A new baseline scoring system may help to predict response to cardiac resynchronization therapy

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Abstract

Introduction: The PROSPECT trial reported no single echocardiographic measurement of dyssynchrony is recommended to improve patient selection for cardiac resynchronization therapy (CRT).
Material and methods: In 100 consecutive patients who received CRT, we analyzed 27 ECG and echocardiographic variables to predict a positive response to CRT defined as a left ventricular (LV) end systolic volume decrease of ≥ 15% after CRT.
Results: Right ventricular (RV) pacing-induced left bundle branch block (LBBB), time difference between LV ejection measured by tissue Doppler and pulsed wave Doppler (T_{TDI-PW}), and wall motion score index (WMSI) were significantly associated with positive CRT response by multivariate regression. We assigned 1 point for RV pacing-induced LBBB, 1 point for WMSI ≤ 1.59, and 2 points for T_{TDI-PW} > 50 ms. Overall mean response score was 1.79 ±1.39. Cutoff point for response score to predict positive response to CRT was > 2 by receiver operating characteristic (ROC) analysis. Area under ROC curve was 0.97 (p = 0.0001). Cardiac resynchronization therapy responders in patients with response score > 2 and ≤ 2 were 36/38 (95%) and 7/62 (11%, p < 0.001), respectively. After age and gender adjustment, the response score was related to CRT response (OR = 45.4, p < 0.0001).
Conclusions: A response score generated from clinical, ECG and echocardiographic variables may be a useful predictor for CRT response. However, this needs to be validated.

Key words: cardiac resynchronization therapy, wall motion score index.

Introduction

Cardiac resynchronization therapy (CRT) improves cardiac performance for patients who have severe congestive heart failure and a wide QRS complex [1-3]. However, patient response to CRT is not homogeneous. Cardiac function is not improved in approximately 30% of patients with a wide QRS who received CRT according to the criteria of the present guidelines [3]. It is also unclear as to which patient profiles will benefit the most from CRT. Cardiac resynchronization therapy is an invasive therapy and associated with a median incremental cost of $107,800 (interquartile range, $79,800 to $156,500) per additional quality-adjusted life year (QALY). Cardiac resynchronization therapy should be avoided in patients in which there is no benefit [4].

The Predictors of Response to CRT (PROSPECT) trial reported that no single echocardiographic measurement of dyssynchrony may be recommended to improve patient selection for CRT [5]. We hypothesized that CRT response is not only related to left ventricular (LV) mechanical dyssynchrony (LVMD), but is also related to other variables such as right ventricular (RV) pacing-induced left bundle branch block (LBBB) [6, 7], LV segmental wall motion score index (WMSI) [8], LV restrictive filling (LVRF) [9], mitral regurgitation (MR) [3], and left atrial volume [10]. We further hypothesized that a response score based on the above factors may be helpful in improving our ability to predict CRT response.

Material and methods

We retrospectively evaluated 147 consecutive patients who received CRT at the Creighton University Medical Center for potential participation in the study. The criteria for biventricular pacemaker implantation followed American College of Cardiology/American Heart Association guidelines [11]. The QRS duration in all patients was measured from surface electrocardiograms using the widest QRS complex in leads II, V1, and V6. Forty-seven patients were excluded because of atrial fibrillation, mitral stenosis, or loss to follow-up. The remaining 100 patients (73 men and 27 women, mean age 70 ±10 years) were included in the study. Of the 100 patients, 66 (66%) had ischemic heart disease, 26 (26%), had 3-vessel coronary artery disease, 32 (32%) had previous myocardial infarction, 75 (75%) had intrinsic LBBB, and 25 (25%) had RV pacing-induced LBBB (pacemaker-dependent right ventricular pacing for at least 6 months, and an upgrade of RV pacemaker or implantable cardioverter-defibrillator to CRT). All 100 patients underwent coronary angiography before CRT.

After informed written consent was obtained, all patients underwent implantation of a biventricular pacer in the cardiac electrophysiology laboratory. The lead was positioned into the left the lateral LV vein. After the pacing and sensing parameters were measured, the LV pacing lead was secured with a supporting style. The RV defibrillation lead was screwed into the RV apex. The atrial pacing lead was screwed into the high lateral right atrium. The results depended on the endocardial lead position.

Conventional transthoracic echocardiography was performed with the Philips Sonos 7500 echocardiographic system and a s3 transducer. Baseline echocardiographic data before CRT and the post CRT follow-up echocardiograms were reviewed for all patients. Left ventricular end-systolic volume, LV end-diastolic volume, LV ejection fraction, and left atrial volume were measured in the apical view from the videotape or Philips Enconcert digital system according to the standard recommended by American Society of Echocardiography [12]. Left ventricular end-systolic and end-diastolic dimensions were measured in the parasternal long-axis view. A positive response to CRT was defined as a LV end systolic volume decreasing ≥ 15% after CRT [13].

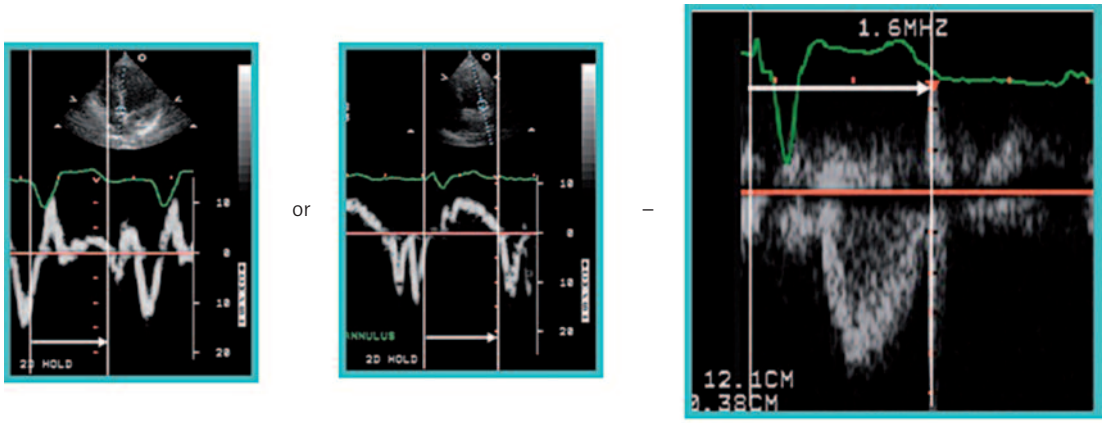
Left ventricular mechanical dyssynchrony was evaluated by Pérez's method by combined pulsed wave Doppler and tissue Doppler [14, 15]. The time difference (T_{PW-TDI}) between the onset of Q wave to the end of the systolic wave in the basal lateral or septal segments with the greatest contraction delay assessed by tissue Doppler imaging (TDI) (T_{TDI}) and the onset of Q wave to the end of LV ejection assessed by pulsed wave Doppler (PW) (T_{PW}) was measured within one month before CRT (Figure 1). T_{PW-TDI} > 50 ms was defined as LVMD [14, 15]. Pulsed TDI was only used in this study. Color TDI was not used.

The motion of individual LV segments was graded as follows: normal = 1, hypokinesia = 2, akinesia = 3, and dyskinesia = 4. The WMSI was analyzed using a 17 segment model and calculated by the total score/number of segments analyzed [12].

Left ventricular filling was evaluated by PW and TDI and classified into 4 patterns: 1) normal, 2) LV relaxation abnormality, 3) pseudo-normalization, and 4) LVRF.

The severity of MR was classified into 3 grades: mild, moderate, and severe by the color flow jet area as recommended by guidelines from the American Society of Echocardiography [16]. A color flow jet area < 40% and > 20% of left atrial area was defined as moderate, and moderate or severe MR was defined as significant MR.

The variables used for analysis are listed in Table I [17]. Continuous variables were presented as a mean ±1 standard deviation and were compared using analysis of variance. Categorical data were assessed with a χ^2 or by a Fisher-exact test if the cell sizes were < 5. A receiver operating characteristic (ROC) curve was used for evaluation of the cutoff value, sensitivity and specificity of the parameter to predict a positive response to CRT. The area under the ROC curve (AUC) was used for comparison between the scoring system and LVMD in evaluation of CRT response. We evaluated the relative variables to CRT response by multivariate logistic regression model using SPSS version 16.0 software. Each variable was evaluated by a forward selection method to select variables for multivariate regression based on the calculated score χ^2 statistic. The variable with the largest score χ^2 statistics was added to the model. For each selected variable, the logistic procedure then calculated the point estimate of odds ratio, Wald statistics, 95%



$LVMD = T_{TDI} - T_{PW}$, if $T_{TDI} - T_{PW} > 50$ ms

Figure 1. The calculation for LVMD is shown. Left ventricular mechanical dyssynchrony was defined as the difference between T_{TDI} and T_{PW} if the difference was more than 50 ms
LVMD – left ventricular mechanical dyssynchrony, TTDI – the onset of Q wave to the end of the systolic wave in the basal lateral or septal segments with the greatest contraction delay, TPW – The onset of Q wave to the end of left ventricular ejection

Wald confidence limits and *p* value. Cardiac resynchronization therapy response score was generated by the variables with a significant level of $p < 0.05$ by multivariate regression. We assigned 1 point for the variables achieving a significance level by multivariate regression. The Wald test was used to evaluate the weight of the variables in order to predict CRT response [18]. We assigned 2 points for the variable with the highest value of Wald. Higher scores represented a higher positive response to CRT. A *p* value of < 0.05 was considered statistically significant.

The study was approved by the Institutional Review Board of Creighton University School of Medicine.

Results

The implantation procedure was successfully performed in all 100 patients. The LV capture threshold was 1.85 ±1.06 volts, and the mean LV pacing impedance was 1,005 ±355 ohms. Of the 100 patients, 75 (75%%) had intrinsic LBBB, and 25 (25%) had RV pacing-induced LBBB. The follow-up duration after CRT was 17.0 ±10.6 months. Forty-three patients (43%) were defined as positive CRT responders. There was no significant difference in follow-up duration between CRT responders (16.6 ±11.1 months) and non-responders (17.4 ±10.3 months, $p = 0.72$).

There were 43 patients with LVRF and 40 patients with MR ≥ moderate. The ECG and echocardiographic measurements before andat the end of follow-up after CRT are listed in Table II. There were significant differences in LVEF and T_{TDI-PW} during follow-up of 14.39 ±10.5 months after CRT compared to baseline ($p = 0.0001$ and $p < 0.0001$). The cutoff point for WMSI to predict negative response to CRT was > 1.59 by ROC analysis.

All study patients were treated with optimal medical therapy. Of 100 patients, 90 (90%) were on a β-blocker, 88 (88%) were on an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker, 55 (55%) were on loop diuretics, 35 (35%) were on spironolactone, 29 (29%) were on loop diuretics and spironolactone, and 72 (72%) were on digoxin.

Table III lists the results of multivariate regression for evaluation of the variables which achieved the largest score χ^2 statistics when the dependent variable was a positive response to CRT. The variables of RV pacing-induced LBBB [odds ratio (OR) = 12.13, $p = 0.005$], T_{TDI-PW} (OR = 1.06, $p < 0.0001$) and WMSI (OR = 0.18, $p = 0.03$) achieved a significant level of $p < 0.05$. The T_{TDI-PW} was associated with the highest value of Wald (wald value = 19.74) compared to the variables of RV pacing-induced LBBB and WMSI (wald value = 7.71 and 4.87).

A 4-point score system was generated based on 3 variables: 1) RV pacing-induced LBBB, 2) T_{TDI-PW} and 3) WMSI that achieved a significant level of $p < 0.05$ to a positive CRT response analyzed by multivariate regression. We assigned 1 point for RV pacing-induced LBBB, 1 point for WMSI ≤ 1.59, and 2 points for $T_{TDI-PW} > 50$ ms (Wald value was the highest compared to others). Higher scores represent a better chance for a positive response to CRT. The overall mean response score was 1.79 ±1.39 (0-4). The cutoff point for a response score to predict positive response to CRT was > 2 by ROC

Table I. Variables used in the analysis

Age
Gender
QRS duration
QRS morphology divided into:
a) left bundle branch block
b) intraventricular conduction disease
c) paced rhythm and
d) right bundle branch block
Ischemic heart disease (coronary stenosis ≥ 70% reduction in luminal diameter)
Hypertension
Diabetes mellitus
Intrinsic or right ventricular pacing-induced left bundle branch block
Left ventricular capture threshold
Left ventricular pacing impedance
T_{TDI-PW} : the time difference between the onset of Q wave to the end of the systolic wave in the basal lateral or septal segments with the greatest contraction delay assessed by tissue Doppler imaging and the onset of Q wave to the end of left ventricular ejection assessed by pulsed wave Doppler
Left ventricular restrictive filling
Wall motion score index
Left ventricular end-diastolic dimension
Left ventricular end-systolic dimension
Left ventricular hypertrophy, defined as left ventricular wall thickness > 11 mm
Left ventricular ejection fraction
Left atrial volume index
Significant mitral regurgitation
Mitral regurgitation degree
β-Blockers
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers
Loop diuretics
Spironolactone
Loop diuretics and spironolactone
Digoxin
New York Heart Association class

analysis. The area under the ROC curve (AUC) was 0.97 (95% CI 0.92-0.99, SE = 0.02, p = 0.0001) (Figure 2). The sensitivity and specificity for prediction of a positive response to CRT at a response score > 2 were 83.7% and 96.5%, respectively. Cardiac resynchronization therapy responders in patients with a response score > 2 and ≤ 2 were 36/38 (95%) and 7/62 (11%, p < 0.001), respectively. After adjustment for age (OR = 1.03, p = 0.54) and gender (OR = 0.13, p = 0.06), the response score was related to CRT response (OR = 45.4, p < 0.0001) by multivariate regression. The response score > 2 was associated with a 45-fold increase in predicting CRT response compared to a response score ≤ 2.

Table II. QRS duration and echocardiographic measurements at baseline and at end of follow-up after cardiac resynchronization therapy

Parameter	At baseline	At end of follow-up	Value of p
QRS duration [ms]	165.4 ±27.9	157.7 ±29.4	0.06
LVDd [mm]	64.6 ±10.5	61.8 ±11.1	0.08
LVDs [mm]	53.7 ±11.5	52.4 ±12.3	0.43
LVVs [ml]	174.0 ±76.0	156.6 ±74.3	0.10
LVEF (%)	20.4 ±6.6	25.8 ±12.2	0.0001
LAVI [ml/m^2]	59.9 ±22.7	57.0 ±19.3	0.32
T_{TDI-PW} [ms]	74.7 ±48.5	48.4 ±31.6	< 0.001

LVDd – left ventricular dimension in end-diastole, LVDs – left ventricular dimension in end-systole, LVVs – left ventricular volume in end-systole, LVEF – left ventricular ejection fraction, LAVI – left atrial volume index

The overall mean T_{TDI-PW} was 74.67 ±48.53 ms. The cutoff point for T_{TDI-PW} to predict a positive response to CRT was > 50 ms by ROC analysis. The area under the ROC curve (AUC) was 0.92 (p = 0.0001). The sensitivity and specificity for prediction of a positive response to CRT at the cutoff point > 50 ms were 98% and 80.7%, respectively. The area under the ROC curve and specificity for the response score to predict a CRT response were significantly higher compared to T_{TDI-PW} (AUC = 0.97 vs. 0.92, p = 0.0001; specificity = 96.5% vs. 80.7%).

Discussion

The PROSPECT trial reported that no single echocardiographic measurement of ventricular dyssynchrony may be recommended to improve patient selection for CRT [5]. Mechanical dysynchrony measures are not in any guidelines for selection of patients for CRT. We generated a new response score system to predict CRT response before biventricular pacemaker implantation based on: 1) RV pacing-induced LBBB, 2) WMSI and 3) T_{TDI-PW}. The score system not only considered the effect of ventricular dyssynchrony, but also considered the effects of the LBBB pattern and LV wall motion abnormality in patients with and without coronary artery disease. The response score > cutoff point was associated with a 45-fold increase in predicting CRT response. The area under the ROC curve and specificity for response score to predict CRT response were

Table III. Results of multivariate regression for evaluation of 10 variables when the dependent variable was a positive response to cardiac resynchronization therapy

	Wald	Odds ratio	Value of *p*	95% CI for odds ratio	
				Lower	Upper
Gender	3.47	0.15	0.06	0.02	1.11
QRS duration	2.62	1.02	0.11	1.00	1.05
New York Heart Association class	0.11	1.33	0.74	0.24	7.39
Ischemic heart disease	0.48	2.22	0.49	0.23	21.18
RV pacing-induced LBBB	7.71	12.13	0.005	2.08	70.67
T_{TDI-PW}	19.74	1.06	< 0.0001	1.04	1.09
Wall motion score index	4.87	0.19	0.03	0.04	0.83
β-Blockers	1.55	0.23	0.21	0.02	2.30
Loop diuretics	0.01	0.88	0.91	0.10	8.02
Spironolactone	1.62	0.20	0.20	0.02	2.40

RV – right ventricular, LBBB – left bundle branch block

significantly higher compared to T_{TDI-PW} (AUC = 0.97 vs. 0.92, p = 0.0001; specificity = 96.5% vs. 80.7%).

Heist *et al.* [19] described a response score to predict both hemodynamic and clinical outcomes from CRT. A 4-point response score was generated using variables associated with $\Delta dP/dt$ by Doppler echocardiography, the dorsoventral LV/RV inter-lead distance by lateral chest radiography, the LV lead electrical delay by ECG, and the maximum time difference to peak systolic velocity by TDI. They found that there was a significant association between response score (0-4 points) and acute hemodynamic response to CRT (p < 0.0001). However, the point for a dorsoventral LV/RV inter-lead distance and the point for a LV lead electrical delay needed to be measured after implantation and during the procedure of biventricular pacemaker implantation. Therefore, the response score was unable to establish a pre-implantation predictor to predict the lack of benefit after CRT. Furthermore, the method for evaluation of the response score neglected the effects of ischemic heart disease on the CRT response.

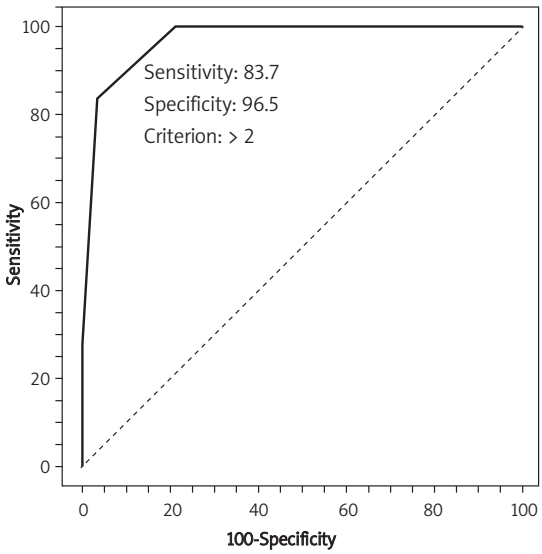


Figure 2. The area under the ROC curve (AUC) was 0.97 (95% CI 0.92-0.99, SE = 0.02, p = 0.0001)

Our previous study showed that patients with heart failure and RV pacing-induced LBBB had a better response rate to CRT when compared to patients with intrinsic LBBB [6]. The percentage of CRT responders in patients with RV pacing-induced LBBB was significantly greater than in patients with intrinsic LBBB (p = 0.04) and was associated with a greater decrease of QRS duration (p = 0.01). This finding is consistent with the data from the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial [20, 21]. One hypothesis is that RV pacing-induced LBBB is truly dissimilar to intrinsic LBBB [22]. However, the upper value of 95% CI for odds ratio in RV pacing-induced LBBB was high (70.67). This suggested that the sample size of RV pacing-induced LBBB was small for predicting CRT response, and that the result may be inaccurate. Further prospective studies using large number of patients appear warranted.

The study demonstrated that higher WMSI had a poorer response to CRT. High WMSI was a result of prior myocardial infarction in patients with ischemic heart disease and myocardial fibrosis in patients with non-ischemic heart disease [8, 23]. Wall motion abnormalities can affect intraventricular conduction and the coordinated mechanical response of the ventricles. Cardiac resynchronization therapy may correct conduction delay in remodeled dilated myocardial segments, but has no effect on extensive myocardial scars or ischemic segments [24].

We selected Pérez's method to determine LVMD in order to measure time intervals of LV ejection by combined tissue Doppler imaging and pulsed wave Doppler [14, 15]. The time derived by pulsed wave Doppler represented the mean time interval of LV ejection, while the time derived by tissue Doppler represented segmental time delay of LV ejection. This method provides reliable and accurate measurements in determining LVMD [14, 15]. It also better defines the endpoint of LV flow and motion velocity spectrum by pulsed wave Doppler and tissue Doppler than the method that defines the endpoint of peak systolic velocity only from a tissue Doppler spectrum because of the blunt nature of the peak velocity profile and double peaks [25].

The detection rate of LVMD is lower in patients with heart failure and wide QRS duration both in Pérez's study (39.4%) [14, 15] and in our current study (43%), compared to other studies (60-75%) [26]. The cause of lower CRT response rate may be related to ischemic heart disease. In our study, 66% of patients had ischemic heart disease with ≥ 70% coronary artery narrowing, 26% of patients had 3-vessel coronary artery disease, and 32% of patients had previous myocardial infarction. These data are consistent with previous studies that suggested CRT may be less beneficial among heart failure patients with ischemic heart disease compared to non-ischemic heart disease [24, 27-29]. However, ischemic heart disease was shown not to be predictive of CRT response in multivariate regression analysis possibly due to a small number of patients with high upper 95% CI (21.2). The cardiac performance may also be affected by the longer follow-up duration in our study compared to typical CRT response studies [26].

This is a single center retrospective study with a relatively small number of patients who received CRT. Our results should only be applied to patients with sinus rhythm because our study population did not include patients with atrial fibrillation. Although the follow-up duration in this study was not constant for each patiernt after CRT, there was no significant difference in follow-up duration between CRT responders and non-responders. This scoring system has not been tested prospectively to determine its utility in a large number of patients receiving CRT.

In conclusion, a response score generated from clinical, ECG and echocardiographic variables may be a useful predictor for CRT response. However, this score needs to be validated prospectively in a large number of patients receiving CRT.

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