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QRS narrowing is associated with reverse remodeling in patients with chronic right ventricular pacing upgraded to cardiac resynchronization therapy

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Abstract

BACKGROUND—Patients with chronic right ventricular pacing (RVP) upgraded to cardiac resynchronization therapy (CRT) have been excluded from the majority of clinical trials of CRT. Little is known about the predictors of response in this population. We hypothesized that reversal of RVP-induced electrical dyssynchrony (indexed by QRS duration) by CRT would predict a favorable response.

OBJECTIVE—The purpose of this study was to identify baseline characteristics associated with response in patients upgraded to CRT from chronic RVP.

METHODS—Consecutive patients presenting for CRT at the Cleveland Clinic between September 30, 2003, and July 8, 2008, with chronic RVP and serial echocardiograms were included in this analysis. RVP was defined as > 485% pacing on a pre-CRT device check, previous AV nodal ablation, or complete pacer dependency per chart notes. Response was defined as a reduction in left ventricular end-systolic volume ≥ 15% from baseline. Clinical, ECG, and echocardiographic data were extracted to determine covariates associated with response.

RESULTS—One hundred twelve patients met inclusion criteria, of whom 72 (64.3%) met criteria for response over median follow-up of 9.9 months (interquartile range [6.5–14.7]). No significant differences were noted in terms of male gender (68.1% vs 75.0%; $P = .52$), ischemic cardiomyopathy (55.6% vs 55.0%; $P = 1$), pre-CRT QRS duration (189.1 ± 20.7 ms vs 185.5 ± 26.8 ms; $P = .47$), duration of RVP before CRT upgrade (5.8 ± 3.9 years vs 6.2 ± 4.0 years; $P = .57$), or baseline left ventricular end-systolic volume (160.0 ± 60.7 mL vs 172.8 ± 67.2 mL; $P = .32$) between responders and nonresponders, respectively. Percent reduction in QRS duration between the right ventricular-paced and first biventricular-paced waveforms was significantly greater in responders compared with nonresponders ($14.4\% \pm 13.2\%$ vs $7.2\% \pm 14.0\%$; $P = .01$). In multivariate analysis, percent reduction in QRS narrowing was the lone factor associated with response (odds ratio 0.02 [0.001–0.42]; $P = .01$).

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Dr. Cheng has received honoraria from Boston Scientific and St. Jude Medical and has served on the Advisory Board of Biotronik and Medtronic. Dr. Spragg has been a Speaker for St. Jude Medical and Medtronic. Dr. Tang has been a Consultant (Minor) for Medtronic and St. Jude Medical. Dr. Wilkoff has served on the Medical Advisory Panel of Medtronic and has maintained a modest relationship with St. Jude Medical and Spectranetics. Dr. Varma Research St. Jude Medical.

CONCLUSION—Reversal of electrical dyssynchrony predicts response to CRT in chronically RV-paced patients upgraded to CRT. Traditional factors associated with a favorable response to CRT in *de novo* implants (female gender, nonischemic cardiomyopathy, and wider baseline QRS duration) are not significantly associated with response in upgraded patients. Duration of RVP before CRT upgrade is not an important determinant of response.

Keywords

Cardiac resynchronization therapy; Chronic right ventricular pacing; QRS narrowing

Introduction

The benefits of cardiac resynchronization therapy (CRT) in patients with heart failure undergoing *de novo* implantation are well established, but patients with chronic right ventricular pacing (RVP) upgraded to CRT were largely excluded from the large clinical trials of CRT.^{1–5} Although both prospective and retrospective studies have confirmed the benefits of upgrading to CRT, these studies have been small in scope.^{6–12} Certain baseline characteristics (eg, female gender, nonischemic cardiomyopathy [NICM], wide QRS duration) have emerged as being associated with favorable outcomes following CRT in a *de novo* population.¹³ Whether such characteristics are associated with response in a large cohort of patients upgraded to CRT from chronic RVP has not been studied. Additionally, it is becoming increasingly clear that CRT-induced reversal of underlying electrical dyssynchrony as assessed by changes in QRS duration is associated with a favorable long-term response.^{14,15} Whether changes in QRS duration between right ventricular (RV)-paced and biventricular-paced QRS waveforms have an impact on response to CRT is unknown. In the current study, we tested the hypothesis that factors linked to CRT response in patients with *de novo* implants would apply similarly to patients upgraded from chronic RVP, paying special attention to the role of electrical dyssynchrony as assessed by the QRS duration both before and after CRT.

Methods

This retrospective study involved the analysis of a cohort of patients with chronic RVP who underwent an upgrade to a cardiac resynchronization device at the Cleveland Clinic, Cleveland, Ohio, between September 26, 2003, and July 8, 2008. The study was approved by the Institutional Review Board of the Cleveland Clinic for retrospective medical records review and performed according to institutional guidelines. For inclusion in the final cohort, all patients had left ventricular ejection fraction (LVEF) $\geq 35\%$, chronic RVP, and pre-CRT and follow-up echocardiograms, with the follow-up study occurring no earlier than 3 months after CRT implant. In instances where more than 1 follow-up echocardiogram was available, the study closest to 1 year after CRT upgrade was selected. Chronic RVP was defined as at least 1 of the following: $> 85\%$ pacing on the pre-CRT upgrade device check, previous AV nodal ablation, or complete pacer dependency determined per chart notes with only RVP noted on all available ECGs after the original RV lead implant date before the upgrade. All echocardiograms were reevaluated by a board-certified cardiologist blinded to the clinical data, with ventricular volumes carefully assessed in the apical 4-chamber view. Response to CRT was defined as a reduction in left ventricular (LV) end-systolic volume $\geq 15\%$ from baseline. Mitral regurgitation was graded on a 9-point scale using multiple gauges of severity according to the 2003 American Society of Echocardiography Guidelines integrated to produce a score as follows: 0–3 mild, 3–6 moderate, and 7–9 severe.¹⁶ QRS duration was compared using the pre-CRT ECG closest to the implant date and the first biventricular-paced ECG recorded after CRT upgrade. QRS duration and morphology from the ECGs were recorded from the computer analysis and confirmed by visual inspection. To account

for baseline QRS duration differences among patients, an index was calculated for each patient as follows: QRS index = (post-CRT biventricular-paced QRS duration minus pre-CRT RV-paced QRS duration divided by pre-CRT biventricular-paced QRS duration) multiplied by 100.

CRT device implantation and management

CRT device implantations were performed transvenously in the vast majority of patients by electrophysiologists targeting a lateral or posterolateral vein for the LV lead position. In instances where a transvenous lead could not be placed due to procedural difficulty, a minimally invasive epicardial lead was placed surgically. CRT devices were commonly programmed with an atrioventricular sensed delay of 100 ms and paced delay of 130 ms, with optimization performed according to standard institutional protocols. Medications were recorded immediately before implantation of the CRT device with subsequent titration of medications made at the discretion of patients' outpatient physicians.

Statistical analysis

Continuous variables are presented as mean $\pm$ SD and dichotomous variables as an absolute number with percentage. Comparisons between continuous variables were made using the Student *t*-test for parametric variables and a Mann-Whitney test for nonparametric variables. Dichotomous variables were compared using a χ^2 test. Age, gender, ischemic cardiomyopathy, and any variables in univariate analysis for $P < .2$ were entered into a forward stepwise multivariate regression model to determine factors significantly associated with response. A two-sided $P < .05$ was considered statistically significant. All analyses were done using SPSS software (version 17.0; SPSS Inc., Chicago, IL).

Results

A total of 856 patients underwent implantation of a CRT device at the Cleveland Clinic between September 26, 2003, and June 18, 2008. From this cohort, 226 patients presented with a paced rhythm. Eighty-eight patients lacked available and appropriately timed pre-CRT and/or follow-up echocardiograms. Twenty-six patients failed to meet criteria for pacemaker dependency. One hundred twelve patients met inclusion criteria and comprised the final cohort, of whom 72 (64.3%) met criteria for response. The follow-up echocardiographic examination occurred at a median of 9.9 months (interquartile range [6.5–14.7]) following CRT initiation, with no significant difference in follow-up times between patients based on response. The follow-up biventricular-paced ECG was recorded 1 day postimplant in the vast majority of patients. Baseline characteristics of the cohort as a whole and based on response are given in Table 1. The majority of baseline variables, including gender, pre-CRT QRS duration, history of atrial fibrillation, LV volumes (Table 2), mitral regurgitation severity, and medications were similar in both groups (Figure 1). The time from the original RV lead implant to upgrade to CRT was also similar between responders and nonresponders (5.8 ± 3.9 years vs 6.2 ± 4.0 years; $P = .57$). There was a nonsignificant trend for responders to be older (70.5 ± 11.1 years vs 67.5 ± 11.5 years; $P = .15$), have a higher baseline LVEF ($23.3\% \pm 7.1\%$ vs $20.9\% \pm 8.4\%$; $P = .12$), and a lower incidence of hydralazine use (6.9% vs 17.5% ; $P = .11$). Of particular note, responders had a significantly greater absolute and percent QRS reduction compared with nonresponders (-26.4 ± 33.2 ms vs -11.1 ± 39.8 ms; $P = .043$; and $14.4\% \pm 13.2\%$ vs $7.2\% \pm 14.0\%$; $P = .01$, respectively; Figure 2). Compared with patients with *de novo* implants, patients with chronic RVP were older (69.3 ± 11.2 years vs 65.4 ± 12.1 years; $P = .002$), had a wider baseline QRS duration (187.8 ± 23.0 ms vs 150.0 ± 26.1 ms; $P < .001$), and had a higher incidence of atrial fibrillation (70.5% vs 47.8% ; $P < .001$; Table 3). Among the entire RVP cohort, 80.0% had some degree of QRS narrowing (Figure 3). In multivariate analysis,

accounting for age, gender, ischemic cardiomyopathy, baseline LVEF, and hydralazine use, QRS reduction indexed to the baseline QRS duration was the lone factor associated with response (odds ratio 0.02 [0.001–0.42]; $P = .01$).

Discussion

The current study sought to identify characteristics associated with reverse remodeling in patients exposed to chronic RVP upgraded to CRT. The primary findings were as follows. Traditional factors associated with response in a *de novo* population receiving CRT, such as female gender, wider baseline QRS duration, sinus rhythm, larger baseline volumes, and NICM, were not significantly associated with response in patients with RVP upgraded to CRT. Second, reversal of electrical dyssynchrony, manifest as a reduction in QRS duration between the RV-paced and biventricular-paced waveforms, was the lone marker of echocardiographic response. Last, duration of RVP before CRT upgrade was not an important factor dictating response in this population.

In patients with symptomatic bradycardia, RVP is the only effective therapy to improve patient symptoms. As a result of slow myocardial electrical conduction, RVP induces LV activation delay and mechanical dyssynchrony, which can lead to impaired LV function. Such adverse effects of RVP are particularly pronounced in patients with preexisting LV dysfunction.¹⁷ The effects of CRT in patients with RVP were studied in one small, short-term, prospective study in patients with LV dysfunction. However, that study was confounded by inclusion of a dominant proportion of patients with underlying left bundle branch block (LBBB).⁶ Small prospective studies have also been performed in less vulnerable patients with relatively normal LV function.¹⁸ Retrospective analyses have suggested similar benefits in terms of clinical response in patients with RVP compared with *de novo* implants in patients with a native LBBB.^{19–25} However, many of these studies either were small or included patients with variable levels of RVP (some with a very light burden) and incomplete echocardiographic sets preventing detailed analyses.^{19–22} Therefore, baseline characteristics associated with response in this population had not been established before the current study.

Pivotal trials of CRT largely excluded patients with chronic RVP. When enrolled, numbers have been restricted according to an arbitrarily chosen RV-paced QRS duration cutoff > 200 ms, preventing full assessment of the RV-paced population and yielding small study groups (eg, 68 patients in the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial [RAFT]) for which separate data have not been reported.^{26,27} In contrast, recent subgroup analyses of *de novo* CRT patients have been performed, reflecting an emphasis on refining candidate selection. These studies have consistently indicated that a wide baseline QRS complex with an LBBB pattern, female gender, sinus rhythm, and NICM are predictive of a favorable outcomes with CRT.^{13,28} In striking contrast, our results indicate that response in patients with RVP is independent of each of these factors, yielding a broader candidate population for CRT compared with *de novo* implants.

Patients undergoing CRT upgrade may have a somewhat different substrate than patients undergoing *de novo* implantation. Our study as well as others have shown upgraded patients to be older, to have an increased incidence of atrial fibrillation, and to have a wider baseline QRS duration than *de novo* patients.^{19–21} In animal studies, RVP leads to early ventricular activation near the RV pacing site, causing prestretch in later activated regions.²⁹ Such a scenario leads to a redistribution of myocardial strain and subsequent impaired function.²⁹ RVP is associated with profound LV electrical delay as manifest by significant QRS widening. In a meta-analysis of the large clinical trials of CRT, QRS duration during intrinsic conduction was found to be one of the most robust indicators of substrate treatable

by CRT.³⁰ Notably, QRS duration is tightly linked to LV depolarization delay during RVP as well as LBBB.³¹ This is important because the QRS duration of patients with RVP in our cohort was almost 40 ms greater than that for *de novo* patients, indicating that RVP patients suffer from more severe electrical dyssynchrony. Although RVP may simulate LBBB in normal hearts, it forces more severe desynchronization in patients with LV dysfunction, in whom QRS prolongation and associated LV activation delay exceed those associated with native LBBB. Thus, in one series where the mean RV-paced QRS duration was 191 ± 20 ms (similar to the current cohort), LV depolarization delay was 169 ± 24 ms, compared with *de novo* candidates with LBBB in whom the mean QRS duration was 163 ± 29 ms with only 137 ± 33 ms of delay.³²

The electrical effect of CRT was important in the current study. The index of QRS narrowing was the single predictor of a favorable outcome to CRT. In this regard, this observation follows the *de novo* CRT population in which reduction in QRS duration correlates with positive response.^{14,15} QRS narrowing is a measure of CRT effect, that is, rectification of the underlying disorder. Our findings support the importance of this concept, as responders in our study had roughly double the percent reduction in QRS duration compared with nonresponders. Our results, however, are also instructive for showing that the CRT effect displayed a fairly normal distribution. Possibly, measures taken to enhance QRS abbreviation (eg, LV lead position and relative timing of paced wavefronts) could improve response rates further.

Several practice points emerge from this study. Our results show that conventional negative predictors in *de novo* implants have a lesser influence on this response in this population. Second, a value of 200 ms for candidate selection of paced patients has been used from the Multisite Stimulation in Cardiomyopathy (MUSTIC) trial published in 2002 to the RAFT trial published in 2011, a time period spanning close to a decade.^{26,27} However, this value was assigned arbitrarily without formal testing. In the current study, the mean baseline QRS duration was 187.8 ± 23.0 ms, and no difference in response was found based on the baseline QRS duration. Therefore, our results suggest abandoning this 200-ms cutpoint. Last, duration of RV pacing was not a significant factor in predicting response in patients upgraded to CRT. Despite a mean duration of approximately 6 years of RVP, roughly 65% of patients in this cohort met our definition of response. This finding suggests that even prolonged periods of RVP-induced dyssynchrony are potentially reversible with CRT.

Study limitations

Our study has several limitations. The retrospective nature cannot account for all confounders despite our best efforts to identify important baseline differences. Patients in our cohort come from a single tertiary-care center and therefore may not be representative of patients presenting to other centers. There is a relatively wide disparity in the timing of follow-up echocardiograms, which reflects the different follow-up practices among cardiologists and the wide referral area of the Cleveland Clinic. We attempted to mitigate this variation by selecting the follow-up echocardiogram closest to one year. Last, a cutpoint for QRS narrowing and response could not be established, likely in part due to the size of our cohort.

Conclusion

The present study to our knowledge is among the largest to report on pacemaker-dependent patients undergoing an upgrade to CRT and among the first to report on characteristics associated with response in this population. Reversal of electrical dyssynchrony as manifest by a reduction in QRS duration between the RV-paced and biventricular-paced waveforms was the lone factor associated with reverse remodeling. Traditional factors associated with

response to CRT in the *de novo* CRT population do not appear to apply to RVP patients undergoing CRT upgrade. The 200-ms cutoff for inclusion of RVP patients in past CRT trials does not appear to be a valid cut point. Last, duration of RVP before upgrade does not appear to be an important factor dictating response. These findings merit prospective evaluation.

ABBREVIATIONS

CRT	cardiac resynchronization therapy
LBBB	left bundle branch block
LV	left ventricle
LVEF	left ventricular ejection fraction
NICM	nonischemic cardiomyopathy
RV	right ventricle
RVP	right ventricular pacing

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Figure 1.

Factors commonly associated with a favorable response to cardiac resynchronization therapy (CRT). LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.

Figure 2.
QRS change indexed to baseline QRS duration and response to cardiac resynchronization therapy.

Figure 3.
Distribution of percent reduction in QRS duration across the cohort.

Table 1

Baseline patient characteristics

	Total cohort (n = 112)	Responders (n = 72)	Nonresponders (n = 40)	P value
Age (years)	69.3 ± 11.2	70.5 ± 11.1	67.5 ± 11.2	.15
Male gender	79 (70.5%)	49 (68.1%)	30 (75.0%)	.52
Pre-CRT QRS duration (ms)	187.8 ± 23.0	189.1 ± 20.7	185.5 ± 26.8	.47
Implantable cardioverter-defibrillator	105 (93.8%)	66 (91.7%)	39 (97.5%)	.42
Time from right ventricular implant to CRT upgrade (years)	6.0 ± 3.9	5.8 ± 3.9	6.2 ± 4.0	.57
Percent change in QRS duration (%)	11.8 ± 13.8	14.4 ± 13.2	7.2 ± 14.0	.01
Absolute change in QRS duration (ms)	−20.9 ± 36.3	−26.4 ± 33.2	−11.1 ± 39.8	.043
Ischemic cardiomyopathy	62 (55.4%)	40 (55.6%)	22 (55.0%)	1
Atrial fibrillation	79 (70.5%)	52 (72.2%)	27 (67.5%)	.67
Serum hemoglobin (g/dL)	12.7 ± 1.8	12.7 ± 1.8	12.7 ± 1.9	.86
Serum creatinine (mg/dL)	1.4 ± 0.7	1.4 ± 0.6	1.4 ± 0.9	.64
Chronic obstructive pulmonary disease	13 (11.6%)	8 (11.1%)	5 (12.5%)	1
Hypertension	63 (56.3%)	43 (59.7%)	20 (50.0%)	.33
Hyperlipidemia	69 (61.6%)	44 (61.1%)	25 (62.5%)	1
Diabetes mellitus	35 (31.2%)	21 (29.2%)	14 (35.0%)	.53
History of cerebrovascular accident or transient ischemic attack	11 (9.8%)	8 (11.1%)	3 (7.5%)	.74
β-Adrenergic blocker	86 (76.8%)	58 (80.6%)	28 (70.0%)	.25
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	87 (77.7%)	58 (80.6%)	29 (72.5%)	.35
Diuretic	85 (75.9%)	54 (75.0%)	31 (77.5%)	.82
Nitrates	28 (25.0%)	16 (22.2%)	12 (30.0%)	.37
Hydralazine	12 (10.7%)	5 (6.9%)	7 (17.5%)	.11
Aldosterone antagonists	40 (35.7%)	17 (23.6%)	23 (57.5%)	.31

Values are given as no. (%) or mean ± SD.

CRT = cardiac resynchronization therapy.

Table 2

Echocardiographic changes in patients based on response

	Total (n = 112)	Responders (n = 72)	Nonresponders (n = 40)	P value
LVEF pre-CRT (%)	22.5 ± 7.7	23.3 ± 7.1	20.9 ± 8.4	.12
LVEF post-CRT (%)	33.1 ± 13.0	39.0 ± 11.8	22.5 ± 6.9	< 0.001
LVEF change (%)	10.6 ± 11.1	15.6 ± 10.0	1.6 ± 6.5	< .001
LVEDV pre-CRT (mL)	164.6 ± 63.1	160.0 ± 60.7	172.8 ± 67.2	.32
LVEDV post-CRT (mL)	147.2 ± 65.8	125.0 ± 50.5	187.1 ± 71.6	< .001
LVEDV change (mL)	-17.4 ± 39.6	-35.0 ± 32.1	14.3 ± 31.5	< .001
LVESV pre-CRT (mL)	122.3 ± 55.1	117.1 ± 50.3	131.5 ± 62.3	.21
LVESV post-CRT (mL)	95.7 ± 59.2	71.7 ± 38.0	138.9 ± 66.0	< .001
LVESV change (mL)	-26.6 ± 36.3	-45.4 ± 26.1	7.4 ± 25.9	< .001
MR pre	3.9 ± 2.4	3.8 ± 2.4	4.2 ± 2.3	.46
MR post	3.3 ± 2.2	2.8 ± 2.0	4.2 ± 2.2	.001
MR difference	-0.7 ± 2.2	-1.1 ± 2.1	0.0 ± 2.1	.012

CRT = cardiac resynchronization therapy; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; MR = mitral regurgitation.

Table 3

Baseline characteristics comparing chronically right ventricular-paced patients with *de novo* patients before CRT

	<i>De novo</i> patients (n = 601) *	Pacemaker-dependent patients (n =112)	<i>P</i> value
Age (years)	65.4 ± 12.2	69.3 ± 11.2	.002
Male gender	418 (69.6%)	79 (70.5%)	.91
Pre-CRT ejection fraction (%)	21.0 ± 7.0	22.5 ± 7.7	.06
Pre-CRT QRS duration (ms)	150.0 ± 26.1	187.8 ± 23.0	< .001
Absolute change in QRS duration (ms)	3.7 ± 28.4	−20.9 ± 36.3	< .001
Percent change in QRS duration (%)	5.0 ± 21.2	11.8 ± 13.8	< .001
Ischemic cardiomyopathy	365 (60.7%)	62 (55.4%)	.30
Atrial fibrillation	281 (47.8%)	79 (70.5%)	< .001
Serum hemoglobin (g/dL)	12.6 ± 2.0	12.7 ± 1.8	.62
Serum creatinine (mg/dL)	1.3 ± 0.7	1.4 ± 0.7	.502
Chronic obstructive pulmonary disease	87 (14.5%)	13 (11.6%)	.46
Hypertension	374 (62.2%)	63 (56.3%)	.25
Hyperlipidemia	340 (56.6%)	69 (61.6%)	.35
Diabetes mellitus	233 (38.8%)	35 (31.2%)	.14
History of cerebrovascular accident or transient ischemic attack	68 (11.3%)	11 (9.8%)	.74
β-Adrenergic blocker	473 (78.7%)	86 (76.8%)	.19
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	458 (76.2%)	87 (77.7%)	.61
Diuretic	462 (76.9%)	85 (75.9%)	.31
Nitrates	168 (28.0%)	28 (25.0%)	.42
Hydralazine	67 (11.1%)	12 (10.7%)	.87
Aldosterone antagonists	191 (31.7%)	40 (35.7%)	.66

Values are given as no. (%) or mean ± SD. CRT = cardiac resynchronization therapy.

* Patients with ejection fraction > 35% or patients with right ventricular pacing who did not meet criteria for dependency were excluded.