**Study Limitations**

A higher-than-projected proportion of patients (40%) initially enrolled in the prerandomization phase did not proceed to...
randomization, highlighting the difficulties associated with implantation and proper functioning of the device (ie, 38% of patients were not randomized for this reason). This resulted in a substantially longer recruitment period and may affect the generalizability of the study results. Nevertheless, the exclusion of inappropriate candidates represents a desirable tradeoff in maximizing internal validity. It is worth noting that NYHA functional class was neither an inclusion nor exclusion criterion. The functional parameter that determined eligibility was a 6-minute walk test limited by heart failure symptoms with a distance walked ≤400 m. The proportion of patients with NYHA class I or II symptoms reflects the discrepancy between subjective and more objective measures of functional capacity. Finally, although the projected study power was attained for primary and secondary functional and structural remodeling outcomes, the study was neither designed nor powered to address event-driven end points.

Conclusions
In this multicenter, randomized, double-blind crossover clinical trial comparing LV and BiV pacing in patients with LVEF ≤35%, a QRS duration ≥120 milliseconds, and symptoms of heart failure, there was no clear advantage for 1 signed nor powered to address event-driven end points.

Acknowledgments
We wish to thank Carmen Leblanc and Johanne Veillette (Montreal Heart Institute) for their expert assistance in project management. We are also indebted to the entire staff at the Montreal Heart Institute Coordinating Center for Data Coordination and Management and to Luce Bégin (Montreal Heart Institute) for secretarial support.

Source of Funding
The study was supported by the Canadian Institutes of Health Research (grant 67914) in partnership with St. Jude Canada.

Disclosures
Dr Thibault is a consultant for St. Jude, Medtronic, and Sorin. The other authors report no conflicts.

References
10. Abraham WT, Gras D, Yu CM, Guzzo L, Gupta MS. Rationale and design of a randomized clinical trial to assess the safety and efﬁcacy of frequent optimization of cardiac resynchronization therapy: the Frequent Optimization Study Using the QuickOpt Method (FREEDOM) trial. Am Heart J. 2010;159:944–948.
Cardiac resynchronization therapy (CRT) is an important adjunctive treatment modality for selected patients with heart failure. The GREATER-EARTH trial tested the hypothesis that left ventricular pacing alone is superior to biventricular pacing. A unique run-in period (with CRT off) between implantation and the baseline assessment allowed for maturation of the left ventricular leads (eg, multipolar or with defibrillation capacity) and novel implantation techniques. The rationale for eliminating a right ventricular lead will likely become increasingly relevant with the development of new left ventricular leads (eg, multipolar or with defibrillation capacity) and novel implantation techniques.
Left Ventricular Versus Simultaneous Biventricular Pacing in Patients With Heart Failure and a QRS Complex $\geq 120$ Milliseconds

Bernard Thibault, Anique Ducharme, François Harel, Michel White, Eileen O'Meara, Marie-Claude Guertin, Joel Lavoie, Nancy Frasure-Smith, Marc Dubuc, Peter Guerra, Laurent Macle, Léna Rivard, Denis Roy, Mario Talajic, Paul Khairy and for the Evaluation of Resynchronization Therapy for Heart Failure (GREATER-EARTH) Investigators

_Circulation._ 2011;124:2874-2881; originally published online November 21, 2011; doi: 10.1161/CIRCULATIONAHA.111.032904

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 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/124/25/2874

An erratum has been published regarding this article. Please see the attached page for:
/content/126/16/e260.full.pdf

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2011/11/18/CIRCULATIONAHA.111.032904.DC1

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/
In the article by Thibault et al, “Left Ventricular Versus Simultaneous Biventricular Pacing in Patients With Heart Failure and a QRS Complex ≥120 Milliseconds,” which published in the December 20, 2011 issue of the journal (Circulation. 2011;124:2874–2881), the authors included an incomplete Disclosure Statement. The Disclosure Statement should read:

“Dr Thibault received a research grant from St. Jude Medical, honoraria from St. Jude Medical, Sorin and Medtronic, and is a consultant for St. Jude, Sorin and Medtronic. Dr Ducharme received research grants from St. Jude Medical and Sorin, speaker’s fees from Abbott and Servier and is a consultant for Bristol-Myers Squibb and Medtronic. Dr Harel received a research grant from the Canadian Institutes of Health Research. Dr O’Meara received research grants from Canadian Institutes of Health Research and Fonds de la Recherche Quebec en Sante, honoraria from Pfizer and Merck. Dr Guerra received speaker’s fees from St. Jude Medical and Medtronic and has ownership interest in Sanofi, Aventis and Bayer. Dr Talajic received research grants from St. Jude Medical, Medtronic and Boston Scientific, speaker’s fees and honoraria from Medtronic, and is on the Advisory Board of Medtronic. Dr Roy received a research grant from St. Jude Medical. Dr Khairy has a Canada Research Chair and received honoraria from Medtronic CryoCath LP. No other conflicts to report.”

Rather than:

“Dr Thibault is a consultant for St. Jude, Medtronic, and Sorin. The other authors report no conflicts.”

The current online version of the manuscript has been corrected. The authors apologize for the error.
SUPPLEMENTAL MATERIAL
Appendix:

Participating centers in Canada:

Dr. John Yeung, St-Paul’s Hospital, Vancouver, British Columbia
Dr. Soori Sivakumaran, University of Alberta Hospital, Edmonton, Alberta
Dr. Paul Dorian, St. Michael’s Hospital, Toronto, Ontario
Dr. Eugene Crystal, Sunnybrook and Women’s College Health Sciences Centre, Toronto, Ontario
Dr. David Birnie, University of Ottawa Heart Institute, Ottawa, Ontario
Dr. Marcio Sturmer, Hôpital Sacré-Coeur, Montreal, Quebec
Dr. Benoit Coutu, Centre Hospitalier de l’Université de Montréal, Montreal, Quebec
Dr. Félix Ayala-Paredes, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Quebec
Dr. François Philippon, Institut universitaire de Cardiologie et de Pneumologie de Québec, Quebec, Quebec
Dr. Magdy Basta, Queen Elizabeth II Health Sciences Centre, Nova Scotia

Members of the steering committee:

Dr. Bernard Thibault, Dr. Anique Ducharme, Dr. François Harel, Dr. Michel White, Dr. Eileen O’Meara, Dr. Denis Roy, Dr. Jean Rouleau, Dr. Paul Khairy, Dr. Marie-Claude Guertin, Montreal, Quebec
Dr. François Philippon, Quebec City, Quebec
Dr. Paul Dorian, Toronto, Ontario
Ms. Linnea Aasen-Johnston, St. Jude Canada
Mr. Irwin Schweitzer, CIHR, Ottawa
Members of the Adverse Event Committee:
Chair: Dr. Paul Khairy, Institut de Cardiologie de Montréal, Montreal, Quebec
Dr. Mario Talajic, Institut de Cardiologie de Montréal, Montreal, Quebec
Dr. Eileen O’Meara, Institut de Cardiologie de Montréal, Montreal, Quebec
Dr. Marcio Sturmer, Hôpital Sacré-Coeur, Montreal, Quebec

Members of the Data and Safety Monitoring Board:
Chair: Dr. Kenneth Ellenbogen, Medical College of Virginia, Virginia
Dr. Christine Schubert, Virginia Commonwealth University, Richmond
Dr. David Taylor, Cleveland Clinic, Cleveland, Ohio
Dr. Jagmeeth Singh, Service Massachusetts General Hospital Harvard Medical School, Boston, Massachusetts

Core labs:
Echocardiography core lab director: Dr. Anique Ducharme. Assistants: Dr. Halyna Prylutska, Ms. Céline Pitre.
Nuclear medicine core lab director: Dr. François Harel. Assistant: Mr. Vincent Finnerty.
Stress test core lab director: Dr. Michel White. Assistants: Ms. Julie Graham and Ms. Geneviève Gravel.
Biomarker core lab co-directors: Dr. Anique Ducharme, Dr. Joel Lavoie and Dr. Eileen O’Meara.
Quality of life questionnaire analyses: Dr. Nancy Frasure-Smith.