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

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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 $>85\%$ 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 $\geq 15\%$ 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 $\pm$ 20.7 ms vs 185.5 $\pm$ 26.8 ms; $P = .47$), duration of RVP before CRT upgrade (5.8 $\pm$ 3.9 years vs 6.2 $\pm$ 4.0 years; $P = .57$), or baseline left ventricular end-systolic volume (160.0 $\pm$ 60.7 mL vs 172.8 $\pm$ 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]; $P = .01$).

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

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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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

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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) $\leq$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 $P \leq .05$ 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 $\pm$ 3.9 years vs 6.2 $\pm$ 4.0 years; $P = .57$). There was a nonsignificant trend for responders to be older (70.5 $\pm$ 11.1 years vs 67.5 $\pm$ 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 non-responders (–26.4 $\pm$ 33.2 ms vs –11.1 $\pm$ 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*