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Citation

Park, Mi Young, Robert K. Altman, Mary Orencole, Prabhat Kumar, Kimberly A. Parks, Kevin E. Heist, Jagmeet P. Singh, and Michael H. Picard. 2012. "Characteristics of Responders to Cardiac Resynchronization Therapy: The Impact of Echocardiographic Left Ventricular Volume." *Clinical Cardiology* 35 (12) (August 9): 779–780. doi:10.1002/clc.22043.

Published Version

doi:10.1002/clc.22043

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Published in final edited form as:

Clin Cardiol. 2012 December ; 35(12): 777–780. doi:10.1002/clc.22043.

Characteristics of Responders to Cardiac Resynchronization Therapy: The Impact of Echocardiographic Left Ventricular Volume

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Summary

Background—One third of patients who receive cardiac resynchronization therapy (CRT) are classified as nonresponders. Characteristics of responders to CRT have been studied in multiple clinical trials.

Hypothesis—We aimed to examine characteristics of CRT responders in a routine clinical practice.

Method—One hundred and twenty five patients were examined retrospectively from a multidisciplinary CRT clinic program. Echocardiographic CRT response was defined as a decrease in left ventricular (LV) end systolic volume (ESV) of 15% and/or absolute increase of 5% in LV ejection fraction (EF) at 6 month visit.

Results—There were 81 responders and 44 nonresponders. By univariate analyses, female gender, nonischemic cardiomyopathy etiology, baseline QRS duration, the presence of left bundle branch block (LBBB) and left ventricular end-diastolic volume (LVEDV) index predicted CRT response. However, multivariate analysis demonstrated only QRS duration, LBBB and LVEDV index were independent predictors (QRS width: Odd ratio [OR] 1.027, 95% CI 1.004 – 1.050, $p = 0.023$; LBBB: OR 3.568, 95% CI 1.284 – 9.910, $p = 0.015$; LV EDV index: OR 0.970, 95% CI 0.953 – 0.987, $p = 0.001$). While female gender and nonischemic etiology were associated with an improved CRT response on univariate analyses, after adjusting for LV volumes, they were not independent predictors.

Conclusion—QRS width, LBBB and LVEDV index are independent predictors for echocardiographic CRT response. Previously reported differences in CRT response for gender and cardiomyopathy etiology are associated with differences in baseline LV volumes in our clinical practice.

Keywords

Cardiac resynchronization therapy; Predictor to CRT response; Left Ventricular Volume

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No conflict of interest

Author's disclosure: Mi Young Park: None. R.K.Altman: None. M.Orencole: None. K.Parks: None. E.Heist: Research Grant; Modest; Biotronik, Boston Scientific, St.Jude Medical. Honoraria; Modest; Biotronik, Boston Scientific, Medtronic, Sorin, St.Jude Medical. Consultant/Advisory Board; Modest; Boston Scientific, Sorin, St.Jude Medical. J.P.Singh: Research Grant; Significant; St.Jude Medical, Medtronic, Boston Scientific, Biotronik. Consultant/Advisory Board; Modest; Boston scientific, Biotronik, St.Jude Medical, Medtronic, Sorin, biosense Webster, CardioInsight, Thoratec Inc. M.H. Picard: None.

Introduction

Despite efforts to identify predictors for cardiac resynchronization therapy (CRT) and thus optimize the selection of candidates for treatment, the current selection criteria for CRT has not changed.¹ Although many echocardiographic parameters including mechanical dyssynchrony have been studied, only left ventricular (LV) ejection fraction (EF) remains in the current criteria.¹⁻⁵ While LV volumes are relatively simple measurements which are generally used for assessing reverse remodeling after CRT, the impact of baseline LV volumes on CRT response has shown varying results in previous trials.⁴⁻⁹ We examined the characteristics of echocardiographic CRT responders based on the information obtained from a single center multidisciplinary CRT clinic.

Method

Study population

We identified 125 patients who completed two follow-up echocardiograms in the multidisciplinary CRT clinic program at Massachusetts General Hospital (MGH) from 2007 to 2010. All patients met the current criteria for CRT and were followed at regular intervals by a team of subspecialists from the electrophysiology, heart failure, and echocardiography services during the first year after CRT (1, 3, 6 month).^{10,11} The protocol was approved by the Institutional Review Board of MGH.

Echocardiography

Standard transthoracic two-dimensional echocardiograms were performed on all patients prior to CRT. Late follow-up echocardiograms were performed at 6 month visit after CRT implantation (212 ± 48 days). LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were measured by biplane method of discs and LV ejection fraction (EF) and LV volume indices were calculated.

Response to CRT was defined as a decrease in LVESV of $\geq 15\%$ and/or an absolute increase of $>5\%$ in LV EF on 6 month visit compared to the baseline echocardiogram.

Statistical Analysis

Data were analyzed using PASW Statistics 18 (version 18.0.0, SPSS, Inc., 2009, Chicago, IL, USA). Continuous variables were expressed as mean \pm SD. Student-t test and Mann-Whitney test were used for the comparison of continuous variables between groups. Paired-t test and Wilcoxon Signed-Rank test were used for the comparison of continuous variables between echocardiographic follow-ups. Chi-square test and Fisher's exact test were used for noncontinuous variables. Logistic multiple regression analysis was used for identifying predictors of CRT response. A two-sided p value less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

There were 81 responders and 44 nonresponders. Table 1 shows baseline characteristics of the study population. There were no significant differences in age, heart rhythm, NYHA class, heart failure medications, and pre-CRT EF between responders and nonresponders. The distribution of the mitral regurgitation (MR) severity at baseline was also similar between responders and nonresponders. Female gender showed a trend toward an improved response. In contrast, there were significant differences in the etiology of cardiomyopathy,

QRS duration, the presence of left bundle branch block (LBBB), and echocardiographic LV volumes and indices between groups. Responders showed more nonischemic etiology, more LBBB presence, longer QRS duration, and smaller baseline LV volumes and indices (Table 1).

At 6 month follow up visit after CRT, as was expected by the definition of CRT response, responders showed significant improvements in LV EF (mean increase of LV EF= 13 ± 7 %) and LV volumes (mean decrease of LVESV = 47 ± 32 mL: mean decrease of LVEDV = 36 ± 38 mL). Regarding MR, overall 26% of patients (29/112) achieved at least grade 1 improvement of MR severity at 6 month, however, there was no significant difference in the prevalence of MR improvement between responders and nonresponders (28% vs 22%, $p=0.617$).

Predictors for CRT response

Table 2 shows univariate and multivariate analyses to identify predictors to echocardiographic CRT response. By univariate analyses, gender, etiology of cardiomyopathy, QRS duration, presence of LBBB and baseline LVEDV index were associated with predicting CRT response. However, when these variables were analyzed in a multiple logistic regression model, only QRS duration, LBBB and indexed LVEDV were independent predictors to CRT response. According to the ROC analysis, indexed LVEDV 101 mL/m^2 predicted response with sensitivity of 61%, specificity of 65% and positive predictive value of 78% (AUC 0.668, CI 0.554–0.781, $p=0.004$). Baseline QRS width 159ms predicted CRT responder with sensitivity of 64%, specificity of 59% and positive predictive value of 74% (AUC 0.652, CI 0.550–0.754, $p=0.005$).

Although female gender was associated with moderately increased odds of response on univariate analysis, after adjusting for the other variables including LVEDV index, it was not a significant independent predictor. Female gender showed smaller baseline LV volumes and indices (female vs male, LVESV index = 68 ± 24 vs $84 \pm 29\text{mL/m}^2$, $p=0.013$; LVEDV index 91 ± 25 vs $110 \pm 33\text{mL/m}^2$, $p=0.009$) and more nonischemic etiology than males (female vs male, 71% vs 33%, $p<0.001$). The presence of LBBB was not significantly different between genders in our population (female vs male, 61% vs 49%, $p=0.301$). Nonischemic etiology was also associated with increased odds of response on univariate analysis; however, after adjusting for indexed LVEDV, etiology was not an independent predictor. Nonischemic cardiomyopathy patients showed smaller baseline LV volumes and indices than ischemic cardiomyopathy patients (Nonischemic vs ischemic, LVESV index: 73 ± 26 vs $86 \pm 30\text{mL/m}^2$, $p=0.012$; LVEDV index: 97 ± 30 vs $111 \pm 33\text{mL/m}^2$, $p=0.022$).

Discussion

This study suggests that in addition to the previously described QRS duration and the presence of LBBB, LV volume prior to CRT implantation may be a determinant for echocardiographic-defined CRT response. In previous studies, female gender and nonischemic etiology were shown as predictors to favorable CRT response.^{5,6,12–15} In our study, while female gender and nonischemic etiology were univariate predictors of improved echocardiographic CRT response, when they were considered together with baseline LV volumes, they were no longer independent predictors.

The impact of baseline LV dimension and volume on CRT response has shown varying and sometimes conflicting results depending on the study population.^{4–9} Study populations from Delgado et al⁸ and Lim et al⁹ showed significant differences in baseline LV volumes between responders and nonresponders, while that from the PROSPECT sub-analysis⁵ presented no significant differences in baseline LV volumes. A recent study by Rickard et

al⁴ demonstrated that the smaller LV dimension prior to CRT showed the most robust improvements in LVEF and in all-cause mortality. In contrast, the MADIT-CRT trial,¹³ a study of patients with mild HF symptoms showed the opposite relationship between baseline LV volumes and CRT response. Because of the differences in the inclusion criteria for each study population and the use of different definitions for CRT response, direct comparisons of each result are difficult. While female gender and nonischemic etiology have been reported as independent determinants of CRT response in some studies, their relationship to LV volume has not been explored in depth.^{6,7,12,13,15}

By virtue of our study being a single center study, it has limitations: Data are retrospective and the sample size of subgroups is relatively small. However, baseline demographics of our study population such as mean age, proportions of responder, gender and cardiomyopathy etiology, QRS width and LV EF are not different from other studies. Importantly, we utilized traditional CRT selection criteria and definitions for echocardiographic CRT response in our study.

Conclusion

In the examination of our multidisciplinary CRT practice, pre-CRT QRS duration, LBBB and LVEDV index were independent predictors for echocardiographic-defined response. This study suggests that traditionally favorable relationships of female gender and nonischemic cardiomyopathy to CRT response may relate to smaller LV volumes of these patients.

Acknowledgments

The statistical analysis was conducted with support from Harvard Catalyst - The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award #UL1 RR 025758 and financial contributions from Harvard University and its affiliated academic health care centers).

No grant nor financial support was given to this study

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Table 1

Baseline Characteristics

Characteristics	Total (n=125)	Responder (n=81)	Nonresponder (n=44)	P value *
Age, years	68 ± 12	67 ± 13	69 ± 10	0.337
Gender, n (%)	94 : 31	56 : 25	38 : 6	
Male: Female	(75% : 25%)	(69% : 31%)	(86% : 14%)	0.050
Etiology, n (%)	53 : 72	42 : 39	11 : 33	
Ncomp : Icomp	(42% : 58%)	(52% : 48%)	(25% : 75%)	0.004
Sinus Rhythm, n (%)	101 (81%)	65 (80%)	36 (82%)	1.000
QRS width, ms	162 ± 23	166 ± 22	154 ± 23	0.006
LBBB, n (%)	65 (52%)	51 (63%)	14 (32%)	0.001
NYHA class II/III/IV, n (%)	7 / 100 / 12 (6% / 80% / 10%)	3 / 67 / 8 (4% / 83% / 10%)	4 / 33 / 4 (9% / 75% / 9%)	0.451
Diuretics/Sp/Digoxin, n (%)	104 / 39 / 29 (83% / 31% / 23%)	66 / 30 / 15 (82% / 37% / 19%)	38 / 9 / 14 (86% / 21% / 32%)	0.619 0.070 0.121
BB/ACEI/ARB n (%)	116 / 81 / 27 (93% / 65% / 22%)	77 / 51 / 18 (95% / 63% / 22%)	39 / 30 / 9 (89% / 68% / 21%)	0.276 0.695 0.826
HTN / DM n (%)	84 / 42 (67% / 34%)	49 / 23 (61% / 28%)	35 / 19 (80% / 43%)	0.045 0.114
CABG / PCI n (%)	40 / 28 (32% / 22%)	22 / 14 (27% / 17%)	18 / 14 (41% / 32%)	0.160 0.075
LV EF, %	25 ± 6	25 ± 6	24 ± 6	0.330
MR mod, n(%)	40/112 (36%)	26/75 (35%)	14/37 (38%)	0.835
LVESV (n), mL	160 ± 59 (111)	148 ± 50 (74)	183 ± 70 (37)	0.004
LVESVI, mL/m ²	81 ± 29	74 ± 23	93 ± 35	0.001
LVEDV (n), mL	208 ± 67 (111)	195 ± 58 (74)	235 ± 76 (37)	0.003
LVEDVI, mL/m ²	105 ± 32	98 ± 26	120 ± 38	0.001

ACEI= Angiotension converting enzyme inhibitor, Sp= Spironolactone, ARB= Angiotension receptor blocker, BB= beta blocker, CABG = coronary artery bypass graft, DM=Diabetes Mellitus, HTN= Hypertension, Icomp = ischemic cardiomyopathy, LBBB= left bundle branch block, ms = millisecond, N= number of case, Ncomp = nonischemic cardiomyopathy, NS= not significance, LV EF = left ventricular ejection fraction, LVESVI= LVESV index, LVEDV=LV end diastolic volume, LVEDVI=LVEDV index, MR=mitral regurgitation, mod=moderate, NYHA Class= New York Heart Association Class, PCI = percutaneous coronary intervention.

* Reponder vs Nonresponder.

Table 2

Single-predictor and Multiple-predictor logistic regression models of predicting CRT response

Variables	Univariate		Multivariate	
	OR (95% C.I.)	p Value	OR (95% C.I.)	p Value
Age (year)	0.985 (0.954 – 1.016)	0.334	0.981 (0.938 – 1027)	0.415
Female gender	2.827 (1.059 – 7.546)	0.038	1.555 (0.403 – 6.006)	0.522
Non ischemic etiology	3.231 (1.438 – 7.260)	0.005	1.533 (0.480 – 4.896)	0.471
QRS width (ms)	1.025 (1.006 – 1.043)	0.008	1.027 (1.004 – 1.050)	0.023
LBBB	3.643 (1.673 – 7.934)	0.001	3.568 (1.284 – 9.910)	0.015
LV EDV Index (ml/m ²)	0.979 (0.965 – 0.992)	0.002	0.970 (0.953 – 0.987)	0.001

C.I = confidence interval, OR = odds ratio