Predictive Power of the Baseline QRS Complex Duration for Clinical Response to Cardiac Resynchronisation Therapy

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Received: 1/3/2011, Reviewed 29/3/2011, Accepted 2/4/2011
Key words: Electrocardiography, cardiac resynchronisation therapy, heart failure, sensitivity, specificity
DOI: 10.5083/ejcm.20424884.42

ABSTRACT

Background: Determination of predictors of response to cardiac resynchronisation therapy (CRT) in patients with moderate to severe heart failure accompanied by a ventricular dyssynchrony can play a major role in improving candidate selection for CRT.

Objectives: We evaluated whether the baseline QRS duration could be used to discriminate responders from non-responders to CRT.

Methods: Eighty-three consecutive patients with moderate to severe heart failure and with successful implantation of a CRT device at our centre were included in the study. QRS durations were measured on a 12-lead surface electrocardiogram before and 6 months after implantation of the CRT device, using the widest QRS complex in leads II, V1 and V6. Clinical response to CRT was defined as an improvement of ≥1 grade in NYHA class.

Results: Optimal cut-off value to discriminate baseline QRS duration for predicting clinical response to CRT was identified at 152 ms, yielding a sensitivity of 73.3%, a specificity of 56.5% as well as positive and negative predictive values of 81.5% and 44.8%, respectively. The discriminatory power of the baseline QRS duration for response to CRT assessed by the ROC curve was 0.6402 (95% CI: 0.4976 – 0.7829). Baseline QRS duration ≥ 152 ms could effectively predict clinical response to CRT after adjusting for covariates (OR = 3.743, p = 0.017).

Conclusion: Baseline QRS duration can effectively predict clinical response to CRT and optimal cut-off value to discriminate baseline QRS duration for response to CRT is 152 ms.

INTRODUCTION

Despite using current therapeutic protocols and guideline-mandated treatments, the increase in prevalence of heart failure and mortality and morbidity related to this condition is a growing medical challenge. Although pharmacologic therapy is considered the gold therapeutic intervention in this work.

Multiple clinical trials have described marked long-term improvement in symptoms and exercise capacity following CRT therapy in patients with advanced heart failure (class III or class IV in New York Heart Association (NYHA) classification) along with ventricular dyssynchrony (2-5). It was also suggested that the use of CRT could lead to sustain progress in long-term quality of life and survival in patients with moderate to severe heart failure (6,7).

Therefore, determination of optimal predictors of response to CRT could play a major role in patient selection for CRT. Currently, some well-known predictors include a less-advanced stage of disease and echocardiographic evidence of interventricular dyssynchrony (8), existence of right branch bundle block (9) and peak VO2 (3). However, the power of duration of the QRS complex to predict patients’ response to CRT is a matter of controversy (10-12).

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In the present study, we attempted to determine potential predictors of response to CRT after 6 months of follow-up in patients with heart failure and also evaluate whether the baseline QRS duration could be used to discriminate responders from non-responders to CRT.

**METHODS**

In a prospective study, 83 consecutive patients with the moderate to severe CHF (class III or class IV in New York Heart Association (NYHA) classification) in whom successful implantation of a CRT device was performed without any major complications at Tehran Heart Center were included into the study. Patients' selection was based on the following criteria: NYHA Class III or IV, normal sinus rhythm and QRS duration more than 120 milliseconds in electrocardiogram (ECG), global ejection fraction less than 0.30 on the basis of echocardiography report and presence of symptoms despite medication therapy for heart failure. Patients with a recent myocardial infarction (<2 months) or decompenated heart failure were excluded. Evaluation of clinical status included assessment of NYHA functional class. Clinical response to CRT was defined as an improvement of ≥1 grade in NYHA class (13). All patients followed over a 6-month period after device insertion.

Patients received deep sedation and underwent implantation of a device on left subclavian area. Left ventricular leads were positioned with the aid of a guiding sheath into lateral or posterolateral distal branches of the coronary sinus. Correct lodgment of the coronary venous or left ventricular lead was subsequently verified radiographically. Right ventricular and atrial leads were placed in right ventricular apex and in right atrial appendix, respectively. This study was approved by the local ethical committee and informed consents were obtained from all participants.

QRS duration was measured from the surface electrocardiogram before and 6 months after implantation of the CRT device. The ECGs were recorded at a speed of 25 mm/second and interpreted by an independent observer without knowledge of patients' clinical status. The widest QRS duration was measured manually using leads II, V1 and V6 on each ECG (11,22±21.96).

The programmed atrioventricular delay was calculated from a proprietary algorithm based on measurements of the intrinsic PR interval, the QRS interval and the intracardiac atrioventricular interval at the time of implantation.

Data were reported as mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables. Comparison of unpaired data was performed using the Student's t test. Paired t test was also used to compare data immediately before and 6 months after CRT in each studied group. The value of the baseline QRS duration to predict late response (6 months follow-up) was determined by receiver operator characteristic (ROC) curve analysis. A value of 0.5 indicates that the model was equivalent to pure chance and a value of 1 indicates perfect discrimination (14).

Cut-off score was estimated for prediction of response to CRT by the ROC curve analysis (the empirical point that maximises sensitivity and specificity of baseline QRS duration for predicting of CRT response). Predictors exhibiting a statistically significant relationship with clinical response to CRT such as gender and NYHA class in the univariate analysis were taken for a multivariate logistic regression analysis to investigate their independence. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 13 (SPSS Inc., Chicago, IL, USA) and the STATA statistical package (version 10.0; College Station, TX, USA).

**RESULTS**

General characteristics were comparable in responders and non-responders to CRT (Table 1). Our study also showed no significant differences between the two groups in the etiology of cardiomyopathy (ischemic or non-ischemic) as well as mean of ejection fraction before and 6 months after CRT. In 21.7% of patients, NYHA score remained unchanged following CRT, whereas 1- and 2- grades reduction in this score were observed in 33.7% and 38.6% of them, respectively. Increase in NYHA score was detected only in 5 patients. Also, none of the study patients were re-hospitalised during follow-up period because of their heart failure progression.

<table>
<thead>
<tr>
<th>Item</th>
<th>Responders (n=60)</th>
<th>Non-responders (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>46/14</td>
<td>16/7</td>
<td>0.505</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.08±9.89</td>
<td>57.17±12.58</td>
<td>0.729</td>
</tr>
<tr>
<td>Etiology (I/nI)</td>
<td>37/23</td>
<td>11/12</td>
<td>0.253</td>
</tr>
<tr>
<td>LVEF (before CRT) (%)</td>
<td>20.05±5.86</td>
<td>20.11±3.88</td>
<td>0.965</td>
</tr>
<tr>
<td>LVEF (after CRT) (%)</td>
<td>26.60±7.99</td>
<td>25.42±6.43</td>
<td>0.629</td>
</tr>
<tr>
<td>NYHA (before CRT)</td>
<td>3.30±0.46</td>
<td>3.26±0.45</td>
<td>0.729</td>
</tr>
<tr>
<td>NYHA (after CRT)</td>
<td>1.78±0.61</td>
<td>3.39±0.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QRS duration (before CRT) (ms)</td>
<td>165.75±25.86</td>
<td>153.96±27.39</td>
<td>0.071</td>
</tr>
<tr>
<td>QRS duration (after CRT) (ms)</td>
<td>136.53±19.79</td>
<td>142.74±24.81</td>
<td>0.238</td>
</tr>
<tr>
<td>QRS duration change (ms)</td>
<td>29.22±24.58</td>
<td>11.22±21.96</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 1: Baseline characteristics of responders and non-responders to cardiac resynchronisation therapy

Data are presented as mean ± SD or number.
Baseline QRS duration in the responders was longer than the non-responders; however, after CRT device insertion there was no significant difference in QRS duration between the two groups (Figure 1). In responder and non-responder patients, after the 6 months follow-up, the QRS duration was significantly reduced. However, as depicted in Figure 2, this reduction was higher in the responders with means reduction of 29.22±24.58 ms vs. 11.21±21.96 ms in non-responder patients.

ROC curve analysis was performed on the baseline QRS duration to define an optimal cut-off value for prediction of clinical response (Figure 3). The optimal cut-off value was identified at 152 ms, yielding a sensitivity of 73.3%, a specificity of 56.5% as well as positive and negative predictive values of 81.5% and 44.8%, respectively. The discriminatory power of the baseline QRS duration for response to CRT assessed by the ROC curve was 0.6402 (95% CI: 0.4976 – 0.7829).

Table 2: Multivariable analysis of the effects of baseline QRS duration for predicting clinical response to CRT with the presence of cofounders

<table>
<thead>
<tr>
<th>Item</th>
<th>Multivariate p-value</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline QRS ≥ 152 ms</td>
<td>0.017</td>
<td>3.743</td>
<td>1.264 – 11.080</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.882</td>
<td>1.095</td>
<td>0.330 – 3.637</td>
</tr>
<tr>
<td>Advanced age</td>
<td>0.561</td>
<td>0.985</td>
<td>0.935 – 1.037</td>
</tr>
<tr>
<td>NYHA score 4</td>
<td>0.641</td>
<td>1.321</td>
<td>0.410 – 4.256</td>
</tr>
<tr>
<td>Ischemic status</td>
<td>0.404</td>
<td>1.596</td>
<td>0.533 – 4.780</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.892</td>
<td>1.007</td>
<td>0.913 – 1.110</td>
</tr>
</tbody>
</table>

Figure 1: QRS duration in responders and non-responders to cardiac resynchronisation therapy at baseline and 6 months after treatment

Figure 2: Changes of QRS duration in responders and non-responders to cardiac resynchronisation therapy

Figure 3: Optimal cut-off value of reduction in QRS duration for prediction of CRT responding.

Multivariable regression analysis showed that the baseline QRS duration ≥ 152 ms could effectively predict clinical response to CRT after adjusting for some covariates such as male gender, age, ischemic status, Functional class and left ventricular ejection fraction (OR = 3.743, p = 0.017) (Table 2).

DISCUSSION

Recent research has focused on prediction of response to CRT and some studies suggested that QRS duration per se may predict the response rate to CRT (11,15), but a systematic study is lacking. Lecoq et al showed that among demographic, clinical and ECG variables, the amount of QRS shortening associated with biventricular stimulation was the only independent predictor of a positive response to CRT (19). Furthermore, it has been demonstrated that the CRT responders had a significant reduction in QRS duration directly after initiation of CRT, whereas, the non-responders did not exhibit such a reduction (11). However, in another study, QRS duration could not effectively predict poor outcome in patients undergoing CRT (12).

In the present study, in line with some recent studies, a significant improvement in NYHA score was observed following CRT protocol in mid-term follow-up (2,4,9). De Marco et al. suggested that the patients with moderate to advanced symptoms of heart failure effectively benefit from the addition of CRT in terms of exercise capacity, functional status and even quality of life in mid-term follow-up. The investigators recommended CRT implantation as a standard therapy in this selected group of heart failure patients (5).

However, the results of CRT were notably different in long-term follow-up studies (12, 16) probably highlighting the role of underlying cardiac pathology severity and concurrent illnesses. Moreover, non-CAD patients have shown a greater decrease in NYHA functional class than CAD patients (9) and it has been demonstrated that the improvement in patients’ characteristics is mainly related to the reduction in left ventricular end-systolic and end-diastolic volumes, and also left ventricular ejection fraction (2,17). Positive effect of CRT on cardiac dimensions is also dependent on the severity of heart failure. Landolina et al. observed that the improvement in functional status is significantly lower for patients in NYHA class I or II than for those in NYHA class III or IV (18).

In our study, the QRS duration was significantly reduced in both responder and non-responder groups but this reduction was greater in the responder group. In addition, we found an acceptable discriminatory power of the baseline QRS duration for response to CRT with an optimal cut-off value 152 ms (sensitivity of 73.3%, specificity of 56.5%).

Furthermore, it has been shown that CRT can potentially improve morbidity and mortality in patients with heart failure with QRS >120 ms (20). In the Molhoek et al. study, the investigators also found no clinically useful cut-off of postimplant QRS duration or of the periprocedural change in QRS duration to separate potential responders to CRT from non-responders (11).

Several other previous studies failed to find a value of QRS duration for CRT patients selection (6,13). We observed that in patients with moderate to severe heart failure undergoing CRT, baseline QRS parameter had an acceptable sensitivity and specificity cut-off value of 152 ms and was a good marker of outcome.

Our study had several limitations. First, responders were defined as those patients who improved at least 1 grade in NYHA score after 6 months of CRT. A clear definition of response to CRT is lacking. It seems that the clinical indices such as an improvement in quality of life score and an increase in 6-minute walking distance and echocardiographic end points are better to determine response to CRT. Second, the present study included 83 patients; additional studies with greater cohorts of patients are needed to confirm the findings. Finally, we did not have data available regarding detailed pharmacologic therapy particularly on heart failure medications which may have changed over time. Furthermore, the lack of a statistically significant association of some of the covariates with outcome at 6 months may be due to sample size limitations, which also precluded a more comprehensive multivariable model with additional covariates, and the assessment of a possible interaction between QRS and some of the covariates. Moreover, the lack of comprehensive echocardiographic data, especially regarding measures of cardiac dyssynchrony that have suggested in some studies to identify response to CRT.

CONCLUSION

In conclusion, CRT devices can effectively induce potential changes in QRS duration, particularly in responders after a 6 months period. Baseline QRS duration can effectively predict clinical response to CRT and optimal cut-off value to discriminate baseline QRS duration for response to CRT is 152 ms, yielding a sensitivity of 73.3% and a specificity of 56.5%.
REFERENCES