Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 60, No. 7, 2012
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.03.059

Differential Response to Cardiac Resynchronization Therapy and Clinical Outcomes According to QRS Morphology and QRS Duration

Matthias Dupont, MD,* John Rickard, MD,* Bryan Baranowski, MD,* Niraj Varma, MD,* Thomas Dresing, MD,* Alaa Gabi, MD,* Michael Finucan, BS,* Wilfried Mullens, MD, PHD,†‡ Bruce L. Wilkoff, MD,* W. H. Wilson Tang, MD*

Cleveland, Ohio; and Genk and Diepenbeek, Belgium

Objectives The goal of this study was to examine the relative impact of QRS morphology and duration in echocardiographic responses to cardiac resynchronization therapy (CRT) and clinical outcomes.

Background At least one-third of all patients treated with CRT fail to derive benefit. Patients without left bundle branch block (LBBB) or patients with smaller QRS duration (QRSd) respond less or not at all to CRT.

Methods We retrospectively assessed baseline characteristics, clinical and echocardiographic response, and outcomes of all patients who received CRT at our institution between December 2003 and July 2007. Patients were stratified into 4 groups according to their baseline QRS morphology and QRSd.

Results A total of 496 patients were included in the study; 216 (43.5%) had LBBB and a QRSd ≥150 ms, 85 (17.1%) had LBBB and QRSd <150 ms, 92 (18.5%) had non-LBBB and a QRSd ≥150 ms, and 103 (20.8%) had non-LBBB and QRSd <150 ms. Echocardiographic response (change in ejection fraction) was better in patients with LBBB and QRSd ≥150 ms (12 ± 12%) than in those with LBBB and QRSd <150 ms (8 ± 10%), non-LBBB and QRSd ≥150 ms (5 ± 9%), and non-LBBB and QRSd <150 ms (3 ± 11%) ($p < 0.0001$). In a multivariate stepwise model with change in ejection fraction as the dependent variable, the presented classification was the most important independent variable ($p = 0.0003$). Long-term survival was better in LBBB patients with QRSd ≥150 ms ($p = 0.02$), but this difference was not significant after adjustment for other baseline characteristics ($p = 0.15$).

Conclusions QRS morphology is a more important baseline electrocardiographic determinant of CRT response than QRSd. (J Am Coll Cardiol 2012;60:592–8) © 2012 by the American College of Cardiology Foundation

In the past decade, cardiac resynchronization therapy (CRT) has been shown to improve cardiac function and heart failure symptoms, induce reverse myocardial remodeling, enhance quality of life, prevent heart failure admissions, and even prolong survival (1–4). Moreover, with publication of the REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction), MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy), and RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial), indications are expanding to less symptomatic patients (5–7). Nevertheless, it is broadly accepted that 30% to 50% of all patients who fall under the broad inclusion criteria of randomized controlled trials do not respond to this therapy (8,9). Improvements in postimplantation management as well as better patient selection may potentially decrease the number of so-called "nonresponders" (10). Regarding patient selection, it has been noticed that certain subgroups, often underrepresented in clinical trials, seem to benefit less or not at all from CRT. Such subgroups include: those of advanced age, males, and those with ischemic cardiomyopathy, atrial fibrillation, non–left bundle branch block (LBBB) morphology, and

From the *Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio; †Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; and the ‡Doctoral School for Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium. Dr. Dupont is supported by a research grant from the Belgian American Educational Foundation. Dr. Varma has served as consultant and investigator in trials (including cardiac resynchronization therapy trials) sponsored by Biotronik/Boston Scientific/Medtronic/St. Jude. Dr. Dresing is on the Electrophysiology Fellowship Advisory Council for St Jude Medical; and has received speaking honoraria from St. Jude Medical, Medtronic, Boston Scientific, and Biosense Webster. Dr. Wilkoff is a consultant for Medtronic Inc., Boston Scientific Inc., and St. Jude Medical. Dr. Tang has served as a consultant for Medtronic Inc. and St. Jude Medical; and has received research support from Abbott Laboratories. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 29, 2012; accepted March 21, 2012.

QRS duration (QRSd) <150 ms (11). However, it is not clear what the main drivers of nonresponse to CRT are because many of the aforementioned negative predictors are interrelated. For example, previous studies demonstrated that patients with non-LBBB morphologies also have shorter QRSd, are more likely to be male, and have more ischemic cardiomyopathy (12). To shed more light on the interaction between QRS morphology and QRSd, the goal of the current retrospective study was to determine echocardiographic response and outcome after CRT implantation as stratified according to both baseline electrocardiographic characteristics.

Methods

Study population. We reviewed the medical records of all patients who received a new CRT device at the Cleveland Clinic (Cleveland, Ohio) between December 2003 and July 2007. Patients without an available pre-implant electrocardiogram (ECG) were excluded. In all other patients, the morphology of their baseline ECG was assessed and classified as either LBBB, right bundle branch block (RBBB), nonspecific intraventricular conduction delay (IVCD), paced rhythm, or narrow QRS complex. The latter 2 morphology types were not studied further. LBBB was defined as QRSd ≥120 ms, a monophasic QS or rS complex in V_1, and a monophasic R-wave in V_6. RBBB was defined as QRSd ≥120 ms, a deep terminal S wave in I and V_6, and an RSR prime, wide R, or qR pattern in V_1. IVCD was defined as QRSd ≥120 ms not meeting criteria for either LBBB or RBBB. Patients with RBBB or IVCD morphology were grouped as having a non-LBBB morphology. Finally, 4 groups were established by dichotomizing LBBB and non-LBBB patients according to the duration of their QRS complex (≥150 ms or <150 ms). The duration of the QRS complex was automatically computed by using ECG analysis software. The medical charts of these patients were reviewed, and demographic, clinical, electrocardiographic, echocardiographic, and outcome data were abstracted. This retrospective study was approved by the institutional review board of the Cleveland Clinic.

Data synthesis. The primary endpoint of this study was the change in ejection fraction (EF). Secondary endpoints consisted of changes in other echocardiographic variables (left ventricular end-diastolic diameter [LVEDD], left ventricular end-systolic diameter, mitral regurgitation [MR]), changes in New York Heart Association (NYHA) functional class, and a composite clinical endpoint (all-cause mortality, heart transplantation, or left ventricular assist device [LVAD] implantation). Mortality was confirmed by querying the U.S. Social Security Death Index. Echocardiograms were obtained as clinically indicated and performed according to standard procedures of the echocardiography laboratory of the Cleveland Clinic. Interpretation was conducted by board-certified cardiologists who were unaware of the current study. MR was graded on a scale of 0 through 9, according to the 2003 American Society of Echocardiography guidelines, with 0 representing no MR and 9 representing 4+ MR. Super-responders were defined as patients with an improvement in EF ≥20%. Negative responders were defined as having no improvement in EF. For the purpose of this analysis, the pre-implant echocardiogram was the last one before implantation and the post-implant echocardiogram (when available) was the one closest to the 1-year follow-up and at least 2 months after CRT initiation. Similarly, NYHA functional class was ascertained closest to a 1-year follow-up period. Medications were recorded immediately before implantation of the CRT device.

Abbreviations and Acronyms

- **CRT** = cardiac resynchronization therapy
- **EF** = ejection fraction
- **IVCD** = intraventricular conduction delay
- **LBBB** = left bundle branch block
- **LV** = left ventricular
- **LVAD** = left ventricular assist device
- **LVEDD** = left ventricular end-diastolic diameter
- **MR** = mitral regurgitation
- **NYHA** = New York Heart Association
- **RBBB** = right bundle branch block
- **QRSd** = QRS duration

All implantations were performed at the Cleveland Clinic. In the vast majority of patients, device implantation was successfully accomplished by using a transvenous approach by electrophysiologists targeting a lateral or posterolateral vein for the left ventricular (LV) lead position. If not, LV lead placement was achieved by a minimally invasive surgical procedure. The CRT devices were programmed at the discretion of the treating physicians.

Statistical methods. Comparisons between the 4 groups were made by using analysis of variance or the Kruskal-Wallis test for continuous variables and chi-square test for discrete variables. For variables that were significantly different among groups, paired comparisons were made to identify which groups were different. The Tukey test was used for continuous variables and the Fisher exact test with Bonferroni correction for discrete variables. A stepwise multivariate linear regression model (probability of 0.05 to enter or leave the model) was constructed to identify significant variables associated with changes in EF after CRT. Kaplan-Meier curves were constructed to compare survival for the primary endpoint between the 4 groups. The log-rank test was used to determine significance. Univariate and multivariate Cox proportional hazards regression models were constructed to investigate the independent value of different baseline characteristics for the primary endpoint. Statistical significance was set at a 2-tailed probability level of <0.05. All statistical analyses were performed by using JMP Pro version 9.0 (SAS Institute, Inc., Cary, North Carolina).

Results

A total of 812 patients underwent CRT device implantation between December 2003 and July 2007. Figure 1 depicts how the final 4 groups were assembled. The final study cohort comprised 496 patients. Of these, 216 (43.5%)

JACC Vol. 60, No. 7, 2012
August 14, 2012:592–8

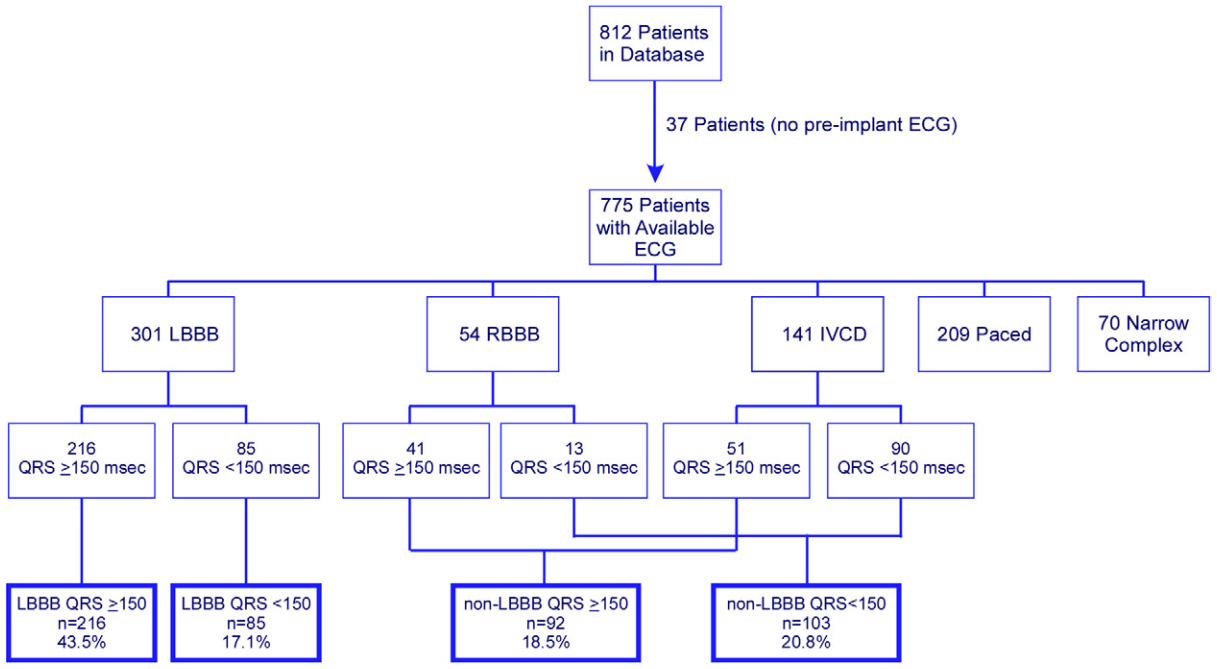

Figure 1 **Composition of the Study Population**

ECG = electrocardiogram; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; RBBB = right bundle branch block.

patients had LBBB and QRSd ≥150 ms, 85 (17.1%) had LBBB and QRSd <150 ms, 92 (18.5%) had non-LBBB and QRSd ≥150 ms, and 103 (20.8%) had non-LBBB and QRSd <150 ms. Patients receiving a CRT device almost always received the defibrillator function as well (98%, 96%, 98%, and 95%, respectively; p = 0.63), and the percentage of biventricular paced beats was similar between the 4 groups (99 [97 to 100], 99 [96 to 100], 99 [97 to 100], and 99 [95 to 100]; p = 0.24). Figure 2 displays the distribution of QRS width in function of QRS morphology.

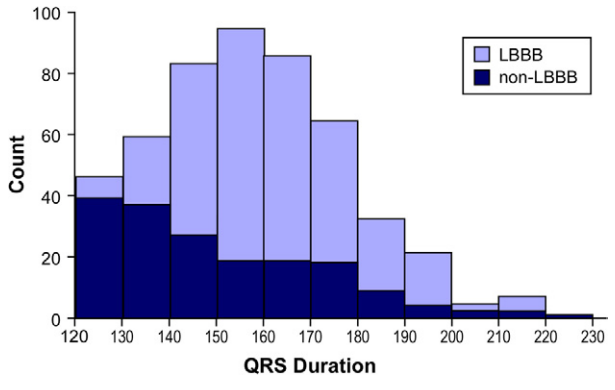

Figure 2 **Histogram of QRS Duration in the Study Population**

LBBB = left bundle branch block.

Baseline characteristics of the 4 groups are listed in Table 1. Both groups with non-LBBB morphologies were more likely to have ischemic cardiomyopathy (p = 0.001) and correspondingly were more likely to be male (p < 0.0001) and have a history of tobacco use (p = 0.009). Patients with non-LBBB morphologies were also on average 4 years younger (p = 0.001) and received more antiarrhythmic drugs (p = 0.0005) than those with LBBB morphologies. There were small differences in baseline EF (p = 0.04), which were not significantly different between individual groups when corrected for multiple comparisons. Patients with a non-LBBB and QRSd ≥150 ms had more LV dilation, both in diastole (p = 0.002) and systole (p = 0.008), compared with other groups.

A total of 475 (96%) and 323 (65%) had echocardiogram data available before and after CRT device implantation, respectively. Comparisons could be made in 313 (63%) of all patients. Survival (freedom of combined endpoint) was worse (p = 0.005) in patients without available echocardiograms for comparison. Patients without available echocardiogram data were also more likely to have non-LBBB and QRSd ≥150 ms and less likely to have LBBB and QRSd ≥150 ms (p = 0.03). Echocardiograms were performed at a mean of 12 ± 10 months after CRT implantation. The improvement in EF was most pronounced in patients with LBBB and QRSd ≥150 ms (12 ± 12%), followed by LBBB and QRSd <150 ms (8 ± 10%), non-LBBB and QRSd ≥150 ms (5 ± 9%), and non-LBBB and QRSd <150 ms

Table 1 Baseline Characteristics

Characteristic	LBBB and QRSd ≥150 ms (n = 216)	LBBB and QRSd <150 ms (n = 85)	Non-LBBB and QRSd ≥150 ms (n = 92)	Non-LBBB and QRSd <150 ms (n = 103)	p Value
Demographic characteristics and history					
Age (yrs)	71 ± 10	71 ± 10	67 ± 13	67 ± 11	0.001
Male	61	56	84	84	<0.0001
BMI (kg/m^2)	28.5 ± 5.6	28.8 ± 6.3	29.2 ± 6.3	29.6 ± 6.4	0.54
NYHA functional class	2.9 ± 0.4	2.9 ± 0.4	2.9 ± 0.5	3.0 ± 0.4	0.48
ICM	53	49	72	69	0.001
CABG	34	36	46	50	0.045
History of tobacco use	60	55	77	66	0.009
History of atrial fibrillation	46	42	51	5	0.52
History of hypertension	67	56	65	56	0.15
History of hyperlipidemia	56	56	67	57	0.26
Renal dysfunction	26	28	36	27	0.41
COPD	13	15	15	16	0.95
Diabetes mellitus	41	38	32	44	0.32
Echocardiography					
EF	21 ± 8	23 ± 8	20 ± 8	23 ± 8	0.04
LVEDD (cm)	6.2 ± 1.0	6.0 ± 1.1	6.6 ± 0.9	6.2 ± 1.1	0.002
LVESD (cm)	5.2 ± 1.2	4.9 ± 1.3	5.5 ± 1.1	5.2 ± 1.2	0.008
MR grades (1–9)	3.8 ± 2.4	3.8 ± 2.3	3.7 ± 2.5	3.3 ± 2.2	0.44
Laboratory					
BNP (pg/ml)	561 ± 808	504 ± 734	584 ± 696	596 ± 713	0.87
Creatinine (mg/dl)	1.29 ± 0.73	1.38 ± 0.93	1.44 ± 0.55	1.38 ± 0.78	0.47
eGFR (ml/min/1.73 m^2)	64 ± 32	67 ± 42	58 ± 32	66 ± 36	0.25
Hemoglobin (g/dl)	12.5 ± 1.8	12.8 ± 1.8	12.8 ± 2.1	12.5 ± 2.0	0.53
hsCRP (mg/l)	12.7 ± 25.3	7.2 ± 8.2	12.7 ± 22.7	11.8 ± 25.5	0.50
Medication					
Coumarins	28	29	37	34	0.38
ASA	62	63	68	66	0.82
Beta-blockers	86	85	81	82	0.70
ACE-I or ARB	85	71	79	80	0.05
Diuretics	80	76	80	84	0.63
Nitrates	24	30	30	39	0.09
Hydralazine	11	12	17	12	0.58
Aldosterone antagonists	29	30	26	35	0.78
Statins	60	56	60	64	0.77
Digoxin	41	48	50	43	0.52
AA drugs	17	8	30	2	0.0005

Values are mean ± SD or %.

AA = antiarrhythmic; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; BNP = B-type natriuretic peptide; BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; eGFR = estimated glomerular filtration rate; hsCRP = high-sensitivity C-reactive protein; ICM = ischemic cardiomyopathy; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; NYHA = New York heart Association; QRSd = QRS duration.

(3 ± 11%) ($p < 0.0001$) (Table 2). The same pattern could be seen for reduction in LVEDD ($p = 0.007$) and left ventricular end-systolic diameter ($p = 0.0005$). When pairwise comparisons were made (with correction for multiple comparisons), the improvement in EF was significantly higher in patients with LBBB and QRSd ≥150 ms compared with non-LBBB and ≥150 ms ($p < 0.0001$) and non-LBBB and QRSd <150 ms ($p = 0.0009$) patients. The difference between LBBB patients with QRSd ≥150 ms or <150 ms approached significance ($p = 0.12$). Moreover, there were significantly more super-responders in the LBBB and QRSd ≥150 ms group ($p = 0.001$) and significantly fewer nonresponders in the 2 LBBB groups ($p = 0.001$). The change in MR was significantly less pronounced in non-LBBB and QRSd <150 ms patients (MR actually worsened [0.5 ± 2.0]) compared with LBBB and QRSd ≥150 ms ($p = 0.001$), and non-LBBB and QRSd ≥150 ms ($p = 0.007$) patients. In terms of clinical response, NYHA class improvement differed significantly between groups ($p = 0.001$). More specifically, there was more improvement in NYHA class in patients with LBBB and QRSd ≥150 ms compared with both non-LBBB groups ($p = 0.002$

Table 2 Echocardiographic and Clinical Response to CRT

Response	LBBB and QRSd ≥150 ms (n = 216)	LBBB and QRSd <150 ms (n = 85)	Non-LBBB and QRSd ≥150 ms (n = 92)	Non-LBBB and QRSd <150 ms (n = 103)	p Value
Echocardiographic response					
EF pre (%)	21 ± 8	23 ± 8	20 ± 8	23 ± 8	0.04
EF post (%)	32 ± 13	32 ± 13	24 ± 10	26 ± 11	<0.0001
EF change (%)	12 ± 12	8 ± 10	5 ± 9	3 ± 11	<0.0001
LVEDD pre (cm)	6.2 ± 1.0	6.0 ± 1.1	6.6 ± 0.9	6.2 ± 1.1	0.002
LVEDD post (cm)	5.8 ± 1.2	5.5 ± 1.2	6.4 ± 1.0	6.1 ± 1.1	0.0002
LVEDD change (cm)	−0.45 ± 0.95	−0.26 ± 0.81	−0.29 ± 0.57	0.02 ± 0.81	0.007
LVESD pre (cm)	5.2 ± 1.2	4.9 ± 1.3	5.5 ± 1.1	5.2 ± 1.2	0.008
LVESD post (cm)	4.5 ± 1.5	4.3 ± 1.2	5.2 ± 1.1	5.0 ± 1.1	0.0006
LVESD change (cm)	−0.76 ± 1.15	−0.36 ± 0.89	−0.47 ± 0.97	−0.04 ± 1.12	0.0005
MR grades pre (1–9)	3.8 ± 2.4	3.8 ± 2.3	3.7 ± 2.5	3.3 ± 2.2	0.44
MR grades post (1–9)	3.1 ± 2.5	3.4 ± 2.3	2.6 ± 1.9	3.5 ± 2.3	0.25
MR grades change (1–9)	−0.8 ± 2.4	−0.3 ± 2.5	−1.0 ± 2.3	0.5 ± 2.0	0.001
Super-responders	28	13	9	10	0.001
Negative responders	26	29	47	51	0.001
Clinical response					
NYHA functional class pre	2.9 ± 0.4	2.9 ± 0.4	2.9 ± 0.5	3.0 ± 0.4	0.48
NYHA functional class post	2.0 ± 0.6	2.0 ± 0.7	2.3 ± 0.6	2.4 ± 0.6	0.0002
NYHA functional class change	−0.9 ± 0.6	−0.8 ± 0.7	−0.5 ± 0.6	−0.6 ± 0.6	0.001

Values are mean ± SD or %.
CRT = cardiac resynchronization therapy; other abbreviations as in Table1.

vs. QRSd ≥150 ms and p = 0.04 vs. QRSd <150 ms). In a stepwise multivariate (linear) regression model (predicting EF improvement), with baseline EF, LVEDD, atrial fibrillation, age, sex, diabetes mellitus, cardiomyopathy type, and the 4 groups as candidate variables, the latter was the strongest and first entered variable in the model (p = 0.0003). Interestingly, when QRS morphology and QRSd were entered as separate candidate variables in a stepwise model, QRSd was no longer significant (p = 0.36).

Outcome data were completed for 478 patients (96%). After a median follow-up of 5.2 ± 0.9 years, 181 subjects (38%) experienced the composite outcome; 171 deaths (36%), 10 heart transplants (2%), and 2 underwent LVAD placement (0.4%). The composite endpoint occurred in 31% of the LBBB and QRS ≥150 ms group, 41% of the LBBB and QRS <150 ms group, 40% of the non-LBBB and QRS ≥150 ms group, and 48% of the non-LBBB and QRS <150 ms group (p = 0.03). Figure 3 displays Kaplan-Meier survival curves for the composite endpoint stratified according to the 4 groups (log-rank test p = 0.02). The specific groups were significant predictors of the composite endpoint in a univariate Cox model (p = 0.02). However, after adjustment for other known predictors (sex, age, type of cardiomyopathy, estimated glomerular filtration rate, and EF), this was no longer significant (p = 0.15) (Table 3).

Discussion

The key findings of this study can be summarized as follows: 1) non-LBBB, as the baseline ECG morphology before CRT implantation, is much more prevalent in real-world practice than in randomized clinical trials; 2) echocardiographic and clinical response to CRT is determined by baseline QRS morphology in the first place and to a lesser degree by QRSd; 3) event-free survival (from death, heart transplantation, or LVAD) is better in CRT-treated patients with baseline LBBB and QRS ≥150 ms. However, this difference is not significant after adjusting for other baseline characteristics.

From the early days of CRT, it was noticed that a substantial subset of patients fail to benefit from this treatment. Although this is in no way different from

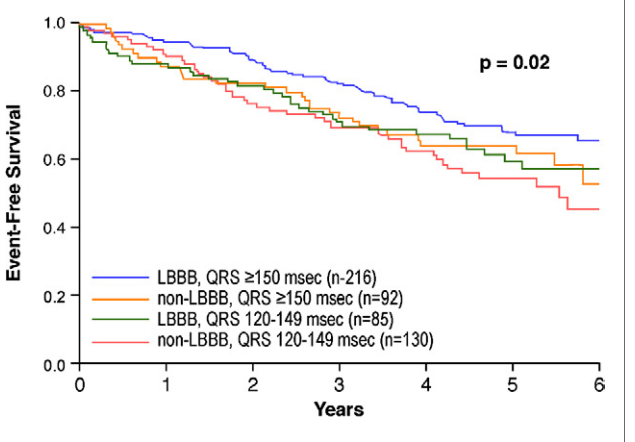

Figure 3 Survival After CRT Implantation

Kaplan-Meier curves for patients stratified into 4 groups according to baseline QRS morphology and QRS duration. The outcome is the composite of death/heart transplantation and left ventricular assist device placement. CRT = cardiac resynchronization therapy.

Table 3 Univariate and Multivariate Cox Proportional Hazards Model for Death, Heart Transplantation, and Left Ventricular Assist Device Placement

	Cox Proportional Hazards			
Variable	Unadjusted Hazard Ratio	p Value	Adjusted Hazard Ratio	p Value
QRS morphology/duration		0.02		0.15
LBBB and QRSd ≥150 ms	1.00		1.00	
LBBB and QRSd <150 ms	1.46 (0.94–2.21)	0.09	1.52 (0.95–2.38)	0.08
Non-LBBB and QRSd ≥150 ms	1.43 (0.95–2.14)	0.09	1.01 (0.65–1.55)	0.96
Non-LBBB and QRSd <150 ms	1.80 (1.23–2.62)	0.003	1.42 (0.93–2.15)	0.10
Male	2.28 (1.59–3.39)	<0.0001	2.17 (1.14–3.44)	0.0003
Age >70 yrs	1.16 (0.85–1.56)	0.35	0.84 (0.60–1.17)	0.30
Ischemic cardiomyopathy	1.86 (1.35–2.58)	<0.0001	1.55 (1.09–2.24)	0.01
eGFR	0.98 (0.98–0.99)	<0.0001	0.98 (0.98–0.99)	<0.0001
Baseline EF	0.97 (0.95–0.99)	0.008	0.97 (0.95–0.99)	0.01

Abbreviations as in Table 1.

treatment with medications, CRT has received considerable attention because of the cost and invasive nature of this therapy. Attempts to predict and subsequently minimize nonresponders have focused on better patient selection by analyzing data from subgroups of the original randomized trials. Patients with non-LBBB morphologies, often underrepresented in clinical trials, or shorter QRSd on their baseline ECG were repeatedly reported to gain less or even no benefit. Stratifying patients, however, according to both the morphology and the duration of the QRS complex has been less frequently done (12,13). Nevertheless, we thought this method was useful because it allows determining the relative importance of these 2 electrocardiographic characteristics. In addition, such classification mimics current clinical thinking. The current results clearly stress the importance of bundle branch type as the major electrocardiographic determinant of response to CRT. Patients with a smaller QRS (120 to 149 ms) but LBBB morphology still have a better echocardiographic and clinical response than patients with a broad QRS (≥150 ms) but non-LBBB morphology. In addition, multivariate modeling to predict improvement in EF demonstrates the current classification in 4 groups to be the most important factor in this multivariate model. However, when QRS morphology and QRSd were entered separately, only QRS morphology stayed in the model. Taken together, our results reinforce the importance of the presence of baseline dyssynchronous LV activation as a prerequisite for response after CRT. QRSd further expresses the extent of this dyssynchrony, and the difference in echocardiographic response to CRT between patients with LBBB and QRSd ≥150 ms or <150 ms trended toward significance ($p = 0.12$ with the conservative Tukey test). Previous work from our group also demonstrated the importance of QRSd within the non-LBBB group as a predictor of echocardiographic response to CRT (14). The findings in our study are in accordance with those of a recent study by Gold et al. (15), emphasizing the importance of LV activation delay. Thereby, a delay of 95 to 100 ms may be a significant predictor of CRT response. QRS configuration is a surface depiction of biventricular activation and may not specifically report inferolateral LV conduction delay (16). In a previous study, significant LV activation delay in patients with LV dysfunction was infrequent when QRSd was <150 ms but consistently high with LBBB and QRSd ≥150 ms. However, similar QRSds in groups with LBBB and RBBB and a wide QRS (164 ms) concealed very dissimilar LV activation delays. Fewer than 25% of patients with RBBB demonstrated delays equivalent to those in patients with LBBB (17). Thus, the probability distribution of LV activation delay according to QRS morphology and QRSd may contribute to likelihood of response to CRT.

There were no significant differences between the 4 groups in adjusted survival rates (free of death, heart transplantation, or LVAD insertion). Unadjusted, the group with the best response (LBBB patients with QRSd ≥150 ms) had improved survival. These results have to be interpreted with caution. There are indeed some differences in baseline characteristics (LBBB patients less often have ischemic cardiomyopathy and are more often female) that might explain that the adjusted survival difference is no longer significant. However, it is important to realize that the natural survival (without CRT) is worse for heart failure patients with LBBB compared with RBBB or IVCD, as shown in an Italian study and in a substudy of the MADIT-CRT trial (13,18). The latter study confirms (although the survival curves were unadjusted), in NYHA class I and II patients, that the poorer prognosis associated with LBBB is eliminated with CRT treatment. Similarly, a recent analysis of the Medicare registry demonstrated that RBBB was an independent predictor of poor outcome in a CRT-treated elderly population (12). Taken together, the division of CRT patients according to branch block morphology and QRSd clearly and independently predicts CRT response. However, in our study, this division does not independently predict outcome anymore, which underscores the prognostic importance of other demographic characteristics or comorbidities that are unequally distributed in our 4 groups. In other words, the 4 groups comprise different clinical phenotypes.

JACC Vol. 60, No. 7, 2012
August 14, 2012:592–8

Because of the lack of a control group without CRT, our study cannot judge the potential clinical benefit of CRT nor can it appreciate differences in treatment efficacy (less benefit or even harm) between the 4 groups. However, results of the MADIT-CRT substudy (which has a control arm) suggest that there is no clinical benefit of CRT in NYHA functional class I and II patients with non-LBBB, both with QRSd ≥150 ms and <150 ms, despite significant echocardiographic improvement in these subgroups (13).

Study limitations. First, this was a retrospective study with inherent imperfections in data collection or missing data. For example, only 63% of patients had echocardiograms available before and after CRT implantation. Patients with missing echocardiogram data were more likely to have non-LBBB with QRSd ≥150 ms and had worse survival. If anything, this finding likely weakened the observed differences in echocardiographic response to CRT. Second, as a single-center study, our patient cohort might be different from that in other centers. Third, the observed differences in response to CRT are ascribed to differences in QRS morphology and duration but could also be the result of other confounding differences between the groups. However, by controlling for the most frequent reported factors known to influence CRT response in a multivariate model, we believe that the observed differences are indeed the result of the different baseline electrocardiographic characteristics. Fourth, heart failure rehospitalization data were not collected as an outcome parameter contrary to most randomized trials. Finally, it remains possible that there are subgroups within subgroups (e.g., RBBB vs. IVCD, male vs. female, ischemic vs. nonischemic) with different responses to CRT. However, the number of patients was too small to perform such analyses.

Conclusions

By comparing QRS morphology and QRSd as baseline characteristics, we identified QRS morphology as the most important predictor of response to CRT. Despite favorable responses in the LBBB groups, there were no statistically significant differences in long-term outcomes among the groups after adjustments, suggesting that comorbid conditions may confound the treatment responses. Due to the lack of sufficiently powered trials in these subgroups, guideline committees have the difficult task of using this and similar studies to refine patient selection for CRT.

Reprint requests and correspondence: Dr. W. H. Wilson Tang, Department of Cardiovascular Medicine, Heart and Vascular Institute, 9500 Euclid Avenue, J3-4, Cleveland, Ohio 44195. E-mail: tangw@ccf.org.

REFERENCES

1. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.
2. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.
3. Yu CM, Chau E, Sanderson JE, et al. Tissue doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002;105:438–45.
4. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.
5. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–38.
6. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385–95.
7. Dickstein K, Vardas PE, Auricchio A, et al. 2010 focused update of ESC guidelines on device therapy in heart failure: an update of the 2008 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Eur Heart J 2010;31:2677–87.
8. Pires LA, Abraham WT, Young JB, Johnson KM. Clinical predictors and timing of New York Heart Association class improvement with cardiac resynchronization therapy in patients with advanced chronic heart failure: results from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE-ICD) trials. Am Heart J 2006;151:837–43.
9. van Bommel RJ, Bax JJ, Abraham WT, et al. 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;30:2470–7.
10. Mullens W, Grimm RA, Verga T, et al. Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. J Am Coll Cardiol 2009;53:765–73.
11. Kaszala K, Ellenbogen KA. When right may not be right: right bundle-branch block and response to cardiac resynchronization therapy. Circulation 2010;122:1999–2001.
12. Bilchick KC, Kamath S, DiMarco JP, Stukenborg GJ. Bundle-branch block morphology and other predictors of outcome after cardiac resynchronization therapy in Medicare patients. Circulation 2010;122:2022–30.
13. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011;123:1061–72.
14. Rickard J, Bassiouny M, Cronin EM, et al. Predictors of response to cardiac resynchronization therapy in patients with a non-left bundle branch block morphology. Am J Cardiol 2011;108:1576–80.
15. Gold MR, Birgersdotter-Green U, Singh JP, et al. The relationship between ventricular electrical delay and left ventricular remodelling with cardiac resynchronization therapy. Eur Heart J 2011;32:2516–24.
16. Varma N. Cardiac resynchronization therapy and the electrical substrate in heart failure: what does the QRS conceal? Heart Rhythm 2009;6:1059–62.
17. Varma N. Left ventricular conduction delays and relation to QRS configuration in patients with left ventricular dysfunction. Am J Cardiol 2009;103:1578–85.
18. Baldasseroni S, Gentile A, Gorini M, et al. Intraventricular conduction defects in patients with congestive heart failure: left but not right bundle branch block is an independent predictor of prognosis. A report from the Italian Network on Congestive Heart Failure (IN-CHF database). Ital Heart J 2003;4:607–13.

Key Words: cardiac resynchronization therapy ■ heart failure ■ left bundle branch block ■ QRS duration.