The Shortest QRS Duration of an Electrocardiogram Might Be an Optimal Electrocardiographic Predictor for Response to Cardiac Resynchronization Therapy

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Summary

QRS duration has been associated with the response to cardiac resynchronization therapy (CRT). However, the methods for defining QRS duration to predict the outcome of CRT have discrepancies in previous reports. The aim of this study was to determine an optimal measurement of QRS duration to predict the response to CRT.

Sixty-one patients who received CRT were analyzed. All patients had class III-IV heart failure, left ventricular ejection fraction not more than 35%, and complete left bundle branch block. The shortest, longest, and average QRS durations from the 12 leads of each electrocardiogram (ECG) were measured. The responses to CRT were determined using the changes in echocardiography after 6 months. Thirty-five (57.4%) patients were responders and 26 (42.6%) patients were non-responders. The pre-procedure shortest, average, and longest QRS durations and the QRS shortening (ΔQRS) of the shortest QRS duration were significantly associated with the response to CRT in a univariate logistic regression analysis (P = 0.002, P = 0.03, P = 0.04, and P = 0.04, respectively). Based on the measurement of the area under curve of the receiver operating characteristic curve, only the pre-procedure shortest QRS duration and the ΔQRS of the shortest QRS duration showed significant discrimination for the response to CRT (P = 0.002 and P = 0.038, respectively). Multi-variable logistic regression showed the pre-procedure shortest QRS duration is an independent predictor for the response to CRT.

The shortest QRS duration from the 12 leads of the electrocardiogram might be an optimal measurement to predict the response to CRT. (Int Heart J 2017; 58: 530-535)

Key words: Heart failure

Cardiac resynchronization therapy (CRT) is a well-known procedure for improving left ventricular function via reverse remodeling in patients with heart failure.1 The QRS durations before implantation and at follow-up may predict the patient’s response to CRT, especially in the presence of left bundle branch block (LBBB).1-3 However, the QRS durations are usually different and diverse among the 12-lead electrocardiogram (ECG).4-6 Additionally, in previous reports, the methods to define the QRS duration in predicting a CRT patient’s outcome have discrepancies and lack standardization of QRS duration measurement.6-8 Many different methods for QRS duration measurement have been used in previous studies, including the QRS duration of one selected lead,1,11,12 the longest QRS duration,13 the average QRS duration of 12 leads,14 and undefined.6,15,16 International guidelines for heart failure management also have not recommended a preferred standard measurement technique for QRS duration for CRT.1,2,10,13,16 Lack of standard measurement in the QRS duration might have a significant influence on the conclusions of different studies.10 Thus, this is the crucial reason why the recommended QRS duration for CRT implantation was different and variable in previous reports. However, the decision-making for suggesting that a patient receive a CRT implantation largely depends on the ECG interpretation and QRS duration. Inaccurate QRS measurement may increase the possibility of exposing patients to unnecessary CRT procedures or deny some patients the beneficial effects ofCRT.10

Apparently, the QRS duration is critical for deciding to perform a CRT implantation and the outcome after CRT. However, the standard method for determining the QRS duration is unclear. It is of interest to investigate the association of different methods for QRS duration measurement of a 12-lead ECG with the response to CRT and to determine appropriate standards for QRS duration measurement.
METHODS

Study population: This study included 61 consecutively eligible patients who received CRT at China Medical University Hospital. All patients underwent a complete baseline evaluation, including a 12-lead ECG, estimation of the appropriate New York Heart Association (NYHA) functional class, and a complete echocardiographic examination. The inclusion criteria were: patients with drug-refractory NYHA class III or IV heart failure, complete LBBB, left ventricular end diastolic diameter (LVEDD) > 55 mm, and left ventricular ejection fraction (LVEF) ≤ 35%. Patients were excluded for the following reasons: recent myocardial infarction (less than 3 months), coronary artery bypass surgery within the previous 3 months, primary valvular heart disease, or hypertrophic or restrictive cardiomyopathy. The protocol of the present study was approved by the Institutional Review Board of China Medical University Hospital in Taiwan. The investigation conformed to the principles outlined in the Declaration of Helsinki.

Measurement of the patient responses to CRT: Assessment of LV dyssynchrony was repeated after CRT implantation, and clinical status was reassessed. The clinical status and changes in LVEF and LV volumes were re-assessed at 6 months after CRT. The NYHA functional classification was performed by an independent researcher who was blinded to other data and analyses. Responders were defined as patients who had no hospitalization because of decompensated heart failure and had a 15% reduction in left ventricle end-systolic volume (LVESV) compared to the baseline data. Those patients who could not meet the criteria of responders with insignificant improvement in heart failure functional class and reduction in LVESV were defined as non-responders.

Electrocardiographic analysis: Standard 12-lead ECGs were acquired at a speed of 25 mm/s and a scale of 10 mm/mV. The QRS durations from the 12 leads of each ECG were measured. The QRS duration is measured from the beginning of the Q wave to the end of the S wave by moving the calipers based on the software incorporated in the ECG recording equipment (MUSE system, General Electric, USA) (Figure 1). The QRS durations were measured not only at 25 mm/s standard paper speed but also at different paper speeds (12.5 mm/s and 50 mm/s) to confirm the results via the MUSE system. The shortest and longest QRS durations of each ECG were identified after measurement. The measurements of QRS duration and morphology were recorded from the 12 leads of the surface ECGs of the study patients by two independent researchers who were blinded to the other data.

Echocardiographic protocol: Echocardiography was obtained at baseline and FU according to the study protocol as previously reported. The echocardiographic studies were performed using a GE Vivid 7 ultrasound system (General Electric, USA). Images were obtained using a 3.5-MHz transducer in the parasternal and apical views. LV end-diastolic volume (LVEDV), LVESV, and LVEF were calculated using the biplane Simpson technique. Echocardiographic parameters were measured according to established American Society of Echocardiography protocols. The echocardiographers who decided on the echocardiographic response at follow-up were blinded to the baseline measurements.

Implantation technique: CRT devices were implanted via a subclavian or cephalic vein. The RV lead was placed in the apex or the high septum based on the implanting physician’s decision. The right atrium (RA) lead was positioned in the RA appendage. A venogram with two different views (left anterior oblique view and right anterior oblique view) was obtained to determine the anatomy of the coronary venous system. The LV lead was targeted to the mid-lateral tributary if an appropriate coronary sinus branch was present. Alternative LV stimulation sites in the anterolateral or posterolateral venous tributaries were selected when a mid-lateral tributary failed LV lead placement or was unacceptable due to phrenic nerve stimulation or had an inappropriate stimulation threshold. Final lead positioning was assessed from 3 different X-ray views (antero-posterior and right and left anterior oblique views). The CRT devices and leads used were from Medtronic (St Paul, MN, USA), St Jude Medical (St Paul, MN, USA), or Boston Scientific (Minneapolis, MN, USA). A fixed atrioventricular (AV) delay of 110–130 ms was chosen at implantation. Thereafter, the AV delay was optimized individually based on Doppler echocardiographic measurements of transmitral flow after implantation.

Statistical analysis: Continuous data are expressed as the mean ± standard deviation (SD). Pearson’s χ² test was used to determine the differences in categorical variables if the observation numbers in all categories were larger than 5; otherwise, the Fisher exact test was replaced for data analysis. One-way analysis of variance (ANOVA) was used for comparisons among numeric variables for the shortest, average, and longest QRS durations. The association of QRS duration and patient response to CRT was analyzed using logistic regression analysis. The measurements of QRS durations that were associated with predicting the response to CRT were further analyzed using a receiver operating characteristic curve (ROC) to determine the optimal cut-off of the QRS durations. A 95% confidence interval (CI) of the odds ratio (OR) and the area under the ROC curve were then calculated. A P value lower than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 18 for windows (SPSS Inc, Chicago, IL, USA).

RESULTS

This study included 61 patients (25 men, 36 women; mean age, 74.0 ± 10.7) who underwent CRT for heart failure with CLBBB. The shortest, average, and longest QRS durations before CRT were significantly different (138.3 ± 16.9 ms, 160.7 ± 16.1 ms, 176.9 ± 19.1 ms, respectively, P < 0.01).

Of the 61 patients, 35 (57.4%) were responders to CRT and 26 (42.6%) were non-responders to CRT. The clinical features of the patients classified as responders and non-responders are summarized in Table I. The baseline characteristics were similar between the 2 groups.

In univariate logistic regression analysis, the pre-procedure shortest, longest, and average QRS durations of the responders were significantly longer than those of the non-responders and were associated with the response for CRT (144.3 ± 14.9 versus 130.1 ± 16.1 ms, P = 0.002; 181.3 ± 18.3 versus 171.1 ± 18.9 ms, P = 0.04 and 164.6 ± 14.5 versus 155.4 ± 16.8 ms, P = 0.03, respectively). The amount of QRS shortening (ΔQRS) of the shortest QRS duration was also significantly higher than that of the non-responders and was asso-
Associated with the response to CRT (27.8 ± 19.2 versus 16.9 ± 18.8, \( P = 0.04 \)). However, the post-CRT QRS durations were not associated with the response to CRT (Table II).

Based on the measurement of the area under curve (AUC) of ROC, only the pre-procedure shortest QRS duration and the \( \Delta \)QRS of the shortest QRS duration showed significant discrimination for the response to CRT (AUC = 0.74, \( P = 0.002 \) and AUC = 0.66, \( P = 0.038 \), respectively). In contrast, the AUC of the average QRS duration and the longest duration did not show significant discrimination for the response to CRT (AUC = 0.65, \( P = 0.052 \) and AUC = 0.63, \( P = 0.078 \), respectively) (Figure 2). The results indicated the shortest QRS duration was a better predictor for the response to CRT than the longest and average QRS durations. With an optimal cut-off of 136 ms, the

Figure 1. QRS durations among the 12-leads of ECG in one patient. The QRS duration is measured from the beginning of the Q wave to the end of the S wave by moving the calipers based on the software incorporated in the ECG recording equipment. The QRS duration showed significant variation among the leads.

Table I. General Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responder n = 35</th>
<th>Non-responder n = 26</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>75 ± 10</td>
<td>73 ± 12</td>
<td>0.42</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>11/24</td>
<td>14/12</td>
<td>0.08</td>
</tr>
<tr>
<td>HT, n (%)</td>
<td>20 (57.1)</td>
<td>10 (38.5)</td>
<td>0.149</td>
</tr>
<tr>
<td>AF, n (%)</td>
<td>10 (28.6)</td>
<td>5 (19.2)</td>
<td>0.402</td>
</tr>
<tr>
<td>Ischemic heart, n (%)</td>
<td>16 (45.7)</td>
<td>16 (61.5)</td>
<td>0.221</td>
</tr>
<tr>
<td>CKD, n (%)</td>
<td>7 (20.0)</td>
<td>8 (30.8)</td>
<td>0.334</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III, n (%)</td>
<td>16 (45.7)</td>
<td>15 (57.7)</td>
<td></td>
</tr>
<tr>
<td>IV, n (%)</td>
<td>19 (54.3)</td>
<td>11 (42.3)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

DM indicates diabetes mellitus; HT, hypertension; AF, atrial fibrillation; CKD, chronic kidney disease; and NYHA, New York Heart Association.
The sensitivity and specificity of the shortest QRS duration were 80% and 61.5%. The positive predictive rate was 73.7% and the negative predictive rate was 69.6%.

Based on the results of univariable logistic regression analysis and AUC of ROC analysis, the pre-procedure shortest QRS duration, LVEDD, and LVEF were selected for multivariable stepwise logistic regression analysis. In the stepwise analysis process, pre-procedure average QRS duration, pre-procedure longest QRS duration, ΔQRS, LVEDD, and LVEF were excluded due to statistical insignificance for an independent predictor. The pre-procedure shortest QRS duration is the only independent predictor for the response to CRT (OR= 1.063, 95%CI = 1.022-1.106, P = 0.002) (Table III).

The distribution of the lead with the shortest QRS duration among the 12 leads showed the count of the lead with the shortest QRS duration is significantly higher in the limb leads (dark grey bars) than in the precordial leads (light grey bars) (53/61 versus 8/61, P < 0.001) (Figure 3). The limb leads tend to show the shortest QRS duration. Additionally, the aVR lead was found to be the most frequent lead with the shortest QRS duration.

Table II. Univariate Logistic Regression Analysis for the Response to Cardiac Resynchronization Therapy

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-responders</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>66.5 ± 7.3</td>
<td>68.4 ± 16.6</td>
<td>0.55</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>25.6 ± 5.8</td>
<td>25.0 ± 6.2</td>
<td>0.70</td>
</tr>
<tr>
<td>Pre-CRT QRS (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortest</td>
<td>144.3 ± 14.9</td>
<td>130.1 ± 16.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Average</td>
<td>164.6 ± 14.5</td>
<td>155.4 ± 16.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Longest</td>
<td>181.3 ± 18.3</td>
<td>171.1 ± 18.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Post-CRT (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortest</td>
<td>116.6 ± 22.8</td>
<td>113.2 ± 17.6</td>
<td>0.53</td>
</tr>
<tr>
<td>Average</td>
<td>133.3 ± 21.6</td>
<td>132.8 ± 18.7</td>
<td>0.92</td>
</tr>
<tr>
<td>Longest</td>
<td>149.7 ± 22.8</td>
<td>150.8 ± 20.2</td>
<td>0.85</td>
</tr>
<tr>
<td>ΔQRS (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortest</td>
<td>27.8 ± 19.2</td>
<td>16.9 ± 18.8</td>
<td>0.04</td>
</tr>
<tr>
<td>Average</td>
<td>31.0 ± 17.7</td>
<td>21.9 ± 20.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Longest</td>
<td>31.5 ± 20.7</td>
<td>21.1 ± 26.8</td>
<td>0.10</td>
</tr>
</tbody>
</table>

LVEDD indicates left ventricular end diastolic diameter; CRT, cardiac resynchronization therapy; and ΔQRS, QRS duration before CRT - duration after CRT implantation.

Table III. Multivariate Stepwise Logistic Regression Analysis for the Response to Cardiac Resynchronization Therapy

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>-</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>-</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-procedure longest QRS duration (ms)</td>
<td>-</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-procedure average QRS duration (ms)</td>
<td>-</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-procedure shortest QRS duration (ms)</td>
<td>1.063</td>
<td>1.022-1.106</td>
<td>0.002</td>
</tr>
<tr>
<td>ΔQRS, shortest (ms)</td>
<td>-</td>
<td>-</td>
<td>NS</td>
</tr>
</tbody>
</table>

– indicates the data unavailable because of removal of these variables from multivariable stepwise logistic regression model; OR, odds ratio; CI, confidence interval; LVEDD, left ventricular end diastolic diameter; ΔQRS, QRS duration before CRT - duration after CRT implantation; and NS, not statistically significant.

Figure 2. AUC of the ROC for the shortest, average, and longest QRS durations and the ΔQRS of the shortest QRS duration in predicting the response to cardiac resynchronization therapy. Based on the AUC, only the pre-procedure shortest QRS duration and the ΔQRS of the shortest QRS duration showed significant discrimination for the response to CRT (AUC = 0.74, P = 0.002 and AUC= 0.66, P = 0.038, respectively).

Figure 3. Distribution of the lead with the shortest QRS duration. The count of the lead with the shortest QRS duration of the limb leads (dark grey bars) is significantly higher than the precordial leads (light grey bars) (53/61 versus 8/61, P < 0.001).
**DISCUSSION**

In this cohort study of patients who received CRT, we investigated different measurements of QRS duration in predicting the response of the patient to CRT. We found that the shortest QRS duration was a better predictor for patients’ response to CRT than the longest and the average QRS durations. This finding provided a possible answer for the lack of standardized measurement of the QRS duration in CRT studies. This finding is also practical in clinical situations because a 12-lead ECG is available for every patient before CRT and provides a reasonable sensitivity and specificity in predicting the response to CRT. Although some other tools are also available for predicting outcome after CRT, such as echocardiography including the tissue Doppler technique, cardiovascular magnetic resonance, and nomograms, QRS duration and complete LBBB on a surface ECG are still the proven independent predictors for the response after CRT.

In the present study, the shortest, longest, and average QRS durations were significantly different. Using the 3 different QRS durations to predict the response to CRT based on the unclear definition of the QRS duration measurement from previous studies may result in different predicted outcomes. The selection process for a candidate for CRT will have significant bias. This bias may increase the possibility of heart failure patients receiving CRT procedures with a poor response or prevent some patients with an excellent possible response to CRT from receiving the beneficial procedure. Based on the analysis of AUC of ROC, we found only the shortest QRS duration measurement and the ΔQRS of the shortest QRS duration among the different measurement methods showed significant discrimination of the response to CRT. In multivariable stepwise logistic regression analysis, the pre-procedure shortest QRS duration, pre-procedure average QRS duration, pre-procedure shortest QRS duration, AQRS of the shortest QRS duration, LVEDD, and LVEF were selected for analysis. The pre-procedure shortest QRS duration was shown to be the only independent predictor for the response to CRT. The results of the present study indicate different methods for QRS duration measurement will have different results for QRS durations, and the shortest QRS duration may be the optimal method for QRS duration measurement in predicting the response to CRT.

In the present study, we found the limb leads tend to be the lead with the shortest QRS duration. In addition, the aVR lead has been shown to be the most frequent lead with the shortest QRS duration. Based on the findings of the present study, we recommend checking the QRS durations of limb leads, particularly the aVR lead, to define the shortest QRS duration and to save time.

The ECG of each surface lead of a 12-lead ECG is correlated with the summation of electrical activity of intracardiac electrograms in the related vector. Patients with similar average or longest QRS duration may have different QRS duration distributions among the 12 leads. QRS duration has been reported to closely associate with left ventricular dyssynchrony via the tissue Doppler image study. In addition, the ventricular activation was found to be heterogeneous with the latest activation of LV that may occur in the lateral base, anterolateral wall, mid lateral or inferior wall in LBBB patients based on the electrocardiographic imaging studies. Pacing over the late activation site could reverse the dyssynchrony.

The QRS duration may be relatively short in some leads and implicates relatively early activation and synchronized depolarization of ventricular myocardium in the vectors of the corresponding leads; therefore, the left ventricle may be not fully dyssynchronized. Accordingly, those patients with a higher average or longest QRS duration might have a lower shortest QRS duration and this implicates relatively early activation and synchronized depolarization of ventricular myocardium in the corresponding vector of the lead with the shortest QRS duration. Therefore, our ability to place the LV electrode at the late activated or dyssynchronized myocardium of the LV may decrease. In contrast, it may represent a near fully dyssynchronized LV and further worsened LV global conduction when the shortest QRS duration is significantly prolonged in a patient with heart failure and CLBBB; thus, the possibility of reversing the cardiac dyssynchrony and the response to CRT are increased because the LV electrode can relatively easily reach the late activated or dyssynchronized myocardium of the LV and have a benefit for near global dyssynchrony. Apparently, the shortest QRS duration plays a more important role than the average and longest QRS duration for predicting the response to CRT. Based on the results of the present study and the supporting evidence, we believe the shortest QRS duration carries more crucial information for the response to CRT than the average and longest QRS durations. To the best of our knowledge, this is the first study to demonstrate the important role of the shortest pre-procedure QRS duration in predicting the response to CRT and provides evidence to clarify the critical issue of the lack of standardization in QRS measurement for CRT.

**Study limitations:** There are some potential limitations of this study. First, the study population was small. These results should be further confirmed by a larger-scale study. Second, the study population was Chinese. Studies in different ethnic groups are needed to replicate our findings.

**Conclusions:** In different measurements of QRS durations, the shortest QRS duration of an electrocardiogram might be an optimal electrocardiographic predictor for the response to CRT. A shortest QRS duration of at least 136 milliseconds measured from a 12-lead surface ECG may predict the response to CRT in patients with CLBBB.

**Disclosures**

The authors have no conflicts of interest to disclose.

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