



Paced left ventricular QRS width and ECG parameters predict outcomes after cardiac resynchronization therapy: PROSPECT-ECG substudy.

Jeff M Hsing, Kimberly A Selzman, Christophe Leclercq, Luis A Pires, Michael G McLaughlin, Scott E Mcrae, Brett J Peterson, Peter J Zimetbaum

► To cite this version:

Jeff M Hsing, Kimberly A Selzman, Christophe Leclercq, Luis A Pires, Michael G McLaughlin, et al.. Paced left ventricular QRS width and ECG parameters predict outcomes after cardiac resynchronization therapy: PROSPECT-ECG substudy.. *Circulation: Arrhythmia and Electrophysiology*, 2011, 4 (6), pp.851-7. .

HAL Id: hal-00907576

<https://hal.archives-ouvertes.fr/hal-00907576>

Submitted on 21 May 2014

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Paced Left Ventricular QRS Width and ECG Parameters Predict Outcomes After Cardiac Resynchronization Therapy: PROSPECT-ECG Substudy

Jeff M. Hsing, Kimberly A. Selzman, Christophe Leclercq, Luis A. Pires, Michael G. McLaughlin, Scott E. McRae, Brett J. Peterson and Peter J. Zimetbaum

Circ Arrhythm Electrophysiol. 2011;4:851-857; originally published online September 28, 2011;
doi: 10.1161/CIRCEP.111.962605

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circep.ahajournals.org/content/4/6/851>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Arrhythmia and Electrophysiology* 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: Arrhythmia and Electrophysiology* is online at:
<http://circep.ahajournals.org/subscriptions/>

Paced Left Ventricular QRS Width and ECG Parameters Predict Outcomes After Cardiac Resynchronization Therapy

PROSPECT-ECG Substudy

Jeff M. Hsing, MS, MD; Kimberly A. Selzman, MD, MPH; Christophe Leclercq, MD, PhD;
Luis A. Pires, MD; Michael G. McLaughlin, MD; Scott E. McRae, MS;
Brett J. Peterson, BS; Peter J. Zimetbaum, MD

Background—For patients with symptomatic New York Heart Association class III or IV, ejection fraction $\leq 35\%$, and QRS ≥ 130 ms, cardiac resynchronization therapy (CRT) has become an established treatment option. However, use of these implant criteria fails to result in clinical or echocardiographic improvement in 30% to 45% of CRT patients.

Methods and Results—The Predictors of Response to CRT (PROSPECT)-ECG is a substudy of the prospective observational PROSPECT trial. ECGs collected before, during, and after CRT implantation were analyzed. Primary outcomes were improvement in clinical composite score (CCS) and reduction of left ventricular end systolic volume (LVESV) of $>15\%$ after 6 months. Age, sex, cause of cardiomyopathy, myocardial infarction location, right ventricular function, mitral regurgitation, preimplantation QRS width, preimplantation PR interval, preimplantation right ventricular-paced QRS width, preimplantation axis categories, LV-paced QRS width, postimplantation axis categories, difference between biventricular (Bi-V) pacing and preimplantation QRS width, and QRS bundle branch morphological features were analyzed univariably in logistic regression models to predict outcomes. All significant predictors ($\alpha=0.1$), age, and sex were used for multivariable analyses. Cardiomyopathy cause interaction and subanalyses were also performed. In multivariable analyses, only QRS left bundle branch morphological features predicted both CCS (odds ratio [OR]=2.46, $P=0.02$) and LVESV (OR=2.89, $P=0.048$) response. The difference between Bi-V and preimplantation QRS width predicted CCS improvement (OR=0.89, $P=0.04$). LV-paced QRS width predicted LVESV reduction (OR=0.86, $P=0.01$). Specifically, an LV-paced QRS width of ≤ 200 ms was predictive of nonischemic LVESV reduction (OR=5.12, $P=0.01$).

Conclusions—Baseline left bundle branch QRS morphological features, LV-paced QRS width, and the difference between Bi-V and preimplantation QRS width can predict positive outcomes after CRT and may represent a novel intraprocedural method to optimize coronary sinus lead placement.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00253357.

(*Circ Arrhythm Electrophysiol.* 2011;4:851-857.)

Key Words: cardiac resynchronization therapy ■ ECG criteria ■ electrocardiography ■ heart failure ■ pacemakers

Cardiac resynchronization therapy (CRT) has become a well-established treatment option for patients with depressed left ventricular function, congestive heart failure, and a prolonged QRS width. Between 30% and 45% of patients who undergo CRT fail to demonstrate clinical benefit or echocardiographic evidence of improved left ventricular function.¹⁻⁴ The Predictors of Response to CRT (PROSPECT) was a prospective, observational, multicenter clinical trial designed to test the predictive value of a comprehensive set of echocardiographic predictors of dyssynchrony to identify response to CRT.⁵ In addition, this trial also evaluated a series

of electrocardiographic parameters to determine their usefulness in predicting outcomes after CRT. We present the results of an analysis of preprocedural and intraprocedural implantation electrocardiographic Predictors of Response to CRT (PROSPECT-ECG), a substudy of PROSPECT.

Clinical Perspective on p 857

Methods

Patients and Study Protocol

Patients included in this analysis were from the PROSPECT trial.⁵ Enrollment criteria were based on standard guidelines, specifically left

Received February 11, 2011; accepted September 1, 2011.

From the Department of Medicine (J.M.H., M.G.M., P.J.Z.), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass; Department of Medicine (K.A.S.), George E. Wahlen VA Hospital, University of Utah, Salt Lake City; Department de Cardiologie (C.L.), Centre Cardio-pneumologique, Centre Hospitalier Universitaire Pontchaillou, Rennes, France; Department of Medicine (L.A.P.), St John Hospital and Medical Center, Detroit, MI; and Medtronic Inc (S.E.M., B.J.P.), Minneapolis, Minn.

Correspondence to Peter J. Zimetbaum, MD, Department of Medicine (Cardiovascular Division), Beth Israel Deaconess Medical Center, Harvard Medical School, 185 Baker Rd, Baker 4, Boston, MA 02215. E-mail pzimetba@bidmc.harvard.edu

© 2011 American Heart Association, Inc.

Circ Arrhythm Electrophysiol is available at <http://circep.ahajournals.org>

DOI: 10.1161/CIRCEP.111.962605

ventricular ejection fraction $\leq 35\%$, QRS width ≥ 130 ms, New York Heart Association functional class III or IV, despite optimal medical therapy, including angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for at least 1 month and β -blocker started at least 3 months before enrollment. Patients were enrolled across 53 centers in the United States, Europe, and Hong Kong from March 2004 to December 2005. A total of 498 patients were enrolled, with 31 early exits and 41 having QRS < 130 ms, leaving 426 for the final study group. There were 2 separate primary outcomes: heart failure clinical composite score (CCS) and left ventricular end systolic volume (LVESV). All 426 patients had complete CCSs. There were 286 patients who had baseline and 6-month echocardiograms for paired LVESV measurements. All centers collected baseline ECG data before CRT implantation. At implantation, ECGs of right ventricular (RV)- and LV-only pacing and biventricular (Bi-V) pacing were collected. A Medtronic market-released CRT device, with or without implantable cardioverter-defibrillator functionality, was used in the study.

Electrocardiographic Core Laboratories

All recorded ECGs were reviewed at the ECG core laboratory, Harvard Clinical Research Institute, for analysis. All centers collected baseline ECG data before the implantation procedure for analysis, including preimplantation QRS width, PR interval, QRS axis, and QRS bundle branch morphological features. During device implantation, the ECG data collected for analysis included RV-paced QRS width, LV-paced QRS width, Bi-V-paced QRS axis, and Bi-V-paced QRS width. The difference between Bi-V and preimplantation QRS width was calculated for analysis. ECG measurements were made using any lead to obtain the largest value. QRS bundle branch morphological features were assessed using lead V1.

Definition of Response to CRT

A response to CRT in the PROSPECT trial was determined through the use of 2 separately analyzed primary outcomes at 6 months: heart failure CCS and relative change in LVESV. The CCS describes patients, regardless of vital status, at 6 months and combines both objective and subjective measures of clinical status, including all-cause mortality, New York Heart Association class, heart failure hospitalization, and patient global assessment.⁶ A patient's CCS was classified as worsened, improved, or unchanged. A *positive response to CRT* was defined as a CCS designation of "improved" and/or a reduction in LVESV of $\geq 15\%$ at 6 months compared with baseline.

Statistical Analysis

The analysis included 14 variables that were used in logistic regression models to assess their association with response to CRT. These included age, sex, cause of cardiomyopathy, myocardial infarction location, RV function, mitral regurgitation, preimplantation QRS width, preimplantation PR interval, preimplantation RV-paced QRS width, preimplantation and postimplantation axis categories, LV-paced QRS width, a variable defined for the difference between Bi-V and preimplantation QRS width, and QRS bundle branch morphological features. Preimplantation QRS width, LV-paced QRS width, and the difference between Bi-V and preimplantation QRS width were all defined in increments of 10 ms. QRS bundle branch morphological features were assessed using lead V1 and were categorized into left bundle branch block (LBBB), right bundle branch block (RBBB), or indeterminate. A QRS morphological comparison was made between LBBB and RBBB.

A univariable logistic regression model was defined for each variable versus the CCS response and the LVESV response. Only those subjects with available data were used in the models. $P \leq 0.10$ was used to select variables for multivariable analysis. Multivariable logistic regression models were then defined for each response variable, with the statistically significant variables from the univariable models used as covariates. Age and sex were also included in all multivariable models as covariates. Covariates that were significant in the final multivariable model, with $P \leq 0.05$, were further analyzed for interactions between the covariate and cardiomyopathy cause (ischemic versus nonischemic), along with the associated subanalyses. Odds ratios (ORs) and associated 95% CIs from the logistic regression models were calculated.

Univariable and multivariable analyses for CCS and LVESV responses were repeated by replacing preimplantation QRS width with dichotomized QRS width < 150 ms versus ≥ 150 ms for comparison with other previously published CRT trials. The multivariable analyses were repeated on a dichotomy of postimplantation LV QRS width for the LVESV response only. The value used as the cut point for the dichotomy was chosen by looking at a 10-ms interval and selecting one that had good sensitivity and balancing specificity.

Results

A total of 498 patients were enrolled and 467 patients completed CRT implantation. CCS was completed in 426 patients, as 41 were removed because of a reduction in the preimplantation QRS width below the required 130 ms at implantation. Of the 426 patients, 363 underwent a baseline echocardiogram; 286 of these patients completed a 6-month visit with an echocardiogram, allowing assessment of the LVESV end point (Figure). Of the 426 patients, 84 were CRT upgrades and 342 were new implants. A total of 413 preimplantation ECGs and 376 postimplantation ECGs were available for analysis. The QRS morphological features on the ECG were distributed as follows: 87% had LBBB, 10% had RBBB, and 3% were indeterminate.

Based on the CCS end point, 69% of patients improved, 16% worsened, and 15% remained unchanged. Based on the LVESV end point, 56% had $> 15\%$ reduction, 9% had $> 15\%$ increase, and 35% had $< 15\%$ increase or decrease in LVESV.

Univariable and Multivariable Models

For the univariable models, $P \leq 0.10$ was considered significant and the corresponding variable was included in the multivariable model. The significant predictors in the univariable models for CCS response were nonischemic cardiomyopathy (OR=0.57, $P=0.01$), preimplantation RV-paced QRS width (OR=0.98, $P=0.10$), preimplantation QRS axis category ($P=0.10$), difference between Bi-V and preimplantation QRS width (OR=0.87, $P=0.01$), and QRS left bundle branch morphological features (OR=2.47, $P=0.01$) (Table 1). The significant predictors in the univariable models for LVESV response were female sex (OR=1.72, $P=0.04$), nonischemic cardiomyopathy (OR=0.60, $P=0.03$), RV function (OR=0.40, $P=0.05$), preimplantation PR interval (OR=0.99, $P=0.01$), preimplantation QRS width (OR=1.10, $P=0.08$), LV-paced QRS width (OR=0.94, $P=0.07$), the difference between Bi-V and preimplantation QRS width (OR=0.81, $P<0.01$), and QRS left bundle branch morphological features (OR=3.38, $P<0.01$) (Table 2). The variables that predicted a significant positive response for both CCS improvement and LVESV reduction were nonischemic cardiomyopathy, difference between Bi-V and preimplantation QRS width, and QRS left bundle branch morphological features.

Variables in the univariable analysis with $P \leq 0.10$, as well as age and sex, were included in the multivariable model. Multivariable significant predictors were defined as having a $P \leq 0.05$. Preimplantation RV-paced QRS width was not used in multivariable analysis because of the few ECGs available for analysis. After multivariable analysis, the significant predictors of CCS response were the difference between Bi-V and preimplantation QRS width (OR=0.89, $P=0.04$) and QRS left bundle branch morphological features (OR=2.46, $P=0.02$).

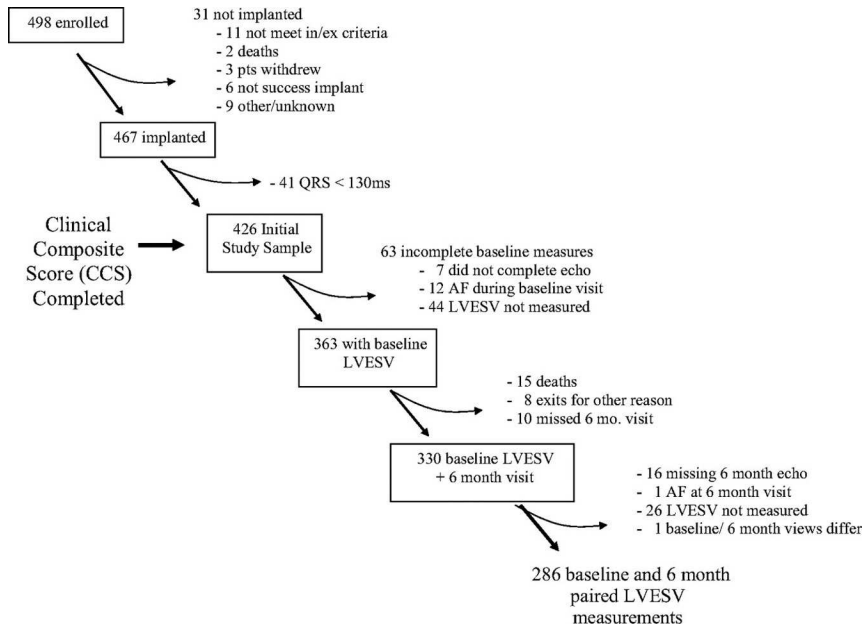


Figure. Enrollment and follow-up of patients in PROSPECT. Reprinted with permission from PROSPECT.

(Table 1). The significant multivariable predictors for LVESV response were LV-paced QRS width (OR=0.86, $P=0.01$) and QRS left bundle branch morphological features (OR=2.89, $P=0.048$) (Table 2). The only variable in the multivariable analysis that predicted a significant positive response for both

CCS improvement and LVESV reduction was QRS left bundle branch morphological features. After adjusting for other significant predictors, LBBB patients were more likely than RBBB patients to have a positive CCS response, with an OR of 2.46, and an LVESV response, with an OR of 2.89.

Table 1. Univariable and Multivariable Analysis for CCS End Point

| Explanatory Variables | Comparison of Levels | Univariable | | Multivariable | |
|---|--|--------------------------------------|----------------|--------------------------------------|----------------|
| | | OR Estimates (95% Confidence Limits) | <i>P</i> Value | OR Estimates (95% Confidence Limits) | <i>P</i> Value |
| Age (n=426) | Continuous | 1.00 (0.98, 1.02) | 0.88 | 1.00 (0.98, 1.02) | 0.98 |
| Sex (n=426) | Female vs male | 1.20 (0.76, 1.91) | 0.43 | 0.89 (0.51, 1.57) | 0.70 |
| Cause of cardiomyopathy (n=426) | Ischemic vs nonischemic | 0.57 (0.38, 0.87) | 0.01 | 0.64 (0.38, 1.10) | 0.11 |
| MI location (n=149) | Anterior vs posterior | 0.54 (0.11, 2.78) | 0.53 | | |
| | Inferior vs posterior | 0.42 (0.08, 2.21) | | | |
| RV function (n=371) | Moderately/severely depressed vs normal/mildly depressed | 0.59 (0.27, 1.29) | 0.19 | | |
| Mitral regurgitation (n=254) | Moderate (20–40%)/severe (>40%) vs none/mild (<20%) | 0.72 (0.42, 1.22) | 0.22 | | |
| Preimplantation QRS width (n=376) | 10-ms Increments | 1.06 (0.97, 1.16) | 0.21 | | |
| Preimplantation PR interval (n=370) | Continuous | 1.00 (1.00, 1.01) | 0.74 | | |
| Preimplantation RV- paced QRS width (n=32) | Continuous | 0.98 (0.95, 1.00) | 0.10 | | |
| Preimplantation axis categories (n=413) | <−75 vs ≥130 | 2.75 (0.86, 8.77) | 0.10 | 1.31 (0.51, 3.35) | 0.34 |
| | −75−<0 vs ≥130 | 1.21 (0.54, 2.68) | | 3.00 (0.62, 14.41) | |
| | 0−<130 vs ≥130 | 1.92 (0.81, 4.55) | | 1.85 (0.69, 4.99) | |
| LV-paced QRS width (n=307) | 10-ms Increments | 0.96 (0.91, 1.02) | 0.20 | | |
| Postimplantation axis categories (n=376) | <−75 vs ≥130 | 1.52 (0.76, 3.04) | 0.34 | | |
| | −75−<0 vs ≥130 | 1.47 (0.80, 2.72) | | | |
| | 0−<130 vs ≥130 | 1.56 (0.81, 3.00) | | | |
| Difference between Bi-V and preimplantation QRS width (n=334) | 10-ms Increments | 0.87 (0.79, 0.96) | 0.01 | 0.89 (0.80, 0.99) | 0.04 |
| QRS bundle branch morphological features in lead V1 (n=405) | LBBB vs RBBB | 2.47 (1.30, 4.68) | 0.01 | 2.46 (1.13, 5.39) | 0.02 |

MI indicates myocardial infarction.

Table 2. Univariable and Multivariable Analysis for LVESV End Point

| Explanatory Variables | Comparison of Levels | Univariable | | Multivariable | |
|---|--|--------------------------------------|---------|--------------------------------------|---------|
| | | OR Estimates (95% Confidence Limits) | P Value | OR Estimates (95% Confidence Limits) | P Value |
| Age (n=286) | Continuous | 1.01 (0.98, 1.03) | 0.68 | 1.02 (0.99, 1.06) | 0.18 |
| Sex (n=286) | Female vs male | 1.72 (1.01, 2.91) | 0.04 | 0.97 (0.45, 2.10) | 0.94 |
| Cause of cardiomyopathy (n=286) | Ischemic vs nonischemic | 0.60 (0.37, 0.96) | 0.03 | 0.93 (0.46, 1.88) | 0.84 |
| MI location (n=95) | Anterior vs posterior | 3.33 (0.28, 39.43) | 0.21 | | |
| | Inferior vs posterior | 1.67 (0.14, 19.76) | | | |
| RV function (n=277) | Moderately/severely depressed vs normal/mildly depressed | 0.40 (0.16, 0.99) | 0.05 | 0.56 (0.17, 1.85) | 0.34 |
| Mitral regurgitation (n=191) | Moderate (20–40%)/severe (>40%) vs none/mild (<20%) | 0.68 (0.38, 1.21) | 0.19 | | |
| Preimplantation QRS width (n=254) | 10-ms Increments | 1.10 (0.989, 1.23) | 0.08 | 1.15 (0.94, 1.40) | 0.18 |
| Preimplantation PR interval (n=251) | Continuous | 0.99 (0.99, 1.00) | 0.01 | 1.00 (0.99, 1.01) | 0.93 |
| Preimplantation RV-paced QRS width (n=22) | Continuous | 0.98 (0.95, 1.01) | 0.19 | | |
| Preimplantation axis categories (n=281) | <−75 vs ≥130 | 0.74 (0.22, 2.47) | 0.26 | | |
| | −75<0 vs ≥130 | 1.55 (0.60, 4.04) | | | |
| | 0<−130 vs ≥130 | 1.70 (0.63, 4.61) | | | |
| LV-paced QRS width (n=214) | 10-ms Increments | 0.94 (0.87, 1.00) | 0.07 | 0.86 (0.77, 0.96) | 0.01 |
| Postimplantation axis categories (n=251) | <−75 vs ≥130 | 0.61 (0.29, 1.26) | 0.25 | | |
| | −75<0 vs ≥130 | 1.59 (0.75, 3.36) | | | |
| | 0<−130 vs ≥130 | 0.95 (0.48, 1.89) | | | |
| Difference between Bi-V and preimplantation QRS width (n=223) | 10-ms Increments | 0.81 (0.71, 0.92) | <0.01 | 0.90 (0.74, 1.09) | 0.27 |
| QRS bundle branch morphological features in lead V1 (n=273) | LBBB vs RBBB | 3.38 (1.53, 7.46) | <0.01 | 2.89 (1.01, 8.27) | 0.048 |

MI indicates myocardial infarction.

QRS Width ≥150 ms

A dichotomized QRS width of <150 ms versus ≥150 ms was also examined, in addition to the prespecified preimplantation QRS width in increments of 10 ms. The dichotomized QRS width results were similar to the preimplantation incremental QRS width, in which the univariable analysis was statistically significant for LVESV (OR=0.37, $P=0.01$), but not CCS response. As was the case with preimplantation incremental QRS width, the dichotomized QRS width did not reach statistical significance in the multivariable analysis.

ECG Parameters by Cause

The interactions were analyzed between cause of cardiomyopathy (ischemic versus nonischemic) and the ECG parameters that were statistically significant for prediction of CCS (difference between Bi-V and preimplantation QRS width and QRS bundle branch morphological features) and LVESV response (LV-paced QRS width and QRS bundle branch block morphological features). Only QRS bundle branch block morphological features for the CCS response showed a significant interaction with cause of cardiomyopathy ($P=0.03$). QRS bundle branch block morphological features were a significant predictor of CCS response for nonischemic cause (OR=6.34, $P=0.01$) (Table 3). LV-paced QRS for the LVESV response did not show any interaction with cause of cardiomyopathy (Table 4).

LV-Paced QRS

LV-paced QRS width was also examined to determine if a cutoff threshold width could be identified. A cutoff threshold

of 200 ms gave the best combination of sensitivity (72%) and specificity (40%) in predicting LVESV response compared with other thresholds. LV-paced QRS width (≤200 ms versus >200 ms) was significant for overall LVESV response (OR=2.27, $P=0.04$). The interaction between the dichotomy of LV-paced QRS width and cardiomyopathy cause was also significant ($P=0.04$) (Table 5). When the cause of cardiomyopathy subgroups were further analyzed, the LV-paced QRS width was significant for nonischemic cause (OR=5.12,

Table 3. Significant Multivariable Parameters of CCS Response by Cause of Cardiomyopathy

| Explanatory Variable | Cause of Cardiomyopathy | Statistic | Response (95% CI) CCS | P Value of Interaction |
|--|-------------------------|-----------|-----------------------|------------------------|
| Difference between Bi-V and preimplantation QRS width (10-ms increments) | Ischemic* | OR | 0.91 (0.79–1.04) | 0.65 |
| | | P value | Not tested | |
| QRS bundle branch morphological features in lead V1 (LBBB vs RBBB) | Nonischemic* | OR | 0.86 (0.72–1.03) | |
| | | P value | Not tested | |
| QRS bundle branch morphological features in lead V1 (LBBB vs RBBB) | Ischemic | OR | 1.33 (0.49–3.61) | 0.03 |
| | | P value | 0.57 | |
| QRS bundle branch morphological features in lead V1 (LBBB vs RBBB) | Nonischemic | OR | 6.34 (1.64–24.46) | |
| | | P value | 0.01 | |

*Subgroup P values were not calculated when the test for interaction was not significant.

Table 4. Significant Multivariable Parameters of LVESV Response by Cause of Cardiomyopathy

| Explanatory Variable | Cause of Cardiomyopathy* | Statistic | Response (95% CI) LVESV | P Value of Interaction |
|--|--------------------------|-----------|-------------------------|------------------------|
| LV-paced QRS width (10-ms increments) | Ischemic | OR | 0.87 (0.74–1.03) | 0.17 |
| | | P value | Not tested | |
| | Nonischemic | OR | 0.80 (0.67–0.96) | |
| | | P value | Not tested | |
| QRS bundle branch morphological features in lead V1 (LBBB vs RBBB) | Ischemic | OR | 2.39 (0.61–9.35) | 0.74 |
| | | P value | Not tested | |
| | Nonischemic | OR | 3.40 (0.57–20.20) | |
| | | P value | Not tested | |

*Subgroup P values were not calculated when the test for interaction was not significant.

$P=0.01$), but not for ischemic cause ($OR=1.35$, $P=0.58$). The LV-paced QRS width using the threshold of 200 ms as a cutoff was not significant for CCS response (data not shown).

Discussion

To our knowledge, the PROSPECT trial was the first large multicenter prospective trial of noninvasive predictors of response to CRT. In that study, no echocardiographic measure of dyssynchrony accurately identified patients who would respond to CRT in a multicenter setting.⁵ The current analysis represents the PROSPECT-ECG substudy, which evaluated electrocardiographic measurements, including a novel LV-paced QRS width to identify CRT responders and to potentially use ECG measurements to guide placement of the CS lead.

The benefit of CRT in RBBB or non-LBBB is unclear. Only 1 study⁷ has shown a benefit for CRT in patients with RBBB. A later pooled analysis using both the MIRACLE and Contak CD studies demonstrated improvement in only New York Heart Association functional class in patients with baseline RBBB.⁸ More recent single-center analyses^{9,10} showed a greater CRT response with LBBB compared with RBBB and intraventricular conduction delay. The multicenter MADIT-CRT subanalysis also found a greater response with LBBB compared with non-LBBB.¹¹ In the PROSPECT-ECG analysis, QRS morphological features significantly predicted CRT response. Patients with baseline LBBB were more likely to respond than patients with baseline RBBB morphological features. In addition, QRS morphological features were the only ECG parameter that

Table 5. Summary of LVESV Response Using Dichotomized LV-Paced QRS Width by Cause of Cardiomyopathy

| Explanatory Variable | Cause of Cardiomyopathy | Statistic | Response (95% CI) | P Value of Interaction |
|---|-------------------------|-----------|-------------------|------------------------|
| LV-paced QRS width (≤ 200 vs >200 ms) | Overall | OR | 2.27 (1.04–4.97) | ... |
| | | P value | 0.04 | |
| | Ischemic | OR | 1.35 (0.46–3.91) | |
| | | P value | 0.58 | |
| | Non-ischemic | OR | 5.12 (1.47–17.81) | |
| | | P value | 0.01 | |

predicted both CCS ($OR=2.46$) and LVESV response ($OR=2.89$) in the multivariable analysis. When further analyzed by cause of cardiomyopathy, QRS bundle branch morphological features were only significant for CCS response in patients with nonischemic cardiomyopathy ($OR=6.34$, $P=0.01$).

Previous studies using preimplantation QRS width to predict CRT response have yielded conflicting results. Early CRT studies^{12,13} showed that an increased preimplantation QRS width predicted short-term hemodynamic improvement. However, subsequent long-term follow-up in large CRT clinical trials found that preimplantation QRS width was a poor predictor of clinical CRT response.¹⁴ In the RethinQ trial,¹⁵ patients with a narrow QRS width and evidence of mechanical dyssynchrony did not benefit from resynchronization. In that study, subgroup analysis demonstrated that patients with a QRS width >120 ms had a much higher response rate than patients with a QRS width <120 ms. A previously reported PROSPECT subanalysis examined characteristics associated with good and poor response.¹⁶ Subjects were classified as a superresponder if they had a decrease in LVESV $\geq 30\%$, as a responder if they had a decrease in LVESV of 15% to 29%, as a nonresponder if they had a decrease in LVESV of 0% to 14%, and as a negative responder if they had an increase in LVESV and a combination of clinical and echocardiographic deterioration. In that analysis, preimplantation QRS width was statistically significant between the 4 LVESV groups ($P=0.03$) and when comparing superresponders with negative responders ($P=0.039$).¹⁶ However, preimplantation QRS width was not significant when comparing the combined clinical and echocardiographic end points ($P=0.18$). A prespecified MADIT-CRT subanalysis found QRS width ≥ 150 ms to be significant for reduction in death and nonfatal heart failure.¹⁷ In this PROSPECT-ECG, preimplantation incremental QRS width was a predictor of LVESV response in univariable, but not multivariable, analysis. Similarly, dichotomized QRS width ≥ 150 ms conferred a greater LVESV response than <150 ms in univariable analysis but was a poor predictor of response after multivariable analysis.

Prediction of CRT response in association with a narrowing of the QRS width with Bi-V pacing has also proved to be an inconsistent finding in clinical trials.^{18–20} However, widening of the QRS after CRT device implantation has been an independent predictor of mortality or progression to heart transplantation.²¹ To our knowledge, there is only 1 prospective study¹⁹ that attempted to minimize the QRS width during CRT implantation and resulted in a 73% response rate. In that study, the LV lead was positioned in the standard lateral or posterolateral vein and the RV lead was positioned in the RV outflow tract, septum, anterior wall, or apex to minimize QRS width. In PROSPECT-ECG, we found that the difference between Bi-V and preimplantation QRS width was predictive for the CCS end point, with an OR of 0.89 ($P=0.04$).

Previous studies^{22–24} have suggested a better CRT response in patients with nonischemic compared with ischemic cause of cardiomyopathy. It is generally accepted that there is a greater amount of focal and diffuse scar associated with infarct-related cardiomyopathy compared with nonischemic cardiomyopathy.^{25,26} Also, scar at the site of pacing and total scar burden decrease the response to CRT because dead tissue is less likely to contract, even with pacing.^{25–29} In PROSPECT-ECG, nonis-

chemic cardiomyopathy patients had a significantly higher likelihood of response to both CCS and LVESV in the univariable, but not the multivariable, model. The reason that the cause of cardiomyopathy was highly significant in univariable, but not multivariable, analysis is explained by the positive correlation between cause of cardiomyopathy and other significant ECG parameters. To further examine the relationship between cause of cardiomyopathy and ECG predictors, significant multivariable parameters for CRT response were analyzed for interaction with cause of cardiomyopathy. Of the 4 parameters that predicted either CCS or LVESV response after multivariable analysis, 3 had no interaction with cause of cardiomyopathy. Only QRS bundle branch block morphological features better predicted CCS response in patients with nonischemic cardiomyopathy (OR=6.34, $P=0.01$) (Table 3). None of the ECG parameters that predicted an improvement in LVESV interacted with cardiomyopathy cause, suggesting the ECG parameters are applicable to both (Table 4). The dichotomized LV-paced QRS width ≤ 200 ms interacted and was significantly more predictive for patients with a nonischemic cause of cardiomyopathy (OR=5.12) (Table 5). Parameters that are affected by lead position, including the difference between Bi-V and preimplantation QRS width and LV-paced QRS width, appear to be predictive for both ischemic and nonischemic cardiomyopathies.

The LV-paced QRS width represents a novel ECG parameter not previously examined. Pacing an area of scar in the left ventricle may not improve dyssynchrony and can lead to nonresponse.³⁰ LV-paced QRS width may be an indirect method of identifying a region near scar or an area of poor conduction. In this case, a narrower LV-paced QRS duration would suggest electrically viable tissue and a wider LV-paced QRS would imply proximity to a region of scar where electric signals conduct slowly and resynchronization is less likely to occur. Overall, we found that the narrower the LV-paced QRS width, the more likely there will be a CRT LVESV response, with an OR of 0.86 ($P=0.01$). Specifically, an LV-paced QRS width of ≤ 200 ms was >2 times more likely to be associated with a positive response than having an LV-paced QRS width >200 ms (OR=2.27, $P=0.04$). Although the nondichotomized LV-paced QRS did not interact with cause of cardiomyopathy, the dichotomized LV-paced QRS did interact. Once again, we found that this parameter was most useful in patients with nonischemic cardiomyopathy, in whom an LV-paced QRS width of ≤ 200 ms was associated with a >5 -fold increased likelihood of an improved LVESV response to CRT (OR=5.12, $P=0.01$).

Clinical Implications

In our PROSPECT-ECG substudy, only QRS left bundle branch morphological features were predictive of both LVESV and CCS response; other ECG parameters were predictive of 1 or the other. Both parameters that predicted either LVESV or CCS response (namely, LV-paced QRS width and the difference between Bi-V and preimplantation QRS width) can be measured intraprocedurally and can be used by the CRT implanter to optimize LV lead placement or pacing. To improve CRT response, as measured by CCS or LVESV, our data suggest only selecting patients with baseline LBBB. In addition, during CRT implantation, particularly in patients with a nonischemic cardiomyopathy, it is recommended that the LV lead be positioned to

minimize both the LV-paced QRS and the Bi-V-paced QRS widths, especially if there are multiple coronary veins, multiple locations within a vein, or multiple pacing configurations from which to choose. This hypothesis will require further study to determine if prospectively optimizing ECG parameters during CRT implantation will result in an increased CRT response rate.

Limitations

First, this was an observational study that will require validation with a future study. Second, no long-term outcome >6 months is available. The current definition of CRT response does not account for disease progression. Patients who are classified as nonresponders may actually represent positive response with attenuation of disease progression.³¹ Without a control group to follow natural progression, this cannot be validated. Other parameters relating to CRT response, including extent of myocardial scar, percentage of Bi-V pacing, and adherence to medical therapy, were not evaluated in this study. Regarding the multivariable analyses involving the dichotomy of postimplantation LV QRS width and LVESV response, the threshold value defining the dichotomy was data derived and subjectively chosen. Statistical methods, such as cross validation, could be used to select a threshold in a more rigorous manner and to investigate the robustness of the estimated effect.

Conclusions

The ECG is a simple and inexpensive tool that can help identify candidates for CRT and guide the selection of the optimal vein for resynchronization. In PROSPECT-ECG, only QRS left bundle branch morphological features predicted both CCS and LVESV response; LV-paced QRS width predicted LVESV response, and the difference between Bi-V and preimplantation QRS widths predicted CCS response. In addition, we present a potentially novel ECG parameter, LV-paced QRS width, as a predictor of LVESV response. Some ECG parameters were more predictive of CRT response in patients with a nonischemic cardiomyopathy.

Sources of Funding

Medtronic Inc provided funding for the PROSPECT study and manufactured the CRT system used in this research.

Disclosures

Dr Leclercq has received research grants from or consulted for Medtronic, Boston Scientific, Soron, St Jude Medical, and Biotronik; Messrs McRae and Peterson are employed by Medtronic.

References

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845–1853.
2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549.
3. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, Wheelan K. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA*. 2003;289:2685–2694.
4. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140–2150.

5. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J III, St John Sutton M, De Sutter J, Murillo J. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation*. 2008;117:2608–2616.
6. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail*. 2001;7:176–182.
7. Aranda JM Jr, Conti JB, Johnson JW, Petersen-Stejskal S, Curtis AB. Cardiac resynchronization therapy in patients with heart failure and conduction abnormalities other than left bundle-branch block: analysis of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *Clin Cardiol*. 2004;27:678–682.
8. Egoavil CA, Ho RT, Greenspon AJ, Pavri BB. Cardiac resynchronization therapy in patients with right bundle branch block: analysis of pooled data from the MIRACLE and Contak CD trials. *Heart Rhythm*. 2005;2:611–615.
9. Wokhlu A, Rea RF, Asirvatham SJ, Webster T, Brooke K, Hodge DO, Wiste HJ, Dong Y, Hayes DL, Cha YM. Upgrade and de novo cardiac resynchronization therapy: impact of paced or intrinsic QRS morphology on outcomes and survival. *Heart Rhythm*. 2009;6:1439–1447.
10. Rickard J, Kumbhani DJ, Gorodeski EZ, Baranowski B, Wazni O, Martin DO, Grimm R, Wilkoff BL. Cardiac resynchronization therapy in non-left bundle branch block morphologies. *Pacing Clin Electrophysiol*. 2010;33:590–595.
11. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichstein E, Pitschner H, Rashtian M, Solomon S, Viskin S, Wang P, Moss AJ. Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation*. 2011;123:1061–1072.
12. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, Klein H, Kramer A, Ding J, Salo R, Tockman B, Pochet T, Spinelli J; The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. *Circulation*. 1999;99:2993–3001.
13. Kass DA, Chen CH, Curry C, Talbot M, Berger R, Fetis B, Nevo E. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation*. 1999;99:1567–1573.
14. Reynolds MR, Joventino LP, Josephson ME. Relationship of baseline electrocardiographic characteristics with the response to cardiac resynchronization therapy for heart failure. *Pacing Clin Electrophysiol*. 2004;27:1513–1518.
15. Beshai JF, Grimm RA, Nagueh SF, Baker JH II, Beau SL, Greenberg SM, Pires LA, Tchou PJ. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med*. 2007;357:2461–2471.
16. van Bommel RJ, Bax JJ, Abraham WT, Chung ES, Pires LA, Tavazzi L, Zimetbaum PJ, Gerritse B, Kristiansen N, Ghio S. Characteristics of heart failure patients associated with good and poor response to cardiac resynchronization therapy: a PROSPECT (Predictors of Response to CRT) sub-analysis. *Eur Heart J*. 2009;30:2470–2477.
17. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA III, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361:1329–1338.
18. Alonso C, Leclercq C, Victor F, Mansour H, de Place C, Pavin D, Carre F, Mabo P, Daubert JC. Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. *Am J Cardiol*. 1999;84:1417–1421.
19. Lecoq G, Leclercq C, Leray E, Crocq C, Alonso C, de Place C, Mabo P, Daubert C. Clinical and electrocardiographic predictors of a positive response to cardiac resynchronization therapy in advanced heart failure. *Eur Heart J*. 2005;26:1094–1100.
20. Molhoek SG, Vane L, Bootsma M, Steendijk P, Van Der Wall EE, Schalij MJ. QRS duration and shortening to predict clinical response to cardiac resynchronization therapy in patients with end-stage heart failure. *Pacing Clin Electrophysiol*. 2004;27:308–313.
21. Iler MA, Hu T, Ayyagari S, Callahan TD, Civello KC, Thal SG, Wilkoff BL, Chung MK. Prognostic value of electrocardiographic measurements before and after cardiac resynchronization device implantation in patients with heart failure due to ischemic or nonischemic cardiomyopathy. *Am J Cardiol*. 2008;101:359–363.
22. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E. 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). *Circulation*. 2006;113:266–272.
23. Woo GW, Petersen-Stejskal S, Johnson JW, Conti JB, Aranda JA Jr, Curtis AB. Ventricular reverse remodeling and 6-month outcomes in patients receiving cardiac resynchronization therapy: analysis of the MIRACLE study. *J Interv Card Electrophysiol*. 2005;12:107–113.
24. Duncan A, Wait D, Gibson D, Daubert JC. Left ventricular remodeling and haemodynamic effects of multisite biventricular pacing in patients with left ventricular systolic dysfunction and activation disturbances in sinus rhythm: sub-study of the MUSTIC (Multisite Stimulation in Cardiomyopathies) trial. *Eur Heart J*. 2003;24:430–441.
25. Ypenburg C, Roes SD, Bleeker GB, Kaandorp TA, de Roos A, Schalij MJ, van der Wall EE, Bax JJ. Effect of total scar burden on contrast-enhanced magnetic resonance imaging on response to cardiac resynchronization therapy. *Am J Cardiol*. 2007;99:657–660.
26. Riedlbauchova L, Brunken R, Jaber WA, Popova L, Patel D, Lanska V, Civello K, Cummings J, Burkhardt JD, Saliba W, Martin D, Schweikert R, Wilkoff BL, Grimm R, Natale A. The impact of myocardial viability on the clinical outcome of cardiac resynchronization therapy. *J Cardiovasc Electrophysiol*. 2009;20:50–57.
27. Birnie D, DeKemp RA, Ruddy TD, Tang AS, Guo A, Williams K, Wassenar R, Lalonde M, Beanlands RS. Effect of lateral wall scar on reverse remodeling with cardiac resynchronization therapy. *Heart Rhythm*. 2009;6:1721–1726.
28. Adelstein EC, Saba S. Scar burden by myocardial perfusion imaging predicts echocardiographic response to cardiac resynchronization therapy in ischemic cardiomyopathy. *Am Heart J*. 2007;153:105–112.
29. Marsan NA, Westenberg JJ, Ypenburg C, van Bommel RJ, Roes S, Delgado V, Tops LF, van der Geest RJ, Boersma E, de Roos A, Schalij MJ, Bax JJ. Magnetic resonance imaging and response to cardiac resynchronization therapy: relative merits of left ventricular dyssynchrony and scar tissue. *Eur Heart J*. 2009;30:2360–2367.
30. Bleeker GB, Kaandorp TA, Lamb HJ, Boersma E, Steendijk P, de Roos A, van der Wall EE, Schalij MJ, Bax JJ. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. *Circulation*. 2006;113:969–976.
31. Mullens W, Verga T, Grimm RA, Starling RC, Wilkoff BL, Tang WH. Persistent hemodynamic benefits of cardiac resynchronization therapy with disease progression in advanced heart failure. *J Am Coll Cardiol*. 2009;53:600–607.

CLINICAL PERSPECTIVE

In our PROSPECT-ECG substudy, only QRS left bundle branch block (LBBB) morphological features were predictive of both left ventricular end systolic volume (LVESV) and clinical composite score (CCS) response; other ECG parameters were predictive of 1 or the other. Both parameters that predicted either LVESV or CCS response (namely, LV-paced QRS width and the difference between biventricular [Bi-V] and preimplantation QRS width) can be measured intraprocedurally and can be used by the cardiac resynchronization therapy (CRT) implanter to optimize LV lead placement or pacing. To improve CRT response, as measured by CCS or LVESV, our data suggest selecting only patients with baseline LBBB. In addition, during CRT implantation, particularly in patients with nonischemic cardiomyopathy, it is recommended that the LV lead be positioned to minimize both the LV-paced QRS and the Bi-V-paced QRS widths, especially if there are multiple coronary veins, multiple locations within a vein, or multiple pacing configurations from which to choose.